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EDITORIAL

Global advances in adult acute lymphoblastic leukemia: when access defines the prognosis

Christian Ramos-Peñafiel[1], Álvaro Cabrera-García[2], Adán Germán-Gallardo[1], and Adolfo Martínez-Tovar[3]*

[1]Department of Hematology, Hospital General de México Dr. Eduardo Liceaga, Secretaría de Salud, Mexico City; [2]Department of Hematology, Hospital Regional de Alta Especialidad Ixtapaluca, Secretaría de Salud, State of Mexico; [3]Laboratorio de Biología Molecular, Hospital General de México Dr Eduardo Liceaga, Secretaría de Salud, Mexico City. Mexico

B or T precursor cell leukemia/lymphoma is a clonal disorder characterized by the uncontrolled proliferation of immature lymphoid cells that block hematopoiesis, affecting the bone marrow and peripheral blood[1]. Although most cases occur in the pediatric population, they are increasingly diagnosed in adolescents and young adults, whose biology differs from that of pediatric patients, which explains a more unfavorable prognosis[2]. Except for Down syndrome, most cases occur in previously healthy individuals, where genetic susceptibility or exposure to environmental factors may play a key role[3]. In adults, some factors associated with an increased risk of relapse include age over 35 years, an elevated white blood cell count (> 30 × 10^3/μL in B precursor leukemia and > 100 × 10^3/μL in T precursor leukemia), as well as extramedullary invasion, which most often affects the central nervous system, the skin, and gonads[4]. Together with clinical and laboratory data, molecular alterations are essential for correct classification.

The measurement of minimal residual disease (MRD) at diagnosis is the main dynamic factor in predicting relapses in acute lymphoblastic leukemia (ALL). Thanks to technologies such as next-generation sequencing and next-generation flow cytometry, it is now possible to detect extremely low leukemic loads, allowing for more precise risk stratification and avoiding intensive treatments in patients with better prognosis[5].

Both risk stratification and MRD measurement allow for a more accurate assessment of the prognosis of patients with ALL. The integration of these factors makes it possible, as far as possible, to individualize the treatment. In cases with specific genetic alterations, such as the presence of the Philadelphia chromosome (breakpoint cluster region [BCR]: Abelson murine leukemia [ABL1]), the addition of tyrosine kinase inhibitors (TKI) to the conventional chemotherapy regimen improves the proportion of overall responses as well as long-term survival[6,7].

The selection of treatment depends largely on age (especially for patients considered adolescents and young adults), the presence of specific mutations such as the Philadelphia chromosome, and the expression of surface markers such as CD20 that allow the use of monoclonal antibodies such as rituximab or ofatumumab[8]. Adolescents and young adults (15-39 years) benefit from the use of therapeutic regimens inspired by pediatric protocols, characterized by increased exposure to asparaginase, intensive steroid use, and shorter, more intensive cycles. In contrast, treatment in older adults is adjusted according to functional status and the presence of comorbidities, prioritizing tolerance and adherence[9].

Older adults continue to be a population of complex management, in which treatment is individualized according to their functionality, comorbidities, tolerance

***Correspondence:**
Christian Ramos-Peñafiel
E-mail: leukemiachop33@gmail.com

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to therapeutic schemes, and, in some cases, the presence of relevant genetic alterations. Among them, the Philadelphia chromosome (BCR: ABL1) stands out, whose expression is more frequent in this age group and conditions the use of TKI as part of treatment[10]. The addition of TKIs radically transformed the prognosis of chronic myeloid leukemia. In Philadelphia chromosome ALL, its combination with chemotherapy has significantly improved complete remission rates and raised 5-year survival to more than 50%[11].

The response to treatment in Philadelphia-positive (Ph+-ALL) depends largely on the potency of the TKI used, with dasatinib and ponatinib being the options that have shown the best results. Its incorporation into chemotherapy regimens or even into chemotherapy-free regimens combined with blinatumomab has significantly increased complete molecular remission rates, improved long-term survival, and, in many cases, reduced the need for hematopoietic progenitor cell transplantation[12].

The efficacy of these treatments has rewritten the prognosis of patients with Ph+-ALL, allowing not only to improve remission and survival rates but also to question the need for allogeneic transplantation in all cases. The emergence of even more potent combinations, such as ponatinib and blinatumomab, has made it possible to achieve sustained deep molecular remissions, allowing the development of chemotherapy-free regimens that achieve similar responses in the pediatric population[13,14].

Beyond chemotherapy, immunotherapy has established itself as a key tool in the treatment of ALL. Blinatumomab is a bi-specific antibody Bi-specific T-cell engager that directs cytotoxic T cells against CD19+ B cells, promoting their targeted destruction. In clinical trials in patients with relapsed or refractory B-cell ALL (R/R B-ALL), blinatumomab as monotherapy has demonstrated superior clinical and molecular remission rates to salvage chemotherapy[15]. In a meta-analysis, an analysis of 18 studies with 1,373 patients showed a complete remission rate of 54% and a molecular response of 43%, with better results in patients with < 50% blasts in the bone marrow. The median overall survival was 8.16 months, and the median relapse-free survival was 6.02 months. Although the incidence of serious adverse events was high (80%), neurological toxicities and grade ≥ 3 cytokine release syndrome were relatively low (7% and 3%, respectively)[16].

In conjunction with bi-specific drugs and immunoconjugates, this is an antibody directed against the CD22 receptor bound to a cytotoxic toxin derived from calicheamicin[17]. Its indication now is in refractory or relapsed patients. The phase 3 INO-VATE study demonstrated significantly higher rates of remission and greater access to hematopoietic transplantation, although with an increased risk of hepatic venoocclusive disease[18]. The future of treatment includes the use of chimeric antigen receptor (CAR-T) cells, and these cells are genetically modified to recognize and destroy cancer cells that express a specific antigen, such as CD19 in B-cell ALL, the most recognized CAR-T cell therapies include tisagenlecleucel, approved for pediatric and young adult patients, and brexucabtagene autoleucel, approved for adults, both directed against the CD19 antigen[19].

When comparing anti-CD19 CAR-T cell therapy and blinatumomab in patients with relapsed or refractory ALL, CAR-T therapy achieved higher rates of complete remission, overall survival, and relapse-free, although with greater toxicity; on the other hand, blinatumomab showed a more favorable safety profile and utility as a bridge treatment before allogeneic transplantation. Both strategies share specific adverse events such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, the severity of which depends largely on the selection of the CAR-T type[20]. Now, the main indication for bi-specific drugs, immunoconjugates, and CAR-T cells are relapsed or refractory patients, but more and more patients are benefiting in earlier lines and even as a bypass before transplantation of hematopoietic progenitors or CAR-T cells. Figure 1 presents the main therapeutic strategies in the treatment of adult ALL.

Recently, blinatumomab has been approved as part of the consolidation schedule, even with measurable negative residual disease[21]. Unfortunately, in our region, the implementation of strategies based on redirecting the immune system remains limited due to restricted access and high costs, which forces the use of highly toxic chemotherapy schemes or the use of other agents, such as proteasome inhibitors[22]. In this context, our group has evaluated the incorporation of bortezomib, a first-generation proteasome inhibitor, in different lines of treatment with the aim of improving the efficacy of chemotherapy. Figure 2 describes the major events that have impacted the prognosis of adult ALL.

Finally, despite global advances in the treatment of ALL, Latin American countries face serious limitations that negatively affect clinical outcomes, especially in pediatric and adult populations. The main barriers include limited access to diagnostic tests, innovative therapies, and immunotherapies, high dropout rates,

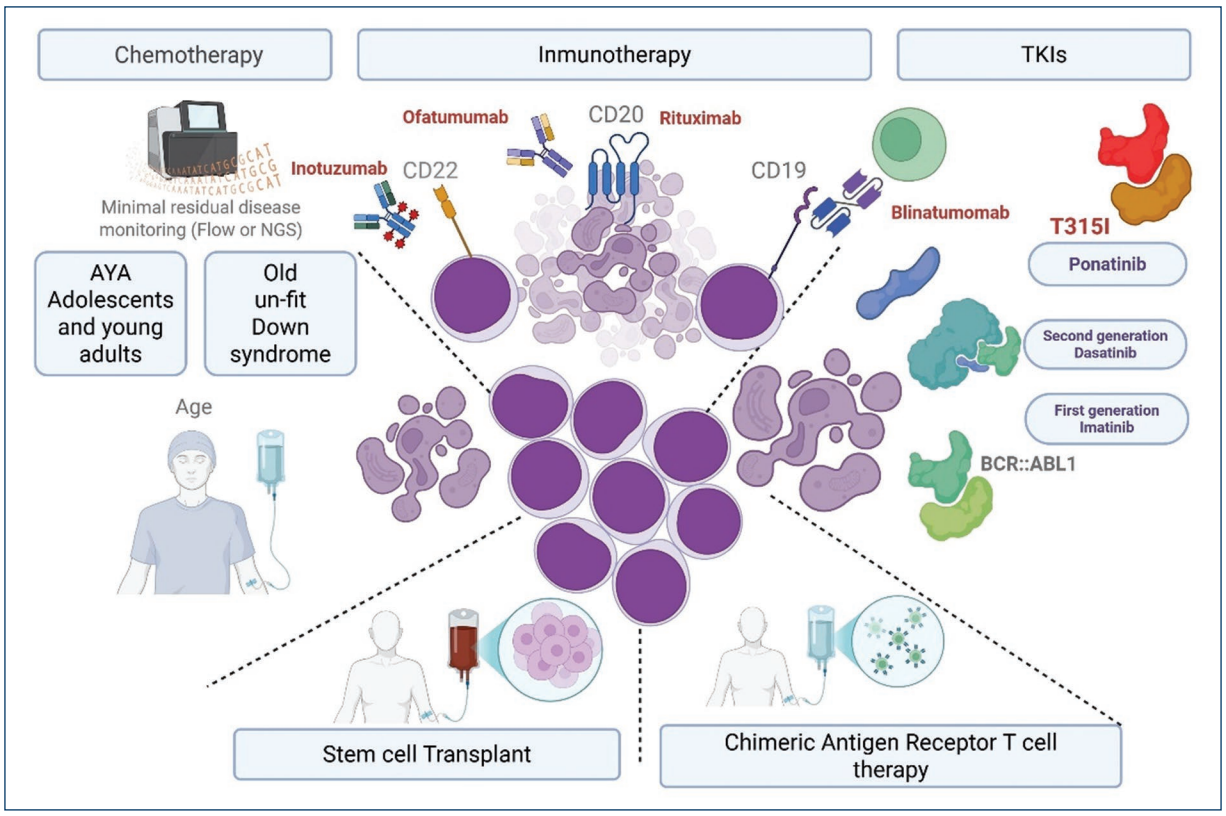

Figure 1. Therapeutic combinations in adult patients with acute lymphoblastic leukemia (chemotherapy, immunotherapy, molecular targets, progenitor cell transplantation and CAR-T).

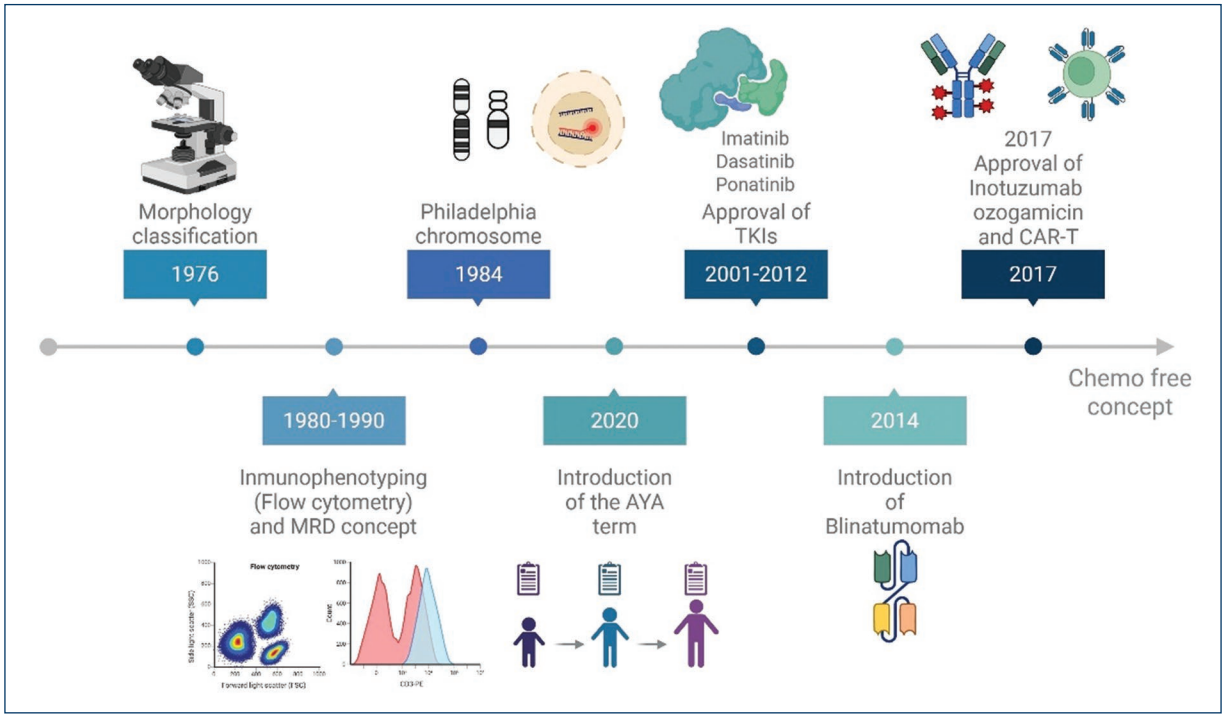

Figure 2. Historical aspects in the treatment of adult acute lymphoblastic leukemia.

treatment-related toxicity, and deficiencies in clinical support strategies[23]. In developing countries, adapting treatments to available resources and working collaboratively has helped improve both survival and quality of life for patients with acute lymphoblastic leukemia.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript.

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ORIGINAL ARTICLE

The efficacy of bortezomib during induction therapy in patients with high-risk acute lymphoblastic leukemia

Camila Terreros-Palacios[1], Daniela Pérez-Sámano[1], Adán G. Gallardo-Rodríguez[2,3], Irma Olarte-Carrillo[4], Carlos Martínez-Murillo[1], Gilberto Barranco-Lampón[1], and Christian O. Ramos Peñafiel[1,5]*

[1]Department of Hematology; [2]Department of Hematology Research. Hospital General de México Dr. Eduardo Liceaga, Secretaría de Salud; [3]Medicine Research Doctoral Program, Medical School, Instituto Politécnico Nacional; [4]Hematology Laboratory, Hospital General de México Dr. Eduardo Liceaga, Secretaría de Salud. Mexico City; [5]Department of Hematology, Hospital Regional de Alta Especialidad de Ixtapaluca, Secretaría de Salud, Ixtapaluca, State of Mexico. Mexico

Abstract

Introduction: *Acute lymphoblastic leukemia (ALL) is characterized by the uncontrolled proliferation of lymphoid precursor cells, most from the B phenotype, which is the result of various cytogenetic mutations and alterations involved in cell division and survival.* **Objective:** *To evaluate the efficacy of bortezomib in patients with ALL through the measurable residual disease (MRD) outcome at 6 weeks (day +45) and response to induction therapy with chemotherapy in combination with a first-generation proteasome inhibitor.* **Material and methods:** *This was cross-sectional, observational, retrospective, and analytical study based on clinical records of patients diagnosed with ALL who received induction therapy plus bortezomib, from January 1, 2019, to May 31, 2024, and comparing it to a historic group.* **Results:** *Twenty patients were included, 60% (n = 12) of whom were male, with an average age of 26 years (range 18-61 years). All cases corresponded to the B phenotype, 85% were negative for BCR: ABL1, without central nervous system infiltration (CNS). After treatment initiation, the most common adverse event was anemia and thrombocytopenia (GIII-GIV) and 30% experienced grade I-II peripheral neuropathy. When compared to the historical record, the odds ratio (OR) to evaluate the treatment response with early response variables, there was no difference (confidence interval [CI] = 0.173-1.630, p = 0.206). In overall survival, there were no statistically significant differences when compared with the historical cohort, OR of 1.538 (CI = 0.502-4.748, p = 0.319).* **Conclusion:** *The addition of bortezomib to the induction chemotherapy did not show a benefit in the percentage of remissions or the proportion of MRD. It is important to continue exploring new options that can be added to this high-risk group of patients to reduce refractoriness and the proportion of early relapses.*

Keywords: *Acute lymphoblastic leukemia. Bortezomib. Measurable residual disease. Complete remission. Overall survival.*

Introduction

Acute lymphoblastic leukemia (ALL) is characterized by the uncontrolled proliferation of lymphoid precursor cells, most from the B phenotype, which is the result of various cytogenetic mutations and alterations involved in cell division and survival[1,2]. The treatment is based on the combination of different types of chemotherapy, with the main combination during induction being vinca alkaloids, anthracyclines, asparaginase, and steroids[3]. Generally speaking, treatment schemes are divided into adequate for adults or focused on a pediatric protocol, which uses a higher dose of chemotherapy with cycles of asparaginase[4,5]. Notably, the Hispanic population is afflicted with in a higher rate and also with a higher proportion of mutations considered of poor prognosis, such as those known as Philadelphia, along with the development at an adverse social setting[6,7]. When comparing the results with the world,

***Correspondence:**
Camila Terreros-Palacios
E-mail: cami.terreros@gmail.com

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the rate of responses in our region is lower, due to a high rate of mortality during the induction period, as well as limited access to strategies such as the bi-specific, hematopoietic progenitors transplant, and immunotoxins (Blinatumomab and inotuzumab)[8,9].

The options for treatment failure are also limited since the rescue is still based on high doses of chemotherapy (FLAG and FLAG-IDA)[10,11]. Due to this, ERM is the main prognosis factor, not only to prevent relapse but also to modify the intensity of the treatment through innovative options such as blinatumomab, inotuzumab, or the therapy based on CAR-T[12,13]. Along with somatic mutations, the limited access to methods to determine the standardized EMR, the Hispanic population also suffers a limited access to treatment therapies, which causes an excess in mortality (25-35% in the pediatric population), as well as a non-negligible quantity of treatment desertion[14]. This has required a selection of accessible and affordable strategies that can be combined with different chemotherapy schemes. Other than chemotherapy, very few drugs are considered adequate to be combined with the treatment of ALL. Bortezomib is a first-generation proteasome inhibitor widely used in the treatment of blood dyscrasias, such as multiple myeloma, or mantle cell lymphoma[15,16]. Nevertheless, in ALL cell lines (MOLT-4), a synergic effect has been proven to stop the cell cycle and maintain the cells in G1, inducing their apoptosis[17]. Bortezomib has been combined with different drugs used during the induction (vincristine, prednisone, pegylated asparaginase, and doxorubicin), which improves the results in specific subgroups such as T-ALL; however, the experience in adult ALL schemes is still limited[18,19].

The response rate (CR) in patients considered to be high risk (age, hyperleukocytosis, cytogenetic abnormalities, or mutations) is limited. Due to this, the effect of the inclusion of the first-generation proteasome inhibitor bortezomib in the chemotherapy scheme was analyzed on the rate of CR as well as the negativity of the measurable residual disease (MRD).

Materials and methods

A retrospective, observational, and analytical study was carried out on clinical records of patients exposed to bortezomib during the induction therapy treated at the Hospital General de México "Dr. Eduardo Liceaga," who have been diagnosed with high-risk ALL from January 1, 2018, to May 31, 2024, and who met the following inclusion criteria: (1) both genders, (2) > 18 years of age, (3) underwent systemic chemotherapy treatment with bortezomib, and (4) MRD results through multiparametric flow cytometry at the end of induction. Patients with BCR: ABL1 were included. Exclusion criteria were as follows: (1) ECOG > 2, (2) diagnosis of phenotypic or bilinear leukemia, (4) palliative scheme or transfusion support, and (5) severe comorbidities that could jeopardize the therapy.

Chemotherapy treatment

The most used chemotherapy scheme was CALGB modified to include vincristine (1.2 mg/m^2 per body surface area) on days 1, 8, 15, and 22 of the treatment; daunorubicin was administered in 25 mg/m^2 per body surface area on days 1, 8, 15, and 22. The pegylated asparaginase was substituted by synthesized asparaginase of E. coli at a dose of 5000 UI/m^2 per body surface area in 6 doses starting at day +5 of the chemotherapy. Prednisone was administered at 100 mg/day as a fixed dose. Intracranial chemotherapy was included following CALGB10403[20]. In older individuals, the most used scheme was the hyper-CVAD scheme[21].

The administration of bortezomib was subcutaneous at 1.3 mg/m^2 per body surface area on days 1, 4, 8, and 11; when it coincided with the administration of vincristine, the administration of bortezomib was carried out to the next day.

The toxicity of the scheme was evaluated following NCI common toxicity criteria for adverse events version 4.016; grade 4 cases were considered as having severe toxicity. In case of severe toxicity (grade 3 or grade 4) associated with bortezomib, the administration was halted for the following cycles.

Procedure

Once the patients met the inclusion criteria, they were followed post-induction chemotherapy. The follow-up took place during the outpatient visit, where their clinical and biochemical indicators, as well as prognosis factors. The final MRD was carried out with samples obtained from the bone marrow, extracting 5 mL of blood from the bone marrow, subsequently placing them in EDTA tubes, and analyzed through flow cytometry, which used the markers for detection of lymphoid blast on the expression of CD19, CD10, and CD34+.

Statistical analysis

The sample size was estimated using a Goodness-of-Fit formula, based on the expected effect size

compared to the effect size reported in other similar studies. The sample size calculation was performed using the G-Power 3.1.9.2 tool. From the calculated effect size of 0.8, a sample size of 21 patient records was obtained for the study.

To describe the demographic variables, the Shapiro-Wilk test was used to estimate the normality of distribution in the numeric variables. To determine the relationship between the main variables and the main outcomes (time until the next treatment and overall survival), we calculated the odds ratio. In addition, we used Kaplan-Meier estimates to analyze the time until the next treatment and overall survival. Regardless of the median value, differences between groups were analyzed with a Log-Rank test, and the data were presented in median values. We established $p < 0.05$ as a statistical difference. We conducted all statistical analyses using the SPSS version 27 (SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp) software and generated figures using GraphPad Prisma version 7.

Ethical consideration

For this study, we used clinical records only. Therefore, informed consent was not necessary. The researchers involved in the study confirm that all ethical aspects of privacy and confidentiality have been met while dealing with retrospective information. This retrospective cohort study was carried out following the Helsinki Declaration and approved by the Biosecurity, Ethics, and Research Committee of Hospital General de México "Dr. Eduardo Liceaga," under the protocol number (DECS/UPO-CT-2296-2024).

Results

A total of 20 patients diagnosed with high-risk ALL were studied during induction therapy at the Hematology Department of the Hospital General de Mexico "Dr. Eduardo Liceaga." Most patients were male (n = 12), with an average age of 26 years (Range 18-61 years). Morphological analysis according to FAB classification showed all cases (n = 20) were classified as L2 subtype, with an average blast count of 82% on microscopic examination at diagnosis. Flow cytometry analysis according to EGIL classification categorized them as BI immunophenotype 10% (n = 2), BII 85% (n = 17), and BIII 5% (n = 1). Regarding the Philadelphia chromosome, 15% (n = 3) tested positive, 5% (n = 1) were undeterminable, and 85% (n = 17) tested negative. Patients with positive results received first-generation tyrosine kinase inhibitors (imatinib) added during the induction therapy. Cytogenetic testing was requested for all patients; however, 60% (n = 12) had undeterminable samples, 20% (n = 4) had a normal karyotype, 15% (n = 3) had complex karyotypes, and 5% (n = 1) had hypodiploidy. No patients presented central nervous system infiltration at diagnosis. The leukocyte counts at diagnosis classified 20% of patients as high risk ($> 30 \times 10^3/\mu L$).

Comorbidities at the time of diagnosis included three patients with systemic arterial hypertension (15%), one with hypothyroidism (5%), one with type 1 diabetes mellitus (5%), and one patient with absence seizures (5%). Most patients had a normal BMI, with 15% classified as overweight or grade I obesity. The most used chemotherapy scheme for induction was CALGB10403 in 70% (n = 14) of cases, 15% (n = 3) received the hyper-CVAD scheme, and the remaining 15% (n = 3) received an induction based on weekly administration of doxorubicin, vincristine, and 28 days of prednisone. One patient receiving CALGB10403 had rituximab added to their scheme due to CD20 positivity.

Adverse effects and complications

During induction therapy, grade IV myelotoxicity was found, characterized by anemia, thrombocytopenia, and neutropenia. Peripheral neuropathy was one of the most frequent adverse events with bortezomib, observed in 30% (6) of patients, classified as grade I-II. Gastrointestinal manifestations occurred in 15% (3) of patients, with diarrhea being the most frequent symptom at grade I. Liver enzyme elevation was observed in 10% (2) of the cases, with one case categorized as grade IV acute liver failure following chemotherapy. Finally, 5% (1) presented asymptomatic hypofibrinogenemia.

During hospitalization, 25% (5) of patients developed febrile neutropenia, 15% (3) were diagnosed with nosocomial pneumonia, 10% (2) had influenza pneumonia confirmed by RT-PCR testing, and 15% (3) showed evidence of bacteremia with isolation of *Staphylococcus aureus*, *Escherichia coli*, and *Acinetobacter baumannii* in blood cultures. Chronic cavitary aspergillosis was diagnosed, confirmed by positive galactomannan in bronchoalveolar lavage in 10% (2) of patients. Two patients died during induction therapy due to septic shock complicating bacteremia caused by acinetobacter baumannii and influenza pneumonia.

Comparison of outcomes between the bortezomib group and the historic group

Clinical outcomes of patients treated with bortezomib (n = 20) were compared with those of a historic group of patients with ALL treated at the same center between 2022 and 2024 (n = 33) who did not receive bortezomib during induction therapy to achieve remission.

The response proportions to induction showed no significant difference between both cohorts (p = 0.137). In the cohort that received bortezomib, 55% of the population (n = 11) had an early complete response compared to 73.5% (25%) of the population that did not receive bortezomib. Regarding the MRD results, the test could not be performed in all patients in the cohort, however, in the group that received bortezomib, only two (12.5%) of 16 patients showed a negative MRD post-induction, in comparison with the group that did not receive bortezomib, where 12 (70.5%) of 17 patients were reported. The proportion comparison analysis could not be performed because the rule of a minimum of five patients per study variable was not met.

OR was used to assess the treatment response between the two groups, with bone marrow aspirate as the response variable, yielding an OR of 0.532 (confidence interval [CI] = 0.173-1.630, p = 0.206), indicating no statistically significant difference. Regarding MRD results, the test could not be performed in all patients in the historic group; however, in the bortezomib group, only 2 (11.1%) out of 18 patients achieved negative MRD post-induction. A comparison of proportions analysis could not be conducted due to not meeting the minimum rule of five patients per study variable. When comparing overall survival between the two groups, there were no statistically significant differences, with an odds ratio (OR) of 1.538 (CI = 0.502-4.748, p = 0.319).

The median survival for the bortezomib group was 96 days (range 26-373 days), compared to the group that did not receive bortezomib which was 91.50 (range 25-327), this difference did not show statistical significance (0.778). On the other hand, the Kaplan-Meier survival curve was estimated for both groups, and a log-rank (0.104) was obtained from the Mantel-Cox test. The curve is shown in figure 1.

Early treatment response

Two clinical parameters were used to assess early treatment response: the first was established through response to pre-induction steroids, where 50% (10) of patients presented a response with lymphocyte count on complete blood count of less than $1 \times 10^3/\mu L$, while the remaining 50% (10) did not show this response. Another measure was through MRD on day +8 of the induction therapy with bortezomib; 25% (n = 5) had less than 5% blasts, whereas 45% (n = 9) had more than 5% blasts, and the remaining had hemodiluted BMA without blast evidence. The relapse proportions in this population were 70% (n = 14).

The early treatment response was contrasted with the overall survival and induction response between the bortezomib and non-bortezomib groups. The response to corticosteroids yielded an OR of 1.063 (95% CI = 0.350-3.227, p = 0.570), which did not reach statistical significance. Regarding MRD on day +8, the outcome OR was 1.299 (95% CI = 0.426-3.958, p = 0.430), considered not statistically significant. Figure 2 displays a Forest plot illustrating the effect of bortezomib on clinical outcomes.

Discussion

Throughout the years, attempts toward improving the induction treatment have been made, focusing on adding drugs when a therapeutic target exists, such as the expression of CD20 in lymphoblasts, or the positivity for BCR: ABL1. The best example is the hyper-CVAD scheme which has forgone multiple modifications since its creation[22,23]. Similar to this scheme, CALGB10403 has also been modified, especially in our country, due to the lack of pegylated asparaginase, and because it is substituted with an asparaginase derived from *Escherichia coli*. Despite these modifications, the rate of complete remissions at 4 weeks remains above 80%, which makes it a plausible option in countries with limited resources[9].

The main objective of this study was to evaluate the effect of the proteasome inhibitor addition on the rate of complete remissions, and the negativity of MRD at 6 weeks of treatment in patients considered to be high risk. This population was of interest to us since, in the Hispanic population, most of the patients are considered to have a high risk of relapse diagnosis, as well as a lower rate of complete remissions[24]. In line with the literature, the patients considered high-risk present a complete remission rate slightly lower than those of standard risk (90% vs. 97%, with a survivability rate at 5 years of 29%)[9]. Similar to this, in the CALGB10403 protocol, individual factors like the leukocyte count ($> 30 \times 10^3$/mcl) had an impact on the survivability (HR = 1.85, 1.14-3.01, 95% CI), but other variables, like being of Hispanic origin, did not present a substantial effect[20].

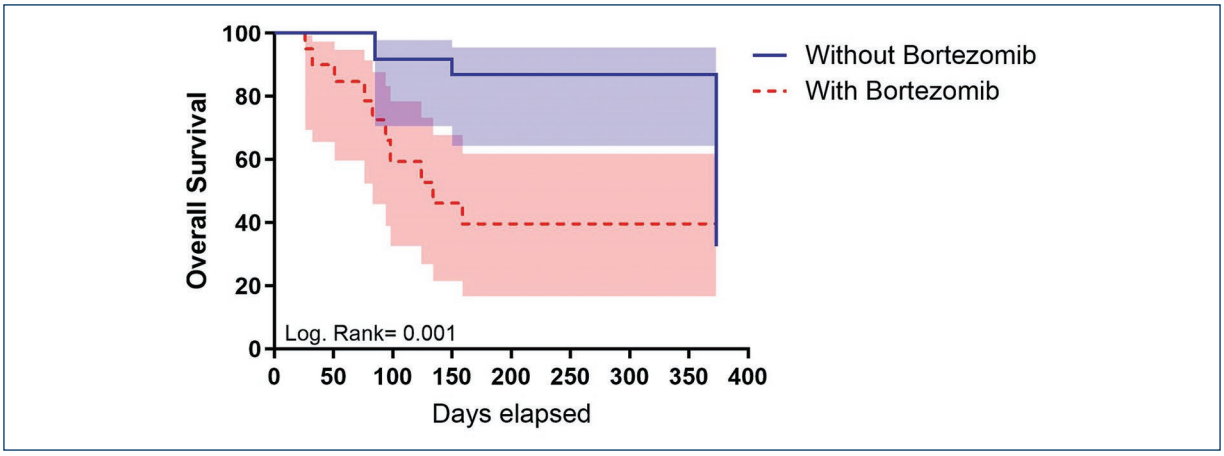

Figure 1. Kaplan-Meier plot comparing the study group (with Bortezomib) and the historical cohort (without Bortezomib).

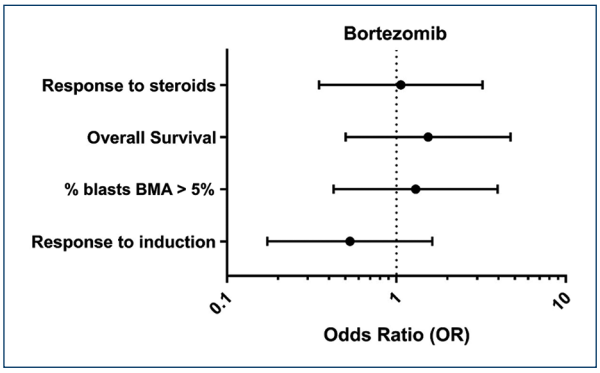

Figure 2. Forest plot on the effect between the main clinical outcomes and the early response.

In this study, we compared treatment response and overall survival between patients treated with bortezomib during induction therapy and a historic group without bortezomib. There was no statistically significant difference in terms of MRD and response at 4 weeks. In Jain et al.'s study, which included CD20+ Ph-negative B-ALL patients, ages up to 20 years, they received a modified BFM-90 scheme with rituximab and bortezomib, achieving a negative MRD in 70.9%, contrasting with our study where only 11.1% had a negative MRD[22]. In Jonas et al phase I study, evaluating newly diagnosed Ph-negative B-ALL patients aged 18-64 years, they used hyper-CVAD plus carfilzomib as induction, achieving a 90% CR rate post-first cycle using MRD assessment[24]. Notably, the addition of anti-CD20 monoclonal antibodies in previous studies suggests that better treatment response rates may be attributed to synergy with this medication.

One factor potentially influencing our results is the age of the sample; in scientific evidence, the population studied comprises children and adolescents due to pharmacokinetic considerations, with rapid proteasome 20S activity inhibition observed immediately after drug administration in adults, contrasting with higher plasma concentrations in the second week in pediatric populations[16]. Another crucial consideration is the ethnicity of patients; studies by Jonas and Iguchi conducted predominantly in Caucasian and Asian populations, respectively, demonstrated treatment responses to Bortezomib[25,26]. Most chemotherapy schemes are developed in the United States and Europe, underscoring the importance of adapting them to the predominantly Hispanic population of Mexico. Basqueira et al. reported complete responses ranging from 64.2% to 79.5% depending on the scheme used, in contrast with other Latin American countries where responses were mostly above 85%. The study reported a 17% non-adherence rate among adult ALL patients, with electronic health records cited as contributing factors[9].

Early response evaluation through pre-induction steroids and day +8 MRD was compared between the bortezomib and non-bortezomib groups, showing no substantial evidence. Literature variations include blood peripheral MRD assessment at day +8, showing a similar 50% response. In Ramos et al.'s study, factors associated with induction therapy response were evaluated, showing associations with steroid response and day +8 response ($p = 0.0045$ and 0.0023)[27].

Adverse effects and complications secondary to chemotherapy were consistent with historical records and Iguchi et al study, where no severe adverse effects

necessitating treatment discontinuation were observed[25]. Ramos et al. did not report neurotoxicity events, contrasting with our study where six cases of grade I-II peripheral neuropathy were managed with gabapentinoids, associated with patient age[28].

In our study, two patients died during induction therapy due to infectious processes compared to August et al.'s study, where three patients died due to chemotherapy toxicity[29]. In the TACL phase II study, three out of 22 patients died due to bacterial sepsis[30]. This emphasizes that the implementation of health programs for timely antibiotic therapy initiation is crucial.

It can be considered that despite *in vitro* synergistic activity, assessing the efficacy of proteasome inhibitors *in vivo* remains challenging as most schemes involve more than two drugs. Evaluating efficacy in relapse and MRD appears to be more beneficial, whereas our study did not demonstrate improvement in increasing remission rates or cases with negative MRD, maintaining the risk of infectious processes or neurological adverse events. Despite all patients receiving antifungal and antiviral prophylaxis, viral reactivation risk and potential vincristine-associated neurological events remain latent. Ultimately, it is proposed that first-generation proteasome inhibitors do not show clear utility when added to first-line schemes, but may be beneficial in achieving negative MRD.

Conclusion

Treating adult ALL remains challenging due to lower response rates compared to pediatric populations. The Latin American population, in particular, exhibits high biological risk factors such as Ph-like abnormalities, and a higher proportion of factors predisposing to relapse or treatment failure. Our objective was to identify whether adding bortezomib to the treatment scheme could improve response rates. Contrary to expectations, the addition of bortezomib did not affect responses, leading us to consider it not useful for induction therapy in ALL. Improvements are still needed in referral systems and the availability of more effective drugs such as bi-specific therapy or immunotoxins. Finally, we propose that bortezomib could potentially be used in other stages of the treatment, such as positive MRD, T-cell precursor leukemias, or through new clinical trials.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Escherichia coli producing extended-spectrum β-lactamases in a hospital in Mayabeque, 2022-2023

Luis M. Abreu-Pereira[1], Ilian E. Tarife-Romero[1], Adriel Herrero-Díaz[2], Maricela Iglesia-Camejo[1], and Leyanis González-Baigorría[1]*

[1]Faculty of Medical Sciences Mayabeque, Mayabeque; [2]Faculty of Medical Sciences Sagua la Grande, Universidad de Ciencias Médicas, Villa Clara. Cuba

Abstract

Introduction: *The indiscriminate use of antibiotics brings with it an increase in antimicrobial resistance, especially in Gram-negative microorganisms and fundamentally in Escherichia coli, which uses the production of β-lactamases as the main mechanism of multidrug resistance.* **Objective:** *The objective of the study is to characterize the behavior of E. coli strains producing extended-spectrum β-lactamases processed in the Microbiology Laboratory of the Aleida Fernández Chardiet Hospital from January 2022 to June 2023.* **Material and methods:** *An observational, descriptive, cross-sectional study was carried out in the Microbiology Laboratory of the Aleida Fernández Chardiet Hospital between January 2022 and June 2023. The population was made up of 30 isolates of E. coli that produce extended-spectrum β-lactamases. The variables were antimicrobial resistance profile, number of samples processed, service of origin of the samples, and type of samples processed. A database was generated in Microsoft Excel 2016 for data analysis using descriptive statistics.* **Results:** *Only 30 samples (9.3%) were E. coli producers of extended-spectrum β-lactamases, 70% (21 strains) coming from outpatients, and 80% from urine samples. Amikacin was effective in 23 isolates, unlike cefepime, which showed resistance in 25.* **Conclusion:** *The frequency of isolation of E. coli producing extended-spectrum β-lactamases was low, and the highest source of positivity was obtained in urine samples and from outpatients. The most effective antimicrobials turned out to be amikacin and cefoxitin.*

Keywords: *β-lactamases. Drug resistance. Microbial. Enterobacteria. Escherichia coli.*

Introduction

At the beginning of the 20th century, the development of the antibiotic era began, it is characterized by molecules that attack bacteria, from this idea, Paul Ehrlich conceived the magic bullet project, which consists of attacking the germ and not human cells. However, it was not until 1928, when Alexander Fleming, through a stroke of luck, discovered an antibiotic that saved the lives of millions of people around the world: penicillin, for these reasons, Fleming was the initiator of the antibiotic era, characterized by the emergence of new antimicrobials with broad-action spectrums for a number of bacteria[1].

A few years later, the first bacterial strains resistant to penicillin and other antibiotics began to emerge. The ability of microorganisms to resist antibiotics and

***Correspondence:**
Luis M. Abreu-Pereira
E-mail: luismanuela99@gmail.com

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therapy is one of the phenomena that attracts the attention of modern science and the World Health Organization (WHO). Scientists such as Vega, who belongs to the field of Microbiology, state that antibiotics begin to lose their activity against bacteria as they are addressed on a massive scale[2]. This use is given by the inappropriate use of antibiotics that bring disadvantages numerous problems and damages, among them, the increase of resistant strains around the world with more than alarming figures; for these reasons, the WHO recommends the monitoring of multidrug-resistant microorganisms, among which *Escherichia coli*, due to the production of extended-spectrum β-lactamases (ESBLs), characterized as their most notable resistance mechanism[3-5].

Bacterial strains that present ESBL enzymes are capable of hydrolyzing the β-lactam ring present in drugs such as penicillin, cephalosporin, and monobactam. These bacteria are pathogens of great importance, both in community-acquired infections and in nosocomial infections, where it is confirmed that 35.3% of bacteremias are caused by an ESBL strain[6].

Research on the spread of ESBLs began in the early 1990s, in the *Enterobacteriaceae* family and more in *E. coli*. According to Carcausto-Huamani[3] more recent studies carried out at the "Cayetano Herenia" Hospital in Peru, a prevalence of *ESBL E. coli* is identified as 28.6%, while 10 years ago, the prevalence is < 5% in the community.

The study for monitoring antimicrobial resistance trends[7] carried out in Spain reveals an increase in the frequency of *E. coli* ESBL, of community origin, in the period from 2002 to 2015, a similar situation in the United States, in its hospitals in the southeast where this type of microorganism is most frequently isolated. In Cuba, despite the low rate of studies on the subject, it is known that between 2014 and 2017, the prevalence of ESBLs-producing *Enterobacteriaceae* varies between 32 and 57%, according to different studies[7].

In the Microbiology Laboratory, of the Aleida Fernández Chardiet Teaching-Clinical-Surgical Hospital, there are isolates of *E. coli* ESBL in the processed samples, great difficulties are generated in the establishment of antimicrobial treatments, due to these reasons and the scarcity of studies on the subject in Cuba, the following research aims to characterize the behavior of the strains of *E. coli*, producers of extended-spectrum β-lactamases processed in the Microbiology Laboratory of the Aleida Fernández Chardiet Teaching-Clinical-Surgical Hospital in the period from January 2022 to June 2023.

Material and methods

An observational, descriptive, cross-sectional study was carried out in the Microbiology Laboratory of the Aleida Fernández Chardiet Teaching-Clinical-Surgical Hospital, between January 2022 and June 2023. The study population consisted of 488 *E. coli*-positive isolates from different cultures and hospital services. The sample consisted of the 30 *E. coli* ESBL strains isolated.

The scarcity of positive cases for this bacterium is due to limitations inherent in the laboratory where the study was conducted. Its infrastructure is insufficient to process a large volume of samples and apply advanced microbiological techniques. Added to this is the reduced hospitalization capacity of the center and the presence of other microbiology laboratories in the municipality, which process most of the samples in the community. These factors contribute to the low number of cases detected annually.

Inclusion criteria: records of ESBL *E. coli* isolation that presented resistance to at least one of the antibiotics tested in the antimicrobial susceptibility test.

Exclusion criteria

Records of isolates that did not have complete information, those that yielded positive isolates for a bacterial etiology other than *E. coli*, and contaminated samples.

The antibiotic susceptibility test was shown with the samples that were analyzed and processed by the technical staff of the hospital's Microbiology Laboratory, and the disk diffusion method described by Kirby Bauer was applied. The guidelines established by the Clinical and Laboratory Standards Institute (CLSI)[8], 2020 were used.

The following antibiotics were tested: Cefoxitin 30 μg, Aztreonam 30 μg, Ampicillin-Sulbactam 10/20 μg, Cefotaxime 30 μg, Cefepime 30 μg, Amoxicillin-Clavulanic Acid 30/10 μg, Nalidixic Acid 30 μg, Sulfaprin 50 μg, Meropenem 10 μg, Ampicillin 10 μg, Ceftazidime 10 μg, Ceftriaxone 30 μg, Cefuroxime 30 μg, and Cefazolin 30 μg. Non-β-lactam antibiotics were tested including Amikacin 30 μg, Levofloxacin 5 μg, Gentamicin 10 μg, Ciprofloxacin 5 μg, and Chloramphenicol 30 μg. All of them are from the commercial house, Liofilchem, in Italy. It was not possible to know the sensitivity to other antimicrobials because they did not exist in the laboratory where the study was carried out.

While antimicrobial susceptibility was assessed using the test described, limitations in laboratory infrastructure prevented the accurate determination of minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (BCs) for each antimicrobial. Therefore, the presentation of susceptibility data is limited to qualitative interpretation; in addition, intermediate sensitivity was not taken into account, nor were the same antibiotics applied in all strains due to input deficit. The lack of quantitative data (CIM/CIB) prevents the graphical representation of the concentration-response curves.

For the phenotypic detection of ESBL, it was performed in all isolates that showed resistance to at least one of the first cephalosporins (Cefazoline 30 μg, second Cefuroxime 30 μg, third Cefotaxime 30 μg/Ceftazidime 10 μg, Ceftriaxone 30 μg, Cefoxitin 30 μg, and fourth-generation Cefepime 30 μg and with the monobactam Aztreonam 30 μg, the disc test combined with inhibitor was used: Cefotaxime 30 μg - Clavulanic acid 10 μg) in accordance with the recommendations of CLSI[8], 2020. It was incubated at 37 °C for 24 h to take the reading. Improvement in cephalosporin inhibition halo when using the disc with an inhibitor indicated ESBL production. The diameters of the zones of complete inhibition were measured in millimeters with a caliper.

The variables analyzed were resistance profile and susceptibility of antimicrobials (amikacin, cefoxitin, aztreonam, ampicillin-sulbactam, cefotaxime, cefepime, chloramphenicol, ciprofloxacin, amoxicillin-clavulanic acid, gentamicin, nalidixic acid, sulfaprim, meropenem, ampicillin, ceftazidime, ceftriaxone, cefuroxime, cefazolin, levofloxacin), number of samples processed for *E. coli* ESBL (positive and negative), Service of origin of the samples: Outpatient, Nephrology, Orthopedics, Surgery, Intensive Care and Emergency Unit and Internal Medicine, type of samples processed: urine, blood, catheter tip, secretion and surgical wound. All study variables were qualitative.

A database was generated in Microsoft Excel 2016, for the statistical analysis of the data, to which the absolute and relative frequency was determined. In addition, the percentage difference was established for the resistance variable.

The percentage difference was calculated as the difference between the value of the last year and the first, divided by the value of the 1st year and multiplied by one hundred.

Table 1. Susceptibility and resistance profile in *Escherichia coli* ESBL isolates to tested antibiotics

Antibiotics	Sensible		Resistant	
	No.	%	No.	%
Amikacin	23	76,7	6	20
Ampicillin	0	0	4	13,3
Ampicillin-Sulbactam	10	33,3	3	10
Aztreonam	9	3	20	66,7
Amoxicillin-Clavulanic acid	2	6,7	15	50
Cloranfenicol	3	10	0	0
Ceftazidime	0	0	18	60
Ciprofloxacin	3	10	14	46,7
Gentamicin	2	6,7	10	33,3
Ceftriaxone	0	0	23	76,7
Cefotaxime	5	16,7	19	63,3
Cefuroxime	0	0	13	43,3
Cefepime	4	13,3	25	83,3
Cefoxitin	19	63,3	0	0
Cefazolin	0	0	14	46,7
Levofloxacin	0	0	3	10
Meropenem	1	3,3	0	0
Nalidyxic acid	2	6,7	11	36,7
Sulfaprin	2	6,7	11	36,7

ESBL: extended-spectrum β-lactamases.
Source: Microbiology laboratory sample log book.

Results

The susceptibility profile of the isolated ESBL *E. coli* strains was shown, the antimicrobials that presented the greatest efficacy were Amikacin and Cefoxitin with 76.7% and 63.3%, respectively, on the other hand, drugs such as Cefepime with 83.3% and Ceftriaxone with 76.7% showed greater resistance to the pathogen (Table 1).

The ambulatory health area obtained the highest positivity with bacterial growth of 70%, and the Nephrology and Internal Medicine services contributed four 13.3% and two 6.7%, respectively (Table 2).

The most common type of sample was urine, followed by peripheral blood and culture of catheter tips in liquid medium (Fig. 1).

Table 2. Prevalence of *ESBL-carrying Escherichia coli*

Health services	*Escherichia coli* BLEE	
	No.	%
Ambulant	21	70
Nephrology	4	13,3
Orthopedics	1	3,3
General surgery	1	3,3
Internal medicine	2	6,7
ICEU*	1	3,3
Total	30	100

*Intensive care and emergency unit.
ESBL: extended-spectrum β-lactamases.
Source: Microbiology laboratory sample log book.

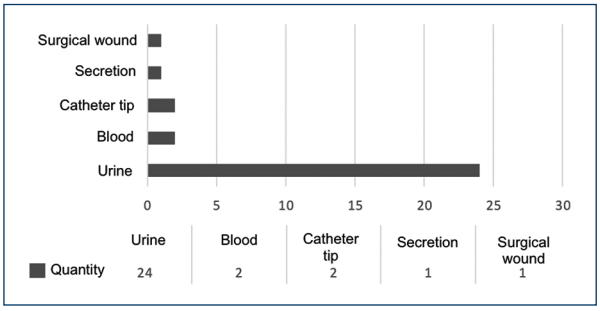

Figure 1. Prevalence of *Escherichia coli* extended-spectrum β-lactamases, by sample type.
Source: Microbiology laboratory sample log book.

Discussion

Gram-negative pathogens and those belonging to the *Enterobacteriaceae* family such as *E. coli* are the ones that most frequently use the production of ESBL enzymes, as the main mechanism of antimicrobial resistance, favored to a large extent by the indiscriminate use of antibiotics both in the community and at the hospital level.

In a study[9] of the health sector of Huesca, it was found that the antibiotics with the best efficacy against the strains of *E. coli* are fosfomycin and nitrofurantoin, followed by gentamicin. The data obtained by Mendieta-Astudillo et al.[10] in Ecuador coincide with the previous study in its entirety.

In this research, the information does not correspond to those of the world literature due to two important aspects. The first corresponds to the lack of blotting paper discs impregnated by antibiotics such as fosfomycin and nitrofurantoin in the center, which makes it impossible to make comparisons with other studies. The second aspect is due to the displacement of Gentamicin as one of the drugs with the highest sensitivity *in vitro* against the strains of *E. coli* ESBL, isolated in the institution.

Regarding the resistance of the *E. coli* ESBL strains, in another study, Chero-Vargas et al.[11] at the Jesús del Norte Clinic in Peru, ampicillin, Ceftriaxone, and Ceftazidime are identified as the antibiotics with the highest degree of resistance, data that correspond to those found by the present research. Barroso-González et al.[12] in Havana discover a pattern of resistance quite similar to what has been proposed in previous research.

In the Microbiology Laboratory, where this research is carried out, the frequency of isolation of ESBL *E. coli* is low. In another study[13] at the National Institute of Health in Lima, Peru, 34.8% isolation was obtained, in another study from that Country, a similar behavior was achieved at 31.1%. At the Salvador Allende Hospital in Havana, the incidence of isolation of *E. coli* ESBL strains is 46%[7]; higher than that reported in the present study.

The variability in the incidence of isolation of this pathogen can be largely related to the number of samples processed by the different health centers, in the year and the time frame used by each researcher to carry out the studies.

In the III-1 hospital located in Chiclayo, Peru,[14] it was found that the incidence of *E. coli* ESBL is higher in the Internal Medicine Services with 39.2%, General Surgery 42.9%, and Emergency 41.70% in isolations that are performed on blood, secretion, and urine samples. Pinguil-Yugsi et al.[15] in Ecuador observe a higher prevalence of this pathogen in Surgery Services and in clinical areas, so its data coincide with those of the previous study. In this research, the highest number of isolations of *E. coli* ESBL corresponds to the outpatient area and the Health Service with the highest incidence is the Nephrology Department.

It is common for the Nephrology Service to be one of the most affected by these multidrug-resistant bacterial strains because most of the patients who come to this area are undergoing hemodialysis, so they have a high risk of presenting infections by resistant microorganisms due to secondary immunodeficiency due to various factors. In a study[16] carried out at the Institute of Nephrology of Havana, an isolation of *E. coli* ESBL was obtained at 68.1%, data that support the results.

The community finding of *E. coli* ESBL is increasing, this is evidenced in this study where the frequency of isolation in this area is the highest, data that correspond to those of Velazquez et al.[17] in Marcos-Carbajal

et al.[18] in Peru, with 52 and 63.6% of strains found, this bacterium produces a wide range of infections in the community which allows a wide distribution and facilitates processes of recombination and transfer with a wide variety of RAM patterns.

As *E. coli* is the etiological agent par excellence of urinary tract infections, the largest number of isolates of this pathogen in the center under study are obtained from urine samples. Surgical site infections are among the main types of infection associated with extraintestinal *E. coli*, as shown by research[19], in Cuba. The data from this study do not coincide with those presented above, but they do correspond to those of Matta-Chuquisapon et al.[20], where the most frequent samples where isolation was performed were urine and blood, with 54 and 42%, respectively.

The main limitations of the study are that it is not possible to compare it with other studies in the hospital due to the lack of these. In the studies analyzed, the same antibiotics are not tested, so in some of them, it is impossible to contrast the information. In addition, the laboratory is limited to processing a small number of samples, due to a lack of resources.

Conclusion

The frequency of isolation of *E. coli*, producers of extended-spectrum β-lactamases, is low, and the highest source of positivity is obtained in urine samples and from outpatients. The most effective antimicrobials are Amikacin and Cefoxitin. Ceftriaxone and Cefepime showed the highest resistance indices.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki Addendum of Taiwan. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed. Privacy was ensured through the encryption of patient data, which were obtained in the sample record book of the Microbiology Laboratory, and were treated with strict confidentiality, avoiding violating their rights. The information was used for investigative purposes only, was not released to the public, and no new investigations were conducted.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Vaccination with a low dose of BCG or BCGΔBCG1419c protects against short-term *Mycobacterium tuberculosis* HN878 infection in male CB6F1 mice

*Jorge A. Barrios-Payan[1], Cristian A. Segura-Cerda[2], Dulce Mata-Espinosa[1], Helle Bielefeldt-Ohmann[3], Rogelio Hernández-Pando[1], and Mario A. Flores-Valdez[2]**

[1]Department of Pathology, Experimental Pathology Section, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Secretaría de Salud, Mexico City; [2]Centro de Investigación y Asistencia en Tecnología y diseño del Estado de Jalisco, Biotecnología Médica y Farmacéutica, Jalisco, Guadalajara. Mexico; [3]School of Chemistry and Molecular Biosciences, University of Queensland St. Lucia Campus, St Lucia, Australia

Abstract

Introduction: *Tuberculosis (TB) causes approximately 1.5 million deaths worldwide and 9 million new cases each year. Vaccination with Mycobacterium bovis Bacillus Calmette-Guerin (BCG) is effective in controlling severe forms of TB in childhood, with limited efficacy in preventing lung disease in adults, which is further reduced by infection with Beijing strains. We previously showed that a standard human dose (10^5 colony-forming units [CFU]) of the BCGΔBCG1419c vaccine candidate delayed the progression of lung necrosis in male BALB/c mice infected with Mycobacterium tuberculosis (Mtb) HN878.* **Objective:** *To determine the protective efficacy of a low dose of 2 BCG strains against challenge with a hypervirulent strain of Mtb in a murine model.* **Material and methods***: In this study, we explored the efficacy of vaccination with a low dose (10^2 CFUs) of BCG or BCGΔBCG1419c against Mtb HN878 infection in male CB6F1 mice, both at the short-term (1 month) and chronic (3 months post-infection) stages of active TB.* **Results:** *Vaccination with a low dose of BCG or BCGΔBCG1419c provided protection against Mtb HN878 challenge only 1 month after infection.* **Conclusion:** *Our results have important clinical translational implications, as they raise the hypothesis that the current vaccine may fail to protect humans against Beijing strains if, for example, problems occur during the handling, transportation, or administration of the current BCG vaccine (or a new one, such as BCGΔBCG1419c), leading to a lower than recommended dose being administered.*

Keywords: *Tuberculosis. Mycobacterium tuberculosis. Beijing. HN878. BCG. BCGΔBCG1419c.*

Introduction

Tuberculosis (TB) annually causes over 1 million deaths worldwide, with close to 10 million new cases per year[1]. The current vaccine, Bacillus Calmette-Guerin (BCG), does not provide sterilizing immunity to *Mycobacterium tuberculosis* (Mtb) infection in humans or effectively protects against lung disease. Therefore, a number of potential avenues to improve its efficacy against TB have recently been proposed[2].

Our vaccine candidate called BCGΔBCG1419c, in its second-generation, antibiotic-less version, has been described in its construction and characterization[3]. Vaccination of male BALB/c mice with a human

***Correspondence:**
Mario A. Flores-Valdez
E-mail: floresv@ciatej.mx

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standard dose (10^5 colony forming units [CFU]) showed that only BCGΔBCG1419c delayed the progression of TB and reduced lung pathology upon Mtb HN878 intratracheal infection[4].

Based on the findings of Khatri et al.[5], where a low dose of BCG Danish (3×10^2 CFU) reduced the bacillary load of Mtb HN878 in CB6F1 mice, we decided to evaluate whether a low dose of BCG or BCGΔBCG1419c (in the order of 10^2 CFU) would still be effective to protect CB6F1 against TB caused by low dose infection with Mtb HN878.

Material and methods

Culture of mycobacteria and experimental model

We performed culture and infection essentially as we recently described[4] with the difference of dose used here, which was in the 10^2 CFU order for all mycobacteria. Thirty male CB6F1 mice (8-9 weeks old) were purchased from Bioterio Morelos (Mexico) and were randomly allocated into three groups: group 1 received 8.8×10^2 CFU of BCG, group 2 received 5.5×10^2 CFU of BCGΔBCG1419c, and group 3 received phosphate-buffered saline (PBS) (unvaccinated controls). Five mice from each group per time point analyzed were anesthetized with pentobarbital intraperitoneally (210 mg/kg) and were sacrificed by exsanguination at 1- and 3-month post-infection as no animal showed signs of overt disease. The Internal Committee for the Care and Use of Laboratory Animals (CICUAL for its acronym in Spanish) from Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán approved the experiments with project number CICUAL-PAT-2043-21-22-1.

Bacillary load determination and morphometric analysis

These analyses were performed exactly as reported in[4]. For CFU enumeration, the right lung, or whole spleens from mice were mechanically disaggregated with 1 mL of PBS, and 10 mL of the lysate was used for culture on 7H10 oleic acid, dextrose, albumin, and catalase plates. CFU values were Log_{10} transformed before statistical analyses. To evaluate lung damage, left lungs from 3 to 4 mice per group randomly chosen were infiltrated with absolute ethanol, then embedded in paraffin and sliced in sections of 4 mm, then stained with hematoxylin-eosin and Masson's trichrome stain and digitally analyzed in a blind manner by an expert pathologist who analyzed the number of lesions apparent in a section. The percentage of involved parenchyma estimated, as well as peribronchiolitis, perivascular leukocyte infiltration ("perivasculitis"), alveolitis, "granuloma" formation (i.e., granulomatous inflammation), and necrosis on a scale of 0-5 (0 = within normal limits [no change from unaffected tissue]; 1 = minimal changes; 2 = mild changes; 3 = moderate changes; 4 = marked changes; and 5 = very severe changes) were assessed individually. A total lung score was calculated as the arithmetic sum of the scores for each tissue. In addition, a morphometrical analysis of the pneumonic area was performed by calculating the percentage of pneumonia in the sections of 4 mm. The digital analysis was done in Aperio Image Scan Scope and Leica application suite X.

Statistical analyses

Continuous data were analyzed by determining its distribution using a Shapiro-Wilk test and presented as mean plus standard deviation or median plus range when results were normally or not normally distributed, respectively. A Kruskal-Wallis followed by Dunn's test or one-way analysis of variance (ANOVA), and a Tukey *post hoc* test was performed to compare CFU. To compare the scores from the histological analysis, an H-Kruskal-Wallis plus a Dunn *post hoc* test was done. The values of Mtb CFU in lungs were log_{10}-transformed before statistical comparison. Groups where comparisons resulted in $p < 0.05$ were considered statistically different. The analysis was performed in the software GraphPad Prism v9 and Statistical Packages for the Social Sciences for Mac OSX.

Results

Male CB6F1 mice vaccinated with either BCG strain had significantly reduced Mtb HN878 burden in lungs at 1-month post-infection (p.i.) with a mean 0.5-log_{10} drop compared with unvaccinated controls ($p = 0.0026$ and $p = 0.0028$, respectively, one-way ANOVA followed by Tukey's multiple comparisons test, Fig. 1A). This control was lost at 3 months post-infection, as the mean CFU increased by 0.5-log_{10} from month 1 to month 3 p.i. (Fig. 1A). Regarding lung pathology, at 1- and 3-months p.i., only BCGΔBCG1419c reduced the percentage of the pneumonic area although this was not statistically significant ($p = 0.0805$ and $p = 0.1052$, one-way ANOVA followed by Tukey's multiple comparisons test Fig. 1B). For the remaining parameters, we found no statistically significant change for any parameter between vaccinated and unvaccinated mice (Fig. 1C-J).

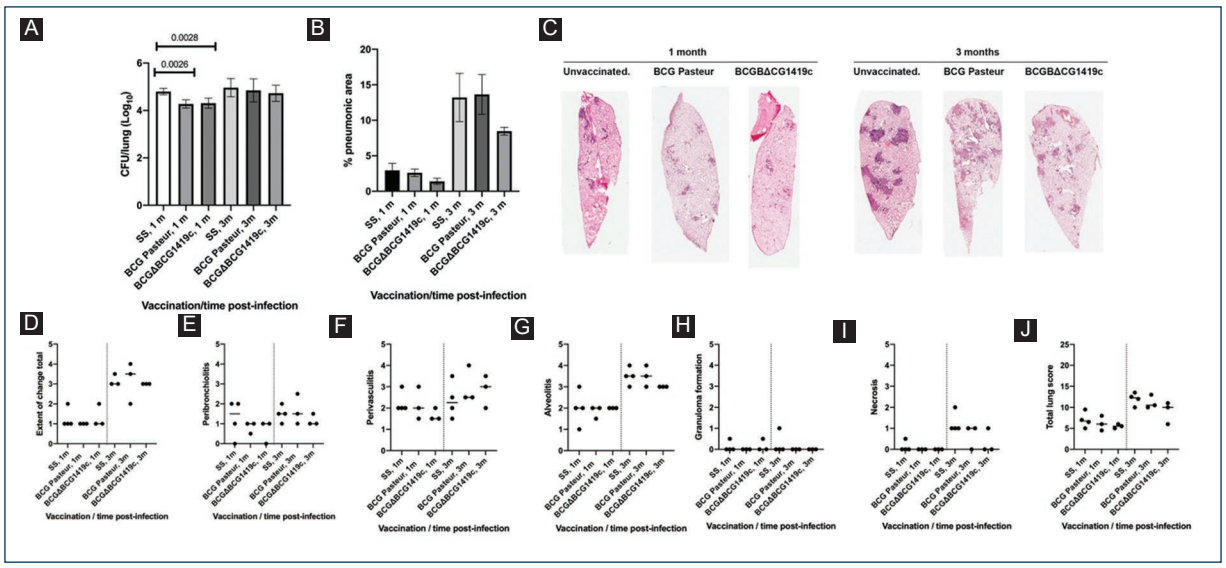

Figure 1. Capacity of BCG or BCGΔBCG1419c to control active (1-month post-infection) or chronic (3 months post-infection) tuberculosis in CB6F1 male mice challenged with a low dose (10^2 Colony-Forming Units) of *Mycobacterium tuberculosis* HN878. **A:** bacillary load in lungs of male CB6F1 vaccinated with either BCG Pasteur or BCGΔBCG1419c. **B:** area of the lung affected by pneumonia, measured by automated morphometry with Leica LAS V4.0 software. **C:** histopathological features of pulmonary TB in a mouse model. Yellow stars: perivasculitis; red star: alveolitis; blue arrow: peribronchiolitis, letter b (bold), bronchiole. BCGΔBCG1419c vaccinated mice showed smaller and well-defined areas of pneumonia with induction of concentric nodular zones in comparison with pneumonia generated in BCG Pasteur vaccine and the unvaccinated control group. **D-J:** detailed histopathological scoring of lesions observed in vaccinated and unvaccinated mice. In all groups, peribronchial and perivenular inflammatory infiltrates and alveolitis were observed. The statistical analysis was carried out with the one-way analysis of variance followed by Tukey's multiple comparisons tests.

Discussion

The results presented in this work suggest that vaccine dose may be relevant for protection against infection with Mtb Beijing strains, as reduction of CFU burden was achieved only at 1-month p.i., as opposed to 3 months p.i. when 10^5 CFU are used to vaccinate BALB/c mice[4]. In support of this notion, other vaccine candidates were shown to be effective in reducing Mtb Beijing strains burden for more than 60 days, but using vaccine doses higher than those used here, such as MTBVAC (10^6 CFU/dose, female C3H/HeNRj mice)[6], and BCGΔureC hly+ (10^6 CFU/dose, BALB/c mice, intravenously administered; mouse sex was not indicated)[7]. Of note, both of these studies used Beijing W strains for challenge, whose virulence as compared with HN878 is presently unknown.

Therefore, we consider that the results presented here raise the hypothesis that a failure to protect against Mtb Beijing strains may arise from the delivery of a lower than recommended dose being administered to vaccinated subjects, which may arise as a consequence of problems occurring during handling, transportation, or administration of the current BCG vaccine (or a new one, such as BCGΔBCG1419c), which alter this vaccine thermal stability; this, in turn, is highly dependent of formulations used to preserve BCG, as it was already demonstrated[8].

In this work, we decided to use CB6F1 mice, a cross between BALB/c and C57BL/6 mice, because these have an increased diversity of major histocompatibility complex class II genes (I-A^b, I-A^d, I-E^d) compared to either of its parental strains, thereby potentially broadening the induction of immunity to infection.

Our results and those reported by Khatri are in agreement, with a few differences: (1) the bacillary load in unvaccinated mice was in the order of 10^5 CFU in this work, compared with 10^6-10^7 in[5], (2) the reduction in mean CFU load was close to 0.5-$\log_{10}$ CFU here, whereas it reached almost 1-$\log_{10}$ in[5]. These differences could be the result of either employing different mouse sex (male here versus female in[5]) or the use of a different BCG strain (Pasteur here versus Danish in[5]). Vaccination dose could also be the source behind the attained burden of Mtb HN878, although this seems unlikely as Khatri et al.[5] did not find a major reduction in CFU when using BCG at doses ranging between 300 and 3×10^5 CFU.

Conclusion

A low dose of BCG or BCGΔBCG1419c was effective in reducing TB disease produced by the highly virulent Mtb HN878 Beijing strain, although only against active and not chronic infection.

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Conflicts of interest

M.A. Flores-Valdez and R. Hernández-Pando are co-inventors on a patent on BCGΔBCG1419c held by the Centro de Investigación y Asistencia en Tecnología y diseño del Estado de Jalisco (CIATEJ), A.C. and the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, which could be construed as a potential conflict of interest. All other authors do not have any conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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REVIEW ARTICLE

Protein turnover, requirements, and how to use it according to the clinical situation in patients with parenteral nutrition

*Adriana Flores-López[1], Martha Guevara-Cruz[2], Armando R. Tovar[2], Nimbe Torres[2], and Aurora E. Serralde-Zúñiga[1]**

[1]Clinical Nutrition Service; [2]Department of Nutritional Physiology. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Secretaría de Salud. Mexico City, Mexico

Abstract

Of the three primary macronutrients, protein requirements vary the most because of different factors that make them change the requirements when we calculate them. The utilization and degradation of amino acids (AAs) may vary according to the pathology or condition of the patient. A better understanding of the basis of protein turnover and its responses to different situations will help to have better prescriptions. In recent years, there has been considerable information about the use of protein and specific AAs, such as branched-chain AAs and glutamine in the treatment of different conditions or pathologies, such as in elderly individuals; in those in intensive care units; and individuals with cancer, sepsis, or kidney or liver diseases. Thus, the present work aims to recapitulate and define the appropriate protein requirements in these different conditions and how to administrate when prescribed parenteral nutrition.

Keywords: *Protein. Amino acids. Requirements. Metabolism.*

Introduction

The complexity of protein prescription in subjects with specific conditions relies on evidence that there are no identical proteins in foods and, consequently, the amino acids (AA) intake pattern shows high inter-individual variability that may preclude receiving an intake according to the requirements. On the other hand, it is known that there is no extra storage location for AA in the body, as is observed for carbohydrates and lipids, which can be stored in the liver or the adipocytes. AA must always be involved in metabolic function. Therefore, if an AA is not used or incorporated into body proteins, it is discarded through the formation of ammonia and urea.

Depending on the way of administration, an organism absorbs the same AA or peptide differently; even in parenteral nutrition (PN), where the administration is in its most elemental form as a mixture of single AA, the utilization and degradation of AA may vary according to the pathology or condition that is present, modifying the protein requirement of the host. There is evidence that in PN, the utilization of AA is greater than that in enteral nutrition, given that AA is infused directly through the vein, skipping the absorption step of enteral nutrition[1]. A list of articles was compiled by searching electronic databases from the National Library of Medicine (PubMed) for English reviews, original research articles in humans, and full-text articles. The initial

***Correspondence:**
Aurora E. Serralde-Zúñiga
E-mail: aurora.serraldez@incmnsz.mx

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search strategy used a combination of the key terms, "Proteins", "metabolism", "Nutritional Requirements", and "PN" to identify potential articles. Articles were included if they were primary sources, published in English from 2000 onward.

Protein metabolism and turnover

Peptides and proteins are formed by peptide bonds where the amine group of one AA and the carboxyl group of another AA bonds. Of the 20 AA that is involved in this process, the body cannot synthesize nine and, therefore, are considered indispensable (essential); these are histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine[2].

The pancreatic proteases, used in the upper part of the gastrointestinal tract, digest almost all proteins when these are provided in an enteral way; however, the few remaining undigested peptides can be utilized by the gut microbiota. Once protein breakdown occurs in the gastrointestinal tract, only free AA and some dipeptides are transported into the enterocyte. The portal vein transports the absorbed free AA into the liver, where AA is partially utilized by the liver, which changes the AA composition distributed through the general circulation to the rest of the body. During this process, AA partially oxidizes, releasing urea and CO_2/HCO_3 and increasing oxygen consumption. Oxidation depends on the body's balance of the different AAs needed to achieve nutritional needs[3].

The body cell mass (BCM), mainly formed by organs such as the liver, intestine, kidney, and muscles, is responsible for the flux and regulation of AA metabolism. BCM represents approximately 50% of the total body weight (BW), and it has been divided into the peripheral protein compartment (skeletal muscle) and the central protein compartment (blood cells, immunocytes, plasma proteins, and fat-free cells). Since protein is not used mainly as a fuel, protein consumption is necessary to maintain or increase BCM under different conditions. Besides, the individual AAs play distinct and important roles during metabolism since they are pre-cursors for the synthesis of different compounds, including dispensable AA, heme groups, carnitine, neurotransmitters, purine, and pyrimidines[4].

The complexity of AA metabolism is partly due to protein turnover, which refers to the capacity of body proteins to be synthesized and degraded depending on metabolic needs. Therefore, the catabolism of AA coming from the diet or protein turnover cannot be wholly prevented; therefore, it is necessary to have at least a minimum dietary protein consumption to avoid a negative nitrogen balance[5]. The lower the AA catabolism, the lower the required protein intake; nonetheless, there is an obligatory nitrogen loss and a minimum protein requirement to maintain homeostasis. The equation to estimate nitrogen loss is 1 g of nitrogen in urea/0.85 + 2 g[4].

Two models have been developed to estimate the AA requirements: the direct AA oxidation model involves a graded increase in the diet of the AA, whose requirement is assessed until the AA consumption increases its oxidation rate, indicative of the AA requirement[6]. The second method, named the indicator AA model, uses an AA different from the AA assessed and indirectly determines the AA requirement[1,4]. This determination aims to calculate the labeled AA's appearance and disappearance rate (Fig. 1).

AA interorgan exchange is a pathway through which AA passes through the body to enable protein synthesis and plasma AA homeostasis and develop different metabolic functions. The flux of AA throughout the body depends directly on whether a feeding or starvation process occurs. In the first condition, the AA is mobilized from the intestine to the rest of the tissues. In the second condition, almost all AA are transported mainly from the skeletal muscle to the liver and kidney.

During starvation or critical illness, carbon skeletons from the degradation of gluconeogenic AA (alanine, glycine cysteine, serine, threonine, asparagine, arginine, aspartic acid, histidine, glutamic acid, glutamine, isoleucine, methionine, proline, valine, and phenylalanine) can be utilized for hepatic glucose synthesis. Leucine is the only one from the rest of the branched-chain AAs (BCAAs) that undergoes complete oxidation to provide energy in the muscle and spare pyruvate oxidation in the Krebs cycle through the formation of acetyl coenzyme-A. During fast, leucine levels rise in the bloodstream and muscle[7] (Fig. 2).

Protein requirements in different conditions

It is difficult to identify if an improvement that occurs in an intervention is exclusively from the protein or energy administration because proteins are ultimately part of the energy administered in any nutritional intervention (each g of protein provides 4 kcal). Nonetheless, if the energy supplied is not adequate or the energy requirements increase, the dietary protein will serve as an energy provider rather than a keeper of the nitrogen balance[8].

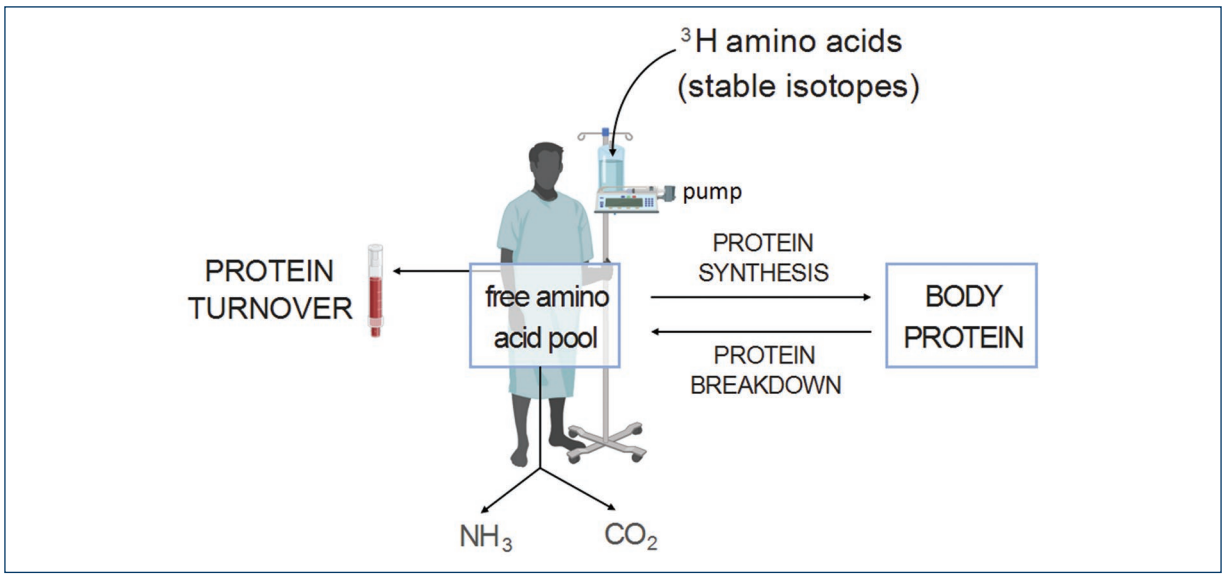

Figure 1. Method of the labeled isotope of specific amino acid. To estimate the requirement of each amino acid, a continuous administration of a tracer labeled amino acid is performed until an isotopic equilibrium is reached, (ratio of tracer infusion equals the ratio of disappearance from the sampling compartment). Labeled isotopes have different masses but the same chemical properties than those found in nature. Thus, the rate of tracee appearance depends on the endogenous protein breakdown, the rate of tracer administration, the protein synthesis, the catabolism, and excretion. Mass spectrometry is commonly used to analyze the amount of labeled isotope excreted through the body.

The concept of non-protein calories (NPC) has been widely used in nutritional support. The NPC-to-nitrogen (N) ratio has the aim to balance the energy provided by dextrose and lipids so that AA can be used to form protein and lean body mass (LBM) and assist in wound healing. However, this ratio does not provide information about the distribution of lipids and dextrose[8]. The range of NPC 125:1g N-225:1 is adequate for non-stressed patients[9], and in critically ill patients, an adequate NCP: N ratio is between 70:1 and 100:1[10].

Although a lot of research has been done on this topic, there is no recent or complete concordance in the prescription of protein particularly in those with special conditions. Table 1 summarizes the most recent prescriptions suggested by experts according to different conditions, but further, a better explanation is presented.

Table 1. Protein requirement according to the clinical situation

Patient type	Protein requirement
Well-nourished, healthy adult	0.8-1 g/kg
Well-nourished, healthy older adult	1.0-1.2 g/kg
Critically ill adult, normal weight	1.2-2.0 g/kg 0.2-0.4 g/kg in acute phase
Critically ill adult, obese	BMI 30-40 kg/m^2: 2.0 g/kg of IBW BMI > 40 kg/m^2: 2.5 g/kg of IBW
Critically ill elderly adult	1.2-1.5 g/kg, if greater losses up to 2.0 g/kg
Kidney disease	0.6-0.8 g/kg CKD non-critically ill > 1.2 g/kg on intermittent RRT non-critically ill 0.8-1.0 g/kg AKI non-critically ill 1.5-1.7 g/kg AKI or CKD with prolonged or continuous RRT.
Hepatic disease	1.5 g/kg, considering dry weight ascites, circulating volume depletion, and hypoalbuminemia
Cancer	Up to 1.5 g/kg

IBW: ideal body weight; BMI: body mass index; CKD: chronic kidney disease; RRT: renal replacement; AKI: acute kidney injury.

Healthy individuals

A key factor in the success of an intervention is the patient nutritional status. However, even in well-nourished, protein/energy malnourishment can occur in approximately 10-15 days if there is inadequate feeding, and this can be reflected in the amount of LBM loss and clinical outcomes related to feeding[11-14].

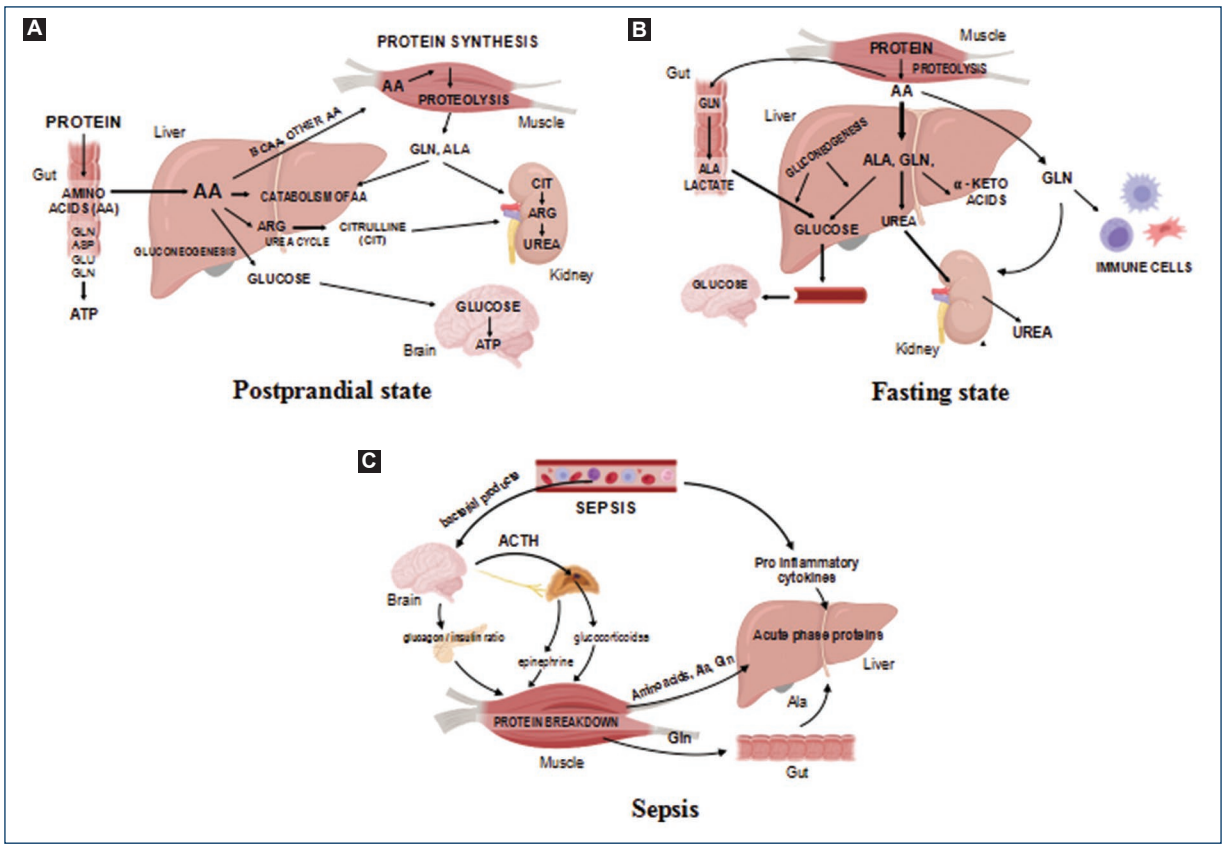

Figure 2. Amino acid (AA) interorgan exchange in the post-prandial, fasting and sepsis states. **A:** during the post-prandial state, ingested AA is mobilized from the intestine to the liver, where they are used for protein synthesis and synthesis of nitrogen compounds. AA released from the liver is taken up by skeletal muscle, kidney, and brain; the excess is oxidized and further excreted mainly by the urine but also by the feces. **B:** during the fasting state, skeletal muscle proteolysis releases mainly Alanine (Ala) and Glutamine (Gln) to circulation to obtain energy and stimulate hepatic gluconeogenesis. The skeletal muscle-derived Ala is a rate controlling for the hepatic mitochondrial oxidation that translates into glucose production during fasting. **C:** during sepsis, the bacterial products induce a pro-inflammatory response leading to skeletal muscle proteolysis, to release mainly Ala or Gln and increases hepatic gluconeogenesis simulating a fasting state, furthermore the proteolysis during sepsis is greater than in a fasting state, so a greater requirement of protein through nutritional support is needed. Asp: aspartic acid; Glu: glutamate; Cit: citrulline; BCAA: branched-chain amino acid; ATP: adenosine triphosphate; ACTH: adrenocorticotrophic hormone.

The reference dietary intake has been estimated at 0.65 g/kg BW/day. Still, given the large inter-individual variation in measurement, a standard deviation from this value was added to ensure a high-quality intake, resulting in a final estimate of 0.8 g/kg BW/day[8].

The World Health Organization and the Food and Agriculture Organization state that protein requirements are not affected by ethnicity or environmental factors unless an outstanding situation deviates from the norm[15]. Therefore, it has been recommended in Mexico to follow international protein requirements unless an individual case requires something different[16,17].

Critically ill adult patients

The high protein turnover that occurs during a critical state of a patient is due to the body's different needs, including gluconeogenesis, the synthesis of proteins necessary for immune system function, and wound repair. This can lead to muscle wasting of approximately 15-25%; the larger the decrease in LBM, the worse the outcome. It has been seen that multiorgan failure is related to increased muscle wasting, patients with organic failure of more than two systems had a muscle loss after a week of 15.7% compared with single organ failure[14,18].

Organ failure diseases cause problems with nitrogen balance, protein turnover, and homeostasis. In addition, conditions that bring stress such as trauma and sepsis, activate neuroendocrine, inflammatory and gastrointestinal pathways, enhancing catabolism, energy expenditure, and proteolysis. In these cases, muscle proteolysis shifts AA into the liver, where they are used for immunoglobulins, glycogenesis, and acute-phase proteins[19]. It is important to recognize the presence of inflammatory response as well as its severity on intermediary metabolism because it can be associated as a diagnostic and therapeutic target, and its presence limits the effectiveness of nutritional interventions compared with other clinical situations without or less intense inflammation[20,21].

Different studies have demonstrated that adequate protein administration is preferred to energy[22] and the effects of prescribed hypocaloric nutrition support on clinical outcomes[23]. The main problems in protein metabolism are muscle wasting, glutamine depletion, hyperglycemia, and hypoalbuminemia. This promotes the loss of LBM and represents a short-and long-term burden for functional recovery; the amount of protein required can be calculated as 1.5 g/kg of ideal BW (IBW)[24].

The most recent European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines suggested that 1.3 g/kg could be an optimal dose if it is administrated progressively and does not fall into overfeeding[25]. On the other side, ASPEN guidelines suggested that 1.2-2.0 g/kg of actual BW is recommended[10,26].

A consensus by experts concluded that 1.2-2.0 g/kg/day is adequate for these patients, although higher doses can be safely used for specific subpopulations as in burn and trauma patients[27]. In the NUTRIREA-3 showed that in the acute phase in critically ill patients who received lower protein and calories (energy 6 kcal/kg and protein 0.2-0.4 g/kg of BW) had fewer complications and a faster recovery than those who were provided since the beginning high doses of protein[28]. Furthermore, the EFFORT Protein study reveals that there is no benefit of using high protein doses in the intensive care unit (ICU) (over 2.2 g/kg of BW) in the time of discharge and on the contrary might worsen the outcomes, especially in those with kidney injury or organ failure compared with those with lower doses of protein (1.2 g/kg of BW)[29].

Glutamine is an important AA that is involved in many metabolic processes and is related to a reduction in mortality and infectious complications, among others. Currently, it is recommended to supplement glutamine in PN as L-glutamine (0.2-0.4 g/kg of BW) or as alanyl-glutamine dipeptide (0.3-0.6 g/kg of BW) for critically ill patients but with caution in multiorgan failure patients[30]. Animal studies have shown that the supplementation with L-glutamine improves ischemic brain injury as it improves oxidative stress damage[31]. Moreover, Cotoia et al., found that in polytrauma patients intravenous supplementation of glutamine (50 mg/kg IBW) improves patient immunity[32].

Critically ill obese patients

Hypocaloric high-protein diets refer to those that provide low energy according to the requirements but a concentration of protein high enough to achieve equilibrium or even positive nitrogen balance. This concept is necessary to achieve lean mass's protein requirements and gain. ESPEN guidelines recommend the use of urinary nitrogen losses or LBM determination (preferably using computed tomography) to determine protein intake; if these are not available, 1.3 g/kg adjusted BW can be used[25].

On the other hand, ASPEN guidelines recommend that the protein goal for a patient with a body mass index (BMI) < 27 kg/m^2 should be 1.5 g protein/kg of BW. When BMI is from 27 to 30 kg/m^2, weight can be corrected to that for a BMI of 27 kg/m^2 to make the calculation. In the case of obese patients when BMI > 30 kg/m^2, IBW should be used and the protein administration is set to 2.0 g/kg of IBW, but when BMI is > 40 kg/m^2, a 2.5 g protein/kg of IBW goal can be set[10,31].

In a regression analysis between nitrogen balance and protein intake, it appears that to maintain the nitrogen equilibrium, critically ill patients with class I and class II obesity must consume approximately 1.9-2.0 g protein/kg of IBW per day, while for patients with class III obesity, the protein intake recommendation increases to 2.5 g/kg of IBW unless a severe renal or hepatic dysfunction is present[33]. Strong enough evidence is still lacking that 2-2.5 g/kg is worth administering, given that there is not always an increase in protein synthesis once this goal is achieved[34].

Critically ill elderly adults

Older adults are considered those[3] 65 years of age, in this population group, it is highly important to maintain muscle mass. When a patient enters the ICU, the greater challenge is to achieve the protein and energy goals to avoid frailty. Muscle mass losses and sarcopenia are conditions of greater importance to consider

given that they function as predictors of extended length of hospital stay and mortality in the ICU[35].

Patients require more protein, especially leucine, to stimulate protein synthesis; the addition of 2.5-2.8 g of leucine per meal is enough to achieve the anabolic threshold and optimize muscle protein synthesis according to PROT-AGE recommendations. The major contributors to muscle protein breakdown are inflammation, the insulin resistance of proteolysis and muscle disuse, ESPEN guidelines recommend that when acute or chronic illness is present, 1.2-1.5 g protein/kg of BW is recommended, and in cases of severe illness, injury or malnourishment, up to 2 g protein/kg of BW can be administered[36].

Kidney and liver diseases

Acute kidney injury is usually secondary to a disease process such as sepsis, hypovolemia, and drug-mediated kidney injury that leads to a homeostatic malfunction. It is known that renal replacement therapy (RRT) increases protein losses (0.2 g AA is lost per liter of filtrate, amounting to a total daily loss of 10-15 g), therefore, protein restriction is not needed[37]. Latest ESPEN guidelines suggested more accurate protein prescriptions according to the state of the pathology, if the patient is hospitalized and if there is or not RRT. The less requirements are for those without critical illness and RRT with a prescription of 0.6-0.8 g/kg of BW up to 1.5-1.7 g/kg of BW to those hospitalized critically ill with RRT[37].

This is not the case with hepatic diseases, in which, according to the pathology, the protein requirement can change and there is still no strong evidence that high protein intake is harmless. For instance, acute liver failure is potentially reversible, and during the disease, glycogen stores and insulin metabolism are reduced and gluconeogenesis and ammonia clearance are impaired, which can lead to multiorgan failure. All this promotes an increase in energy and protein requirements. Unfortunately, decompensated liver cirrhosis is an irreversible late-stage disease; the most common complications are portal hypertension, hepatic encephalopathy, ascites, hepatorenal syndrome, and pre-existing protein-energy malnutrition.

Contrary to the previous recommendation and thoughts, there is no protein restriction with liver diseases, primarily because of the catabolic state that persists during the disease[19]. The general recommendation to avoid sarcopenia in these patients (if they are not overweighted) is to provide from 1.2-1.5 g/kg/BW[38,39], but it will be necessary to take into consideration the calculations of dry weight given the conditions of ascites, circulating volume depletion and hypoalbuminemia.

It has been reported that an infusion of BCAAs brings some benefits as improvement in glucose metabolism by the synthesis of glutamine and leucine; leucine induces the stimulation of hepatic growth factor, the prevention of tissue triglyceride accumulation, and an improvement in neutrophil phagocytic function. However, there are no sufficient data to demonstrate the improvement in this type of patient, and only the ESPEN recommends its use[19].

Cancer

One of the major problems in patients with cancer is nutritional deficiency, with primary weight and LBM loss, which increases the length of stay in the hospital, infections, and mortality. This can be due not only to the disease itself, as it is characterized by a catabolic state, but also to the site of the tumor and the cancer therapies that have several side effects. The protein recommendations for these patients should be > 1.0 g/kg up to 1.5 g/kg of BW; however, they can reach up to 2 g/kg if the catabolic state is greater[40].

Arginine, glutamine, BCAAs, and hydroxyl-methyl-butyrate leucine derivate (HMB) have been used to avoid catabolic state, but still with inconclusive results about their use[40]. In a systematic review Prado et al., found that the HMB has been used usually in a dosage of 3.0 g/day to improve muscle mass and function however they suggested that better well-designed trials are needed[41].

PN and its protein administration

PN is indicated when there is an intestinal failure or there is no other way to fully nourish a patient by oral or enteral access[42-44]. Depending on the patient's needs, PN includes macronutrients (AAs, carbohydrates, and fat), micronutrients (electrolytes, vitamins, trace elements, minerals), and water[42,44].

When AAs are administered in PN, they provide less energy than protein because once they are metabolized in the organism, the bonding of peptides releases water. Therefore, 100 g of AAs provides 340 kcal and 83 g of protein substrate; roughly, if the protein requirement for an individual is 0.8 g/kg, the infusion of AAs would be approximately 1 g/kg of weight[45]. In the case of PN, AA solutions are formed by different amounts of AAs; however, none of them has cysteine because of its

instability in the solution (but it can be added as N-acetylcysteine instead) and tyrosine is limited given that it is not quite soluble in water (but N-acetylated tyrosine can be added instead)[4,45]. Moreover, these solutions usually lack glutamine but have sufficient glycine and other non-essential AAs[45].

All standard AA mixtures for PN contain high amounts of essential AAs as well as arginine and amine N from some of the non-essential AAs (for their synthesis) to ensure the fulfillment of daily needs. Specialized mixtures can be found for specific requirements, for example, increased BCAAs and reduced methionine, phenylalanine, and tryptophan (usually for hepatic disease) or solutions exclusively of essential AAs (usually for renal insufficiency) or increased BCAAs (for protein-catabolic critical illness). Additional glutamine can be added to PN solutions, such as alanyl-glutamine (20 g/100 mL)[45].

It is important to remember that PN administration varies according to the needs and availability, from single-bottle systems where each nutrient is parallel administrated from separated bottles into a common IV catheter, to the all-in-one system that combines all components of PN in a single infusion line. In this last one, there are individually or ready-to-use admixtures. Special attention has to be taken with the ready-to-use admixtures if the protein requirements want to be met because it can result in calorie overfeeding, usually these types of admixtures have an NCP: N ratio from 160:1 to 90:1[45].

Finally, even rare AAs can cause an admixture instability showing a dark color, especially when the cysteine and tryptophan are degraded. Therefore, it is important to avoid high temperatures and avoid residual oxygen in the containers for storage or administration[46].

Conclusion

The present review remarks on the importance of protein metabolism and the physiological changes that are frequently observed in patients. The scientific evidence and the technological advances available allow us to provide the amount of protein required for the support and treatment of patients to prevent or reduce the negative effects of protein depletion on nutritional status, and to reduce adverse clinical outcomes associated with this condition. This is one of the few works that not only englobes the basics of the function of protein metabolism but also the recommendations for prescriptions in different conditions, such as age, clinical condition, and body composition, and the ways of infuse through PN, facilitating to the healthcare provider all the information necessary for the decision-making regarding protein prescription, especially in those with PN.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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REVIEW ARTICLE

Utility of electroencephalography in the evaluation of sleep disorders

Adrián Poblano[1,2] and Rafael Santana-Miranda[1]*

[1]Sleep Disorders Clinic, Faculty of Medicine-Universidad Nacional Autónoma de México, sede Hospital General de México; [2]Cognitive Neurophysiology Laboratory, Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra, Secretaría de Salud. Mexico City, Mexico

Abstract

The electroencephalogram (EEG) consists in the simultaneous recording in many channels in the scalp of the cortical-subcortical electric brain activity, spontaneous or evoked by means of surface electrodes. EEG is an electro-physiological tool used in the neurological, psychiatric, and in sleep medicine diagnoses. EEG helps in the identification, classification, and prognosis of patients with sleep disorders (SD). In this review, we update the state of knowledge about EEG and polysomnographic techniques, and their characteristics and alterations in SDs, and in epilepsies with clinical manifestations during sleep. The review shows that EEG/polysomnography is a tool that has many important utilities for the study of SDs.

Keywords: *Electroencephalography. Polysomnography. Sleep disorders. Somnology. Epilepsy.*

Introduction

The electroencephalogram (EEG) is the simultaneous recording in several channels at the extra-cerebral level, of cortico-subcortical electrical activity, spontaneous or provoked, by means of the placement of superficial electrodes[1].

The EEG is one of the most widely used electro-physiological auxiliary tools in neurological, psychiatric, and other speciality diagnosis such as sleep medicine or somnology. This is because it is a non-invasive method auxiliary in clinical diagnosis that can be carried out on an outpatient basis (under some conditions), it is easy to perform; It can be requested urgently and in intensive care units or operating theatres. The EEG helps in the clinical diagnosis, classification, and prognosis of the patient. The presentation of the results is agile, can be sent by telemetry, and is applicable to all ages. For these reasons, in this review, we will update the state of knowledge about the EEG technique, its normal characteristics, and the pathologies in which it is indicated in the evaluation of sleep and its diseases[1].

Neurophysiological basis of EEG

The origin of the cortical electrical activity observed in the EEG comes from the post-synaptic potentials (PSP)[2]. PSP are temporal variations in the resting membrane potential at synapse. PSP can be excitatory and inhibitory. PSP have the property of being able to be recorded in fields far from their neural generators and can be conducted by volume to the skin of the skull. When various neural networks synchronize to oscillate together, different oscillatory frequencies or brain rhythms are produced. For example, the temporal functional coupling of certain neural networks in the range of 8-13 cycles/s (Hz) can determine the electro-physiological oscillation in the alpha frequency in the temporo-parieto-occipital regions[3].

***Correspondence:**
Adrián Poblano
E-mail: drdislexia@yahoo.com.mx

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Electroencephalographic rhythms

The recorded electrical activity is characterized by a series of more or less regular temporal oscillations according to the functional state (FS). The well-characterized FS for EEG in humans are: (1) wakefulness-eyes closed-physical and mental rest; (2) wakefulness-eyes open; (3) sleep in the initial or transitional sleep phase or N1; (4) sleep in light sleep or N2 phase; (5) sleep in deep sleep or slow wave or N3; and (6) sleeping in the rapid eye movement (REM) phase.

Brain rhythms are classified according to the frequency they present: oscillations between 0.1 and 3.9 Hz are known as delta rhythms; those between 4 and 7.9 Hz are called theta rhythms; between 8 and 13 Hz, are called alpha and between 14 and 35 Hz, are called beta rhythms[4]. There are other EEG rhythms, the best known of which are sigma rhythms, which are present during the N2 phase of sleep. Sigma rhythms have a frequency between 12 and 16 Hz, with a duration of between 0.5 and 1.5 s, in central regions and are of fusiform morphology, which is why they are also called: Sleep spindles[5].

In the phase of wakefulness-eyes closed-physical and mental rest, the EEG is characterized by the presence of alpha rhythms in the temporo-parieto-occipital areas and frontal beta rhythms forming an anteroposterior amplitude gradient. In the wake-eyes open phase, the EEG shows generalized beta rhythms due to a cortical desynchronization phenomenon known as alpha rhythm blocking caused by eye-opening.

EEG rhythms in the initial sleep or N1 phase are characterized by a loss of alpha-based activity and the appearance of diffuse delta and theta rhythms of low to medium amplitude. In preschoolers, schoolchildren, and adolescents, slow-wave outbreaks may appear in the theta range of greater fronto-parietal amplitude called: hypnogenic hypersynchrony. In the N2 phase, sleep spindles or sigma rhythms are present in frontoparietal areas, as well as acute waves of the vertex that when grouped together are called K complexes. In the N3 phase, irregular or monorhythmic delta activity appears, in a generalized way, of high voltage. Finally, in the REM phase, the activity presents as generalized low-voltage rhythms, of higher frequency and lower amplitude, with a predominance in the range in diffuse theta and beta frequencies, and the typical sawtooth waves[6].

Summary of the neurophysiological mechanisms of sleep

There are several neural networks that promote the various FS that occur during wakefulness and sleep. In the vigila, the ascending activating reticular formation and the posterior hypothalamic nucleus influence the non-specific thalamic nuclei to increase the tone of the cerebral cortex. To mantain wakefulnes, the hypothalamus secretes hypocretins, on the other hand, in the brainstem, the raphe nucleus releases serotonin while the locus ceruleus secretes noradrenaline. For its part, Meynert's nucleus releases acetylcholine and the amygdala and suprachiasmatic nucleus dopamine[7], there is much evidence that all these neurotransmitters are promoters of wakefulness.

In non-REM sleep, hypocretin secretion is inhibited by GABAergic and galinergic discharges from the ventro-lateral pre-optic nucleus that decreases the activity of wakefulness-promoting networks. The activity of the thalamic reticular nuclei generates sleep spindles by cortical desaferentation, inhibiting non-specific afferent sensory fibers. On the other hand, the nucleus of the solitary fasciculus is activated, influencing the activity of the midbrain, hypothalamus, thalamus, and limbic system, producing a progressive hyperpolarization of the thalamic reticular nuclei until the sleep spindles disappear and the dorsal thalamic nuclei are activated, projecting to the cortex, producing the delta activity characteristic of deep sleep (Fig. 1)[8].

The neural networks that promote REM sleep originate mainly in the pontine oralis reticular nucleus which, through activating ascending fibers, originate REM discharges, aided by the *locus coeruleus* (noradrenergic) and the raphe nucleus (serotonergic), which increase the activity of the geniculate nucleus and the cerebral cortex[9]. The behavior of these cycles is circadian coordinated daily by the suprachiasmatic nucleus in the hypothalamus, which clocks the duration of each sleep-wake cycle (Fig. 1).

On the other hand, there is a neuroendocrine system that promotes sleep. This system is especially active in the early stages of development through the secretion of melatonin, a hormone that is produced mainly by the pineal gland and to a lesser extent by the retina. Its secretion is stimulated by darkness and inhibited by ambient lighting. It acts by inhibiting the neural networks that promote wakefulness in a circadian way[10].

The study of clinical EEG in sleep disorders

A clinical EEG for the study of sleep disorders (SD) includes the recording of the following conditions:

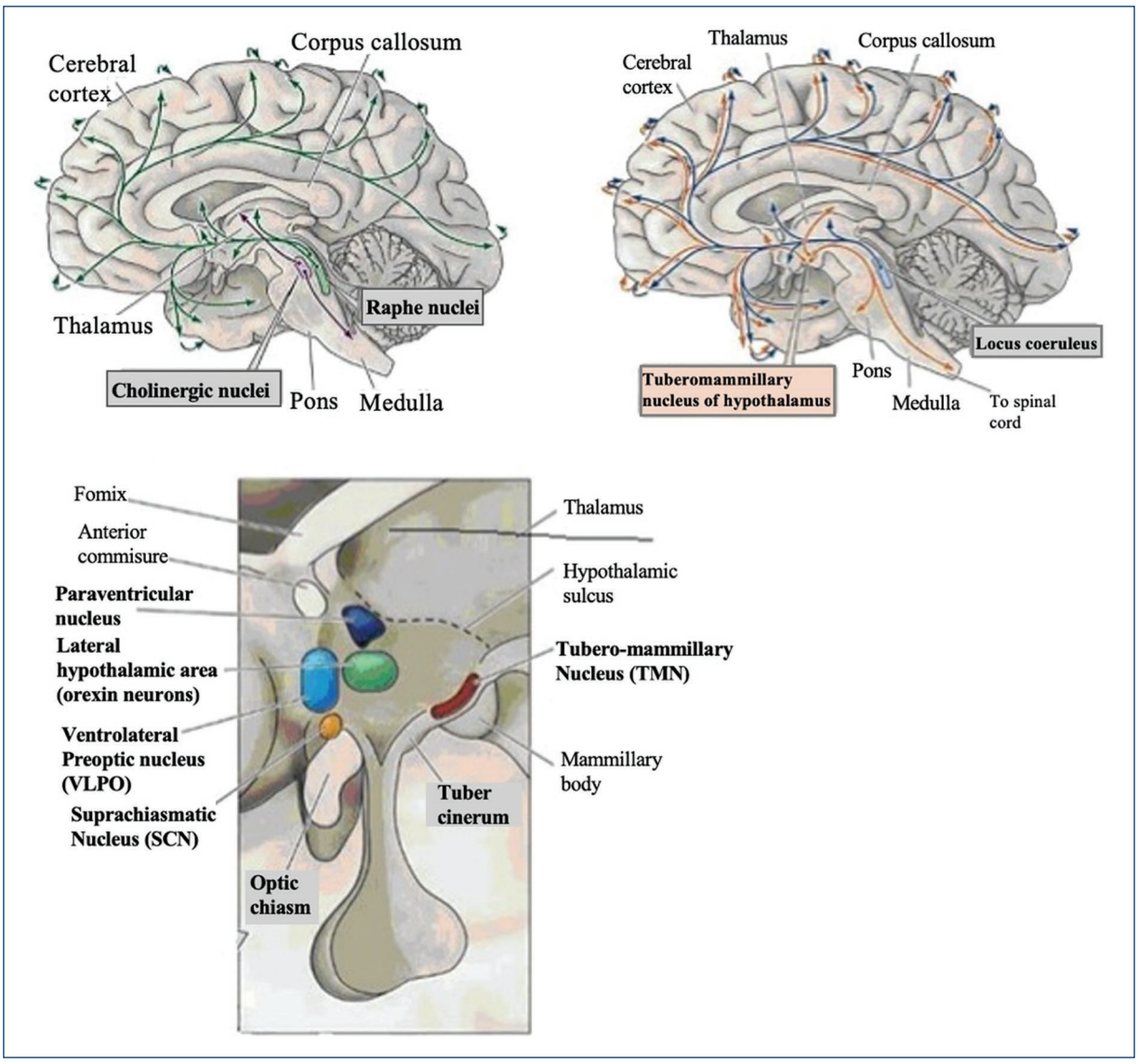

Figure 1. Brain structures and their sleep-generating circuits. Upper left panel, raphe core, and its cholinergic pathways. Upper right panel, *locus coeruleus*, and nordrenéric pathways. Bottom panel, hypothalamic nuclei involved in the generation of sleep. Explanation in the text (*inspired by Purves et al. 2012*).

(1) wakefulness-eyes closed-physical and mental rest; (2) wakefulness-eyes open; (3) intermittent light stimulation; (4) hyperventilation; and (5) asleep. The duration of the study ranges from 30 min to 8-12 h. The condition of wakefulness in closed eyes at physical and mental rest causes the appearance of alpha temporo-parieto-occipital rhythms and faster activity and lower frontal voltage or base activity. Wakefulness: eyes open: blocks the alpha rhythms and desynchronizes cortical activity, causing the appearance of generalized beta rhythms[1,3].

Intermittent light stimulation consists of flashes of intermittent light at different frequencies under conditions 1, 2, or 5. The light stimulation frequencies can follow the following order: 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 40, 60, 30, 10, 5 and 1 flash/s. The physiological response is a drag or synchronization to the stimulation frequencies when they are within the EEG rhythms or the generalized desynchronization of the base rhythms. The pathological response consists of the presentation of focal or generalized epileptiform graphoelements as in absence epilepsy (ELF), or reflex or photosensitive epilepsies[11].

Hyperventilation is achieved by asking the subject to breathe deeply and rapidly, at a frequency of 1 Hz for 2-3 min; the maneuver produces a slowing of the baseline activity or the appearance of generalized slow

waves in the theta-delta range. In pathological conditions, abnormal epileptiform graphoelements will appear. The patient should be warned that this exercise may cause dizziness, paresthesias, or a mild transient headache[12].

In the interpretation of a clinical EEG study, the following parameters will be taken into account: (1) temporal organization, how cortical electrical activity is distributed over time; (2) spectral organization, what are the electroencephalographic rhythms present in the recording; (3) topographic organization, how electroencephalographic rhythms are geographically distributed in the skin of the skull; (4) inter-hemispheric symmetry, since there should be no inter-hemispheric amplitude differences > 25% between electrodes of homologous areas; (5) synchrony, since there should also be no inter-hemispheric differences > 50 ms between graph-elements of homologous areas; (6) presence of normal patterns, for example,: hypnogenic hypersynchrony, lambda waves, acute transitions, etc.; (7) presence of abnormal patterns, for example: spikes, sharp waves, slow spikes-waves, spikes-slow waves, etc.

Abnormal items in the EEG log

There are graphoelements in the EEG that are related to pathological conditions. We can highlight: (1) points: elements with an acute cusp, of variable amplitude that usually stand out above the base amplitude, with a duration < 70 ms; when 2 or more are grouped together, they are known as polypoints. (2) Acute waves, elements with a punctiform cusp that last 70-200 ms. (3) Slow spike-wave complexes. Association of a tip with a sine wave with a rounded edge > 200 ms. (4) Polypoint-slow wave: association of 2 or more points with a slow wave. (5) Acute wave-slow wave. Association between a high and a slow wave. (6) Slow waves: presentation of rounded elements > 200 ms that stand out from the base activity, sometimes they are usually grouped into trains or discharges of 2 or more elements. The identification of these elements in the EEG tracing suggests the presence of abnormal activity of neural networks in the cerebral cortex associated with pathologies such as epilepsy.

EEG and polysomnography (PSG) in the study of SD

PSG is the simultaneous recording of the electrical activity of the EEG and various extra-cerebral variables during sleep that help determine the succession of the various phases of sleep (the architecture of the sleep that forms the hypnogram) and other elements that help in the diagnosis of SD. The EEG is usually reduced to the recording of only 2-4 channels of central and occipital regions, in addition, eye movements are recorded to identify non-REM sleep and REM, surface electromyography of the axial musculature (lower lip depressor muscle) and appendicular (tibialis anterior muscles) to determine the movements that accompany wakefulness, sleep apnea, periodic limb movements and bruxism, movements in parasomnias and epileptic seizures, atony in cataplexy and sleep paralysis; nasal airflow, plethysmography of thoracic movements, oxygen saturometry and electrocardiography are also recorded to determine respiratory behavior, its effect on blood chemistry and repercussions on heart rhythm. PSG is one of the most important objective and quantitative diagnostic aids in the study of SD[13].

Methods

A review was carried out according to the PRISMA criteria[14]. The inclusion criteria of the articles were on original EEG articles in some phase of sleep, the exclusion criterion was experimental articles carried out in sleep in animals. The source of information was the basis of the U.S. National Library of Medicine, through PubMed. The search strategy was to use the terms MeSH (medical subjects headings) “electroencephalography” AND “sleep” IN “humans”, 7,473 articles were found. The selection process of articles was based on the title and abstract due to their probable usefulness for the purposes of the review (n = 253 articles). The data extraction process was carried out by downloading and reading the final pertinent articles by each of the researchers, leaving 40 articles (Fig. 2).

Results

Indications of an EEG and PSG study in SD

Insomnia

Although EEG is not indicated for the diagnosis and monitoring of the treatment of these alterations, some research studies have detected a reduction in beta, gamma, and anteroposterior synchronization activity in subjects with acute sleep deprivation[15]. PSG is also not very useful in the diagnosis and management of insomnia since it will only reveal an increase in the time of sleep onset and will only be indicated based on the associated comorbidity[16].

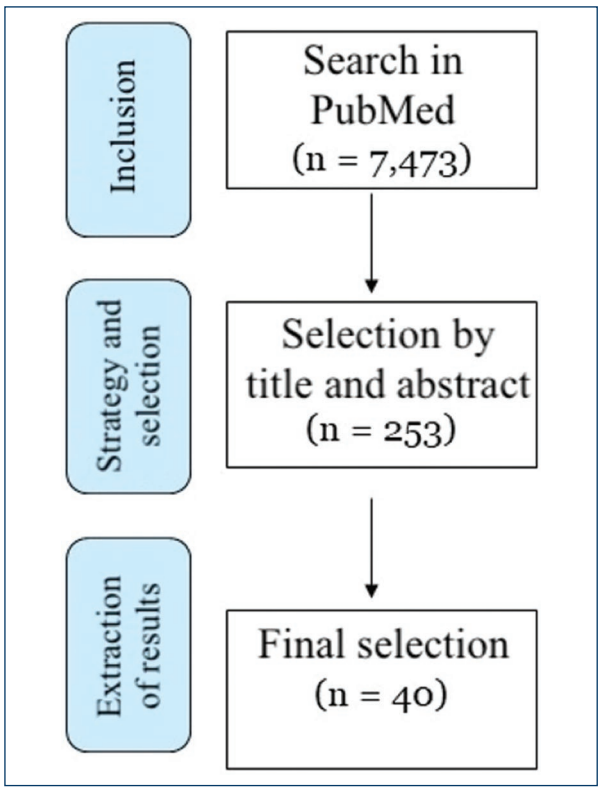

Figure 2. Flowchart of the search for information for the current review.

Sleep-disordered breathing

The EEG is also not indicated for the diagnosis and monitoring of the treatment of these alterations. However, some research studies carried out in patients with obstructive sleep apnea have detected a reduction in beta activity in wakefulness, a reduction in sigma, beta, and gamma activity during non-REM sleep, and an increase in delta activity in REM sleep[17]. However, the PSG is the cornerstone in the identification, diagnosis, classification, and therapeutic monitoring of primary snoring and apnea, both central, obstructive, and mixed.[18] However, of all the sensors used for this study, respiratory variables such as nasal airflow, thoracic respiratory movements, and oxygen saturation are the ones that provide the most information to the SD clinic[18].

Central alterations with hypersomnia

EEG is also not indicated for the diagnosis and monitoring of the treatment of these alterations; although in narcolepsy a lower density of delta potency has been observed during light sleep[19]. In PSG, the study of multiple sleep latencies has been developed, in which the patient is given four brief opportunities to sleep (30 min each) in the morning, measuring the latency to REM sleep. If a latency shortened to active sleep is recorded, then it is considered a positive result to suggest central hypersomnia[20].

Parasomnias

Outbreaks of atypical delta frequency activity have been detected during slow-wave sleep, immediately before or during an episode of pseudo-awakenings, for example, in non-REM parasomnia such as night terrors or sleepwalking[21]. However, EEG is not routinely indicated for the evaluation of these disorders. However, in PSG, an increase in latency to REM and non-REM sleep has been observed, as well as a reduction in the N1 and N2 states in a non-specific manner[22]. In REM parasomnias such as sleep paralysis, muscle atony has been documented in episodes of paralysis[23], while in REM sleep behavior disorder; tone leakage and increased activity of electromyography activity are reported, associated with bizarre behavior during REM sleep[24]. In all these parasomnias, the events that characterize each of them can be recorded objectively and simultaneously on video recording.

Disorders of circadian sleep-wake rhythm

EEG is not very useful in these disorders; however, in irregular sleep rhythm disorder, an interhemispheric dyssynchrony between sleep spindles has been reported[25]. In PSG, in the disorder of advanced and delayed phase of sleep, the architecture of sleep is adequate, only that the time of sleep onset responds to the patient's rest schedules, which occur at times that are out of step with those socially accepted[26]. In shift work disorder, alterations in sleep onset time, total sleep time, and sleep efficiency are reported in patients with these disorders[27].

Sleep-related movement disorders

In restless legs syndrome (RLS) and periodic limb movement disorder during sleep (PLMD), the presence of an alternating cyclical pattern has been reported[28] However, in general terms, EEG recording is not indicated in the evaluation of sleep-associated motor disorders. In PSG, sleep latency is prolonged, leg movements may be noticed when awake or shortly before the onset of sleep accompanied by increased activity of the appendicular muscles. There are usually

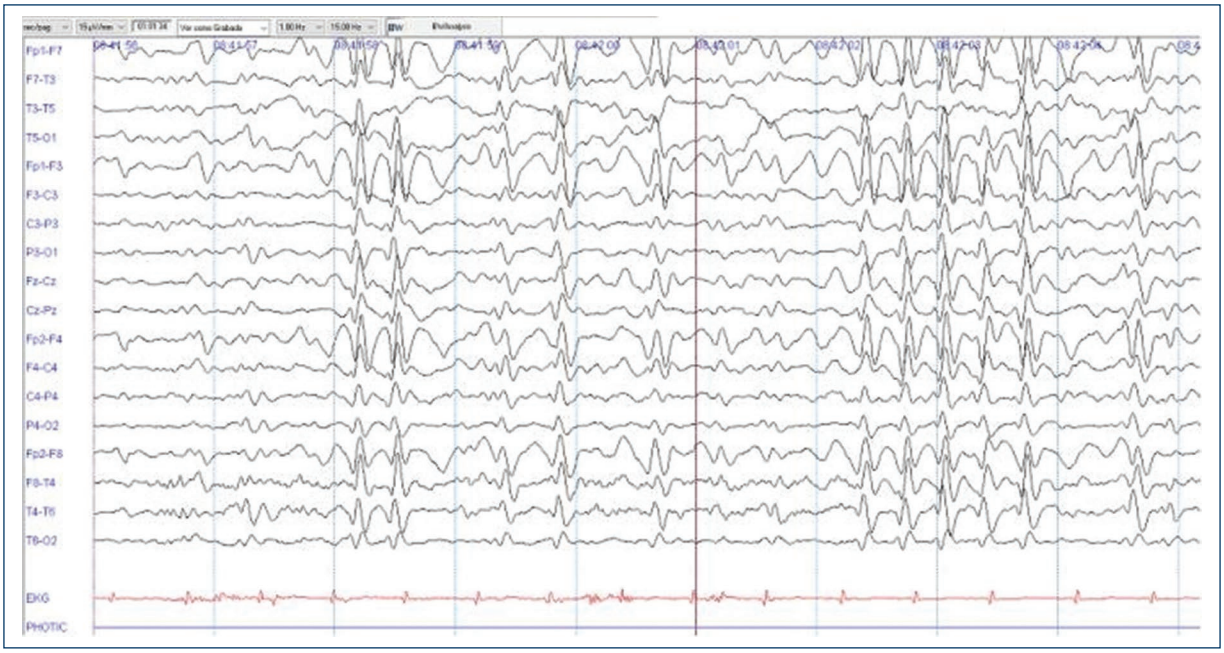

Figure 3. Example of an electroencephalographic tracing of an epoch of 10 s in the N2 phase of sleep, in superior and inferior longitudinal assembly, right and left, showing two isolated tips that stand out from the base activity due to a left temporal-parietal phase inversion (between T3-T5/T5-O1 and C3-P3/P3-O1 electrodes), which presented a patient with focal temporal lobe epilepsy as an example of focal epilepsy.

several nighttime awakenings with long latency to restart sleep[29]. The rate of periodic limb movements in the sleeping state is increased to > 5 movements/hour, which supports the diagnosis of PLMD. A frequent association of RLS with PLMD can be found in the order of 70-90%. RLS and PLMD will produce morning sleepiness due to the alteration of sleep continuity. In nocturnal bruxism, an increase in rhythmic muscular masticatory activity is observed during sleep during various sleep states and is accompanied by micro-awakenings and therefore occurs with excessive daytime sleepiness, as well as pain and dental wear[30].

Sleep-related medical and neurological disorders

Epilepsies. Several types are favored by sleep in the N1 and N2 states because they increase the synchronization of the neural networks that produce the characteristic K complexes and sleep spindles and at the same time synchronize the abnormal epileptogenic tissue[31]. These include frontal lobe FLE, temporal lobe TLE, benign childhood epilepsy with centrotemporal spikes, benign BEOS with occipital tips BCECT, juvenile myoclonic ELF, generalized tonic-clonic seizures on awakening BEOS, West syndrome, Lennox-Gastaut syndrome, Landau-Kleffner syndrome, and continuous spike epilepsy during non-REM sleep (CSEnREM).

FLE. As the frontal lobe is the largest and contains numerous areas associated with various brain functions, including the primary motor and associative areas, eye movements, the motor area of language, for example, the FLE can present several symptoms of various modalities such as generalized tonic-clonic seizures, complex partial seizures, paroxysmal nocturnal pseudo-awakenings, paroxysmal nocturnal dystonia, paroxysmal nocturnal wandering, or sleep-related hypermotor seizures[32]. The interictal EEG pattern in wakefulness and sleep presents as spikes or slow wave-onset in the frontal and central regions that may evolve into a generalization of abnormal activity (Fig. 1).

TLE. The temporal lobe is also associated with various functions, but the clinical expression during sleep is less until the crisis is generalized. Seizures that come from deep regions such as the amygdala can be associated with complex partial seizures with bizarre behavior during the night[33]. Interictal EEG abnormalities can be observed in wakefulness and sleep in temporal leads with a tendency to generalization (Fig. 3).

BCECT. It presents as focal seizures characterized by ocular deviation, facial contractures, and vomiting that can produce rapid generalization. In the natural

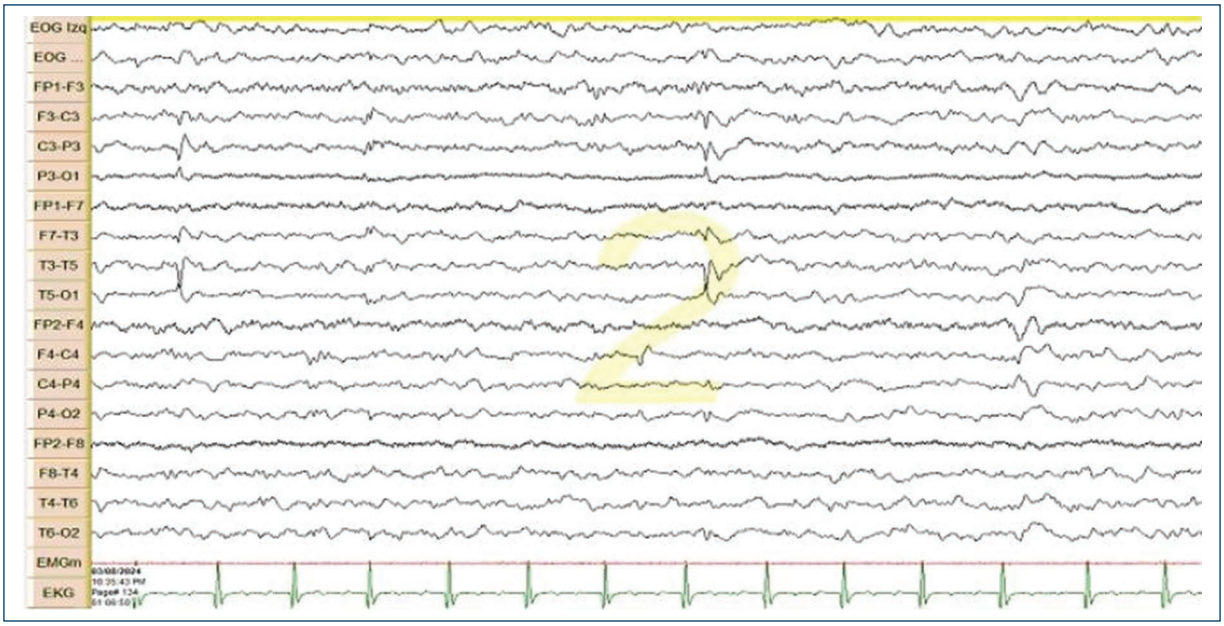

Figure 4. Example of a 10-s electroencephalographic tracing in the N2 sleep phase, in upper and lower, right and left longitudinal assembly showing slowed base activity, with scarce, asymmetrical and poorly organized sleep spindles and with brief outbreaks of 1-2 s, with generalized slow spike-wave complexes in a patient with Lennox-Gastaut syndrome as an example of generalized epilepsy.

history of the disease, this alteration evolves into remission of the problem in a benign form. One of its main triggers is sleep deprivation. In the interictal EEG in wakefulness and sleep, it is observed that the abnormalities come from the central leads. Most seizures occur quickly after sleep or in the early morning hours[34].

BEOS. It is a common epilepsy in childhood. Clinical presentation includes visual hallucinations, gaze deviation, and vomiting or discomfort induced primarily by flashes of light or from the television, computer, video games, or a screen phone. In this condition, spikes in the parieto-occipital and temporo-occipital leads are observed on the interictal EEG in wakefulness and light sleep. These alterations usually increase during intermittent light stimulation[35].

JME. It is a hereditary condition characterized by the presence of myoclonic seizures with synchronous daytime shaking without loss of consciousness, some absence seizures, and generalized seizures. Myoclonic and generalized seizures frequently occur on awakening, they have a tendency to increase due to photosensitivity. It usually begins in adolescence. A characteristic generalized polyspike-slow wave pattern is usually observed on the interictal EEG, in wakefulness and sleep[36].

West syndrome. It is a severe epileptiform encephalopathy that occurs in the 1st year of life. It consists of three main features: epileptic spasms, delayed psychomotor development, and a characteristic abnormal EEG pattern during sleep known as hypsarrhythmia (from Greek: *hypsos* = vertex, *a* = sin, *rhythmos* = rhythm). In the interictal EEG in sleep, the baseline activity is abnormal with the presence of generalized high-voltage slow waves, multifocal spikes, and poor inter- or intra-hemispheric coherence alternating with short periods of voltage depression[37].

Lennox-Gastaut syndrome. It is another encephalopathy condition present in childhood. It is characterized by a delay in psychomotor development, clonic, myoclonic, atonic epileptic seizures, and atypical absences, EEG with generalized slowing, and multifocal and generalized epileptiform elements. During interictal EEG recording in sleep, slowed background rhythm is observed with the presence of paroxysmal rapid activity, spikes, spike-wave complexes, and multifocal slow waves (Fig. 4)[38].

CSEnREM. The abnormality initially presents as a delay in language development without motor alterations (Landau-Kleffner syndrome), generalized seizures may be observed in wakefulness. Subsequently, it is usually accompanied by significant motor, language,

and cognitive impairment. In the EEG in sleep presents persistent generalized slow spike-wave complexes persistent during deep sleep without adequate organization of the initial phases of sleep[39].

SDs induced by substance use

Anti-epileptic drugs can produce an increase in diffuse rapid activity of medium voltage[40,41]. Various antidepressants can cause voltage depression and increased rapid rhythms[42,43]. Computerized EEG analysis has been used to evaluate the alterations caused by the abuse of alcohol, nicotine, cannabinol, cocaine, opiates, and amphetamines, among other substances. Abnormalities of intrinsic activity, neural hyperactivation, and decreased neuronal communication between specific brain regions have been found. These alterations show partial recovery with abstinence[44,45].

Conclusion

The EEG/PSG has proven to be a very useful para-clinical auxiliary tool in the evaluation of SD as it helps in the identification of various SDs and in the classification of various classes of sleep-associated epilepsies. It can also help to identify candidates for the use of non-invasive ventilation and the drugs necessary for its treatment. Other utilities are manifested in the study of wake/sleep rhythm and related research.

The spectral analysis of the EEG and the measurement of cortical connectivity will be useful tools in the near future for the evaluation of SD in which the EEG has had a lower use, such as in the study of insomnia, sleep-disordered breathing, hypersomnias, parasomnias, circadian rhythm disorders, and sleep-associated movement disorders.

Another useful use may be in the investigation of the pathophysiological mechanisms and effects of pharmacological and non-pharmacological treatment in SD.

As SD medicine is a relatively new and developing specialty, EEG can be used in the identification and description of new SDs and sleep-associated epilepsies.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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Status of medical articles on religion and spirituality from past to present

Hüseyin Çaksen

Department of Pediatrics, Divisions of Pediatric Neurology and Genetics and Behavioral-Developmental Pediatrics, Faculty of Medicine, Necmettin Erbakan University, Meram, Konya, Türkiye

Abstract

In this article, we have evaluated the status of medical articles related to religion and spirituality published in the last 50 years in the literature to determine the distribution of studies on religion and spirituality by the major religions in the world and decades. There was a continuous increase in the number of articles related to "religion, religious, spiritual, or spirituality," and the major religions including Islam, Christianity, Judaism, Buddhism, and Hinduism except for Sikhism from 1971-1980 to 2011-2020. A continued increase was also noted in the number of articles on the Quran and the Bible, but not on "Hebrew Bible." Furthermore, the articles related to Islam and Buddhism showed the highest increase among the major religions. In conclusion, religion and spirituality have been linked to medicine for centuries. Religion and medicine are inseparable because religion is the very life of life, its light, and its basis. We believe that medical articles on religion and spirituality will increase significantly over the next decade as faith is on the rise around the world.

Keywords: *Medicine. Article. Religion. Spirituality.*

Introduction

Religion is an "explanation of the ultimate meaning of life, and how to live accordingly, based on some notion and experience of the transcendent." Each religion has four "C's": Creed (the "explanation of life"); Code (of behavior and ethics); Cult (actions relating the believer to the transcendent); Community structure (monarchical, republican, individualistic, etc.)[1]. Spirituality in its general meaning is the quality or state of being spiritual or being attached to questions and values concerned with religion. Spirituality is defined as the presence of a relationship with Allah that affects the individual's self-worth, sense of meaning, and connectedness with others[2].

Religion and spirituality have been linked to medicine and healing for centuries. However, in the early 1900s, the Flexner report noted that there was no place for religion in medicine; that medicine was strictly a scientific field, not a theological or philosophical one. In the mid to latter 1900s, there were several lay movements that started emphasizing the importance of religion, spirituality, and medicine. Lay religious movements found spiritual practices and beliefs to be important in how people cope with suffering and find inner healing even in the midst of incurable illness. Since the 1960s there has been increased research done in the area of religion and health and spirituality and health[3]. In this article, we have evaluated the status of medical articles related to religion and spirituality published in the last 50 years in the literature to determine the distribution of studies on religion and spirituality by the major religions in

Correspondence:
Hüseyin Çaksen
E-mail: huseyincaksen@hotmail.com

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Table 1. Distribution of articles on religion and spirituality listed on Pubmed

Articles between	Keywords	
	Religion OR religious OR spiritual OR spirituality	
	No.	%
1971 and 1980	1,209	1.9
1981 and 1990	3,591	5.7
1991 and 2000	7,371	11.7
2001 and 2010	13,226	20.9
2011 and 2020	24,602	39.0
2021 and 2023	13,150	20.8
Total Articles	63,149	100.0
Percentage of increase from 1971-1980 to 2011-2020		2,035

Table 2. Distribution of articles by the major religions in the world listed on Pubmed

Articles between	Keywords											
	Islam OR Muslim		Christianity OR Christian		Judaism OR Jewish		Buddhism OR Buddhist		Hinduism OR Hindu		Sikhism OR Sikh	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1971 and 1980	86	1.3	459	5.5	436	4.5	15	0.9	70	4.4	9	3.3
1981 and 1990	342	5.2	798	9.6	911	9.5	97	6.1	157	9.9	44	16.2
1991 and 2000	620	9.4	1,357	16.3	1,802	18.7	146	9.1	195	12.3	32	11.8
2001 and 2010	1,154	17.6	1,574	18.9	2,541	26.4	361	22.6	304	19.1	53	19.5
2011 and 2020	2,872	43.7	2,720	32.7	2,880	29.9	684	42.8	586	36.9	97	35.7
2021 and 2023	1,492	22.7	1,411	17.0	1,050	10.9	296	18.5	273	17.2	37	13.6
Total Articles	6,566	100.0	8,319	100.0	9,620	100.0	1,599	100.0	1,589	100.0	272	100.0
Percentage of increase from 1971-1980 to 2011-2020		3339.5		592.6		660.6		4560.0		837.1		1077.8

the world and decades. To the best of our knowledge, this is the first study about this subject in the literature.

Methods

In this study, articles related to religion and spirituality, listed on Pubmed between 1971 and 2023, were searched using the keywords "Religion OR religious OR spiritual OR spirituality." The keywords "Islam OR Muslim," "Christianity OR Christian," "Buddhism OR Buddhist," "Hinduism OR Hindu," and "Sikhism OR Sikh" were used to search for major religions. Regarding the Holy Books, the keywords "Quran OR Qur'an OR Koran," "Bible OR Gospel" OR "New Testament" and "Hebrew Bible" OR Torah OR "Old Testament" were used. "Tanakh" used as a synonym for "Hebrew Bible" was also searched on Pubmed, but no result was found. Religions sent by Allah through prophets to lead people from heresy to guidance are called Divine religions. Today, only Islam, Christianity, and Judaism among the Divine religions, continue to exist[4]. Although true religion cannot be of human origin[3], articles on major human religions such as Buddhism, Hinduism, and Sikhism were also included in our study.

Table 3. Distribution of articles by the Holy Books in the world listed on Pubmed

Articles between	Keywords					
	Quran OR Qur'an OR Koran		Bible OR Gospel OR "New Testament"		"Hebrew Bible" OR Torah OR "Old Testament"	
	No.	%	No.	%	No.	%
1971 and 1980	14	3.5	59	5.3	13	6.5
1981 and 1990	13	3.2	101	9.0	24	12.1
1991 and 2000	42	10.4	222	19.8	41	20.6
2001 and 2010	60	14.9	292	26.1	58	29.1
2011 and 2020	186	46.3	321	28.7	44	22.1
2021 and 2023	87	21.6	126	11.3	19	9.5
Total Articles	402	100.0	1,119	100.0	199	100.0
Percentage of increase from 1971-1980 to 2011-2020		1328.6		544.1		338.5

Results

The distribution of articles on religion and spirituality listed on Pubmed by the major religions in the world and decades is seen in tables 1-3. There was a continuous increase in the number of articles related to "religion, religious, spiritual, or spirituality," and the major religions including Islam, Christianity, Judaism, Buddhism, and Hinduism except for Sikhism from 1971-1980 to 2011-2020. Regarding the Holy Books, a continued increase was noted in the number of articles on the Quran and the Bible, but not on "Hebrew Bible" from 1971-1980 to 2011-2020. Furthermore, articles related to Islam and Buddhism showed the highest increase among the major religions.

Discussion

Since ancient ages, human beings have tried to examine and evaluate the relationship between spirituality, religion, and medicine[5]. In fact, religion and medicine are no strangers. They have a long, intertwined, tumultuous history, going back thousands of years. Only within the past 200-300 years have these twin healing traditions been clearly separate. The physical disease was understood largely in religious or spiritual terms until several hundred years ago[6]. Nowadays, physicians are not well-prepared to deal with the patient's psychological experience of illness, particularly in situations where medical treatments are not working and both doctor and patient feel helpless against the relentless advance of the disease. It is in such situations that religion has provided comfort and hope for millennia[6]. The interface of spirituality, quality of life, and mental health is fascinating and sublime religion and spirituality particularly play an essential role in the caregiving of patients with terminal illnesses and chronic medical conditions[5]. In addition, awareness of our patients' spiritual or religious beliefs helps us to be more aware of our own motivations, as spirituality and religion are important components that shape the behaviors of many clinicians[7].

Religion has existed since the first man and the first Prophet Adam (Alayhi As-Salam) and will continue until the Day of Judgment. Religion is the most fundamental social institution, and, in one form or another, will always be a part of social life. Today faith is on the rise and 85% of people around the globe identify with a religion[8,9]. On the other hand, studies in the 21st century suggest that, in terms of percentage and worldwide spread, Islam is the fastest-growing major religion in the world[10]. In parallel with the increase in religious belief in the world's population, we have found that the number of articles on religion and spirituality markedly increased in the medical literature in the last decades. Based on the number of articles between 2021 and 2023, it can easily be said that articles on religion and spirituality will increase much more in the next decade.

Conclusion

Religion and spirituality have been linked to medicine for centuries. Religion and medicine are inseparable because religion is the very life of life, its light, and its basis[11]. Our findings showed that medical studies about

religion, spirituality, and the major religions including Islam, Christianity, Judaism, Buddhism, and Hinduism except for Sikhism continuously increased from 1971 to 2020. The articles related to Islam and Buddhism showed the highest increase among the major religions. We believe that medical articles on religion and spirituality will increase significantly over the next decade as faith is on the rise around the world.

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Conflicts of interest

The author declares that he has no conflicts of interest.

Ethical considerations

Protection of humans and animals. The author declares that no experiments were performed on humans or animals for this study.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The author declares that no generative artificial intelligence was used in the writing of this manuscript.

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CLINICAL CASES

Genital reconstruction and urethral plasty after Fournier's gangrene and urethral fistula

Hugo Rivera Astorga[1]*, *Ma. del Pilar Vazquez-Tabares*[2], *Paulina L. León-López*[2], *Francisco J. Hernández-Calderón*[1], *Ángel Gurrola-Ortega*[1], *Jorge Jaspersen-Gastelum*[1], *José F. Virgen-Gutiérrez*[1], *Eloy Rico-Frontana*[1], *and Cesar A. Rivera-Colín*[3]

[1]*Department of Urology, Hospital General de México, Secretaría de Salud;* [2]*School of Medicine, Universidad Justo Sierra;* [3]*Faculty of Medicine, Universidad Nacional Autónoma de México, Mexico City, Mexico*

Abstract

Fournier's syndrome is necrotizing fasciitis of the soft tissues of the perineum. Diagnosis is clinical, and treatment involves stabilization, antibiotics, and debridement of necrotic tissue, which can lead to esthetic and functional sequelae that may be corrected later. A 62-year-old male presents for genital reconstruction due to post-Fournier gangrene penile scarring with an inter-scrotal urethrocutaneous fistula. A term-to-term urethral plasty, bilateral testicular descent, and penile ascent are performed. The available information on reconstructive surgery for external genitalia following Fournier's gangrene is insufficient to establish a standard approach.

Keywords: *Fournier's gangrene. Urethral fistula. Genital reconstruction. Urethral plasty.*

Introduction

Fournier's syndrome is described as necrotizing fasciitis of the soft tissues of the external genital organs, the perianal region, the perineum, and sometimes the abdominal wall, leading to thrombosis of the subcutaneous vessels and necrosis of the adjacent skin[1], caused by a polymicrobial infection generated by aerobic and anaerobic bacteria. In which the following stand out: *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus*, *Klebsiella*, *Streptococcus* species, *Staphylococcus aureus*, *Enterococcus*, *Clostridia*[2-4].

It affects both sexes, with a male predominance in a 10:1 ratio; it is present in all ages, although it is reported more in patients over 50 years of age with a history of diabetes mellitus, acquired human immunodeficiency syndrome, alcoholism, genitourinary infections, malignancies, and liver and kidney diseases[5]. This surgical emergency has an incidence of 1.6 cases/100,000 inhabitants, and its mortality exceeds 40% due to septic shock[6,7]. It is associated with other etiologies such as anal abscesses, hemorrhoidal pathology, anal fistulas, and rectal carcinomas[2,5].

The diagnosis is mainly clinical, and X-ray, ultrasound, computed tomography, and magnetic resonance imaging are used for initial evaluation and exclude diagnoses such as scrotal abscess, balanitis, pyoderma gangrenosum, polyarteritis nodosa, and ecthyma gangrenosum[2,3]. Treatment is based on hemodynamic stabilization, administration of broad-spectrum antibiotics, and surgical debridements that

***Correspondence:**
Hugo Rivera-Astorga
E-mail: hugolch_9@hotmail.com

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result in a substantial loss of tissue that will be corrected later with reconstructive procedures such as primary closure, scrotal advancement flaps, fasciocutaneous flaps, myocutaneous flaps, testicular transposition, skin grafts and phalloplasty[8,9]. The reconstruction of this type of patient due to the characteristics of the tissues is extremely complex and not only depends on the skill and resources of the surgeon but also on the binomial.

Case report

A 62-year-old male patient, originally a resident of the State of Mexico, with no chronic degenerative history. With a history of obstructive prostatic growth that does not respond to medical treatment (α-blocker). It was decided to perform transurethral resection of the prostate with a noticeable lesion from the urethra to the rectum (urethrorectal fistula) and subsequent Fournier's gangrene, requiring surgical washing, debridement of the external genitalia, and intestinal diversion with colostomy of the descending colon. The patient continued with conservative treatment until the wound was closed by second intention, presenting genital dysmorphism (public testicles and penile descent) and urethrocutaneous fistula (Fig. 1).

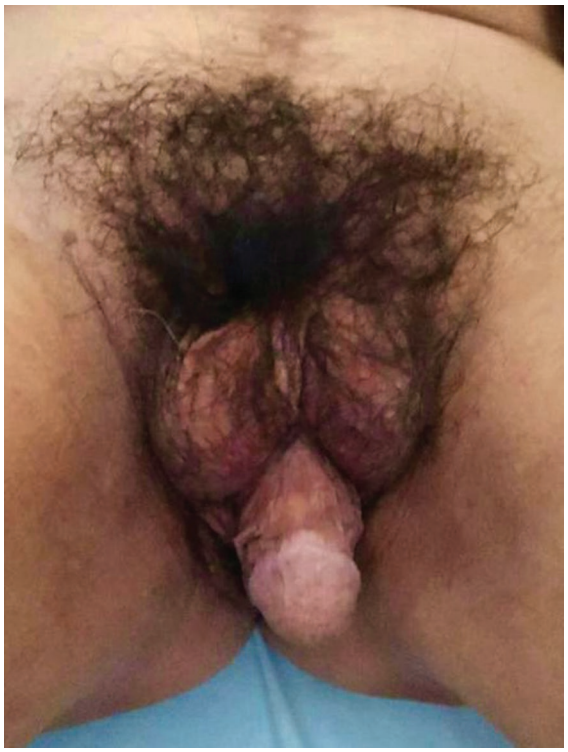

Figure 1. Post-Fournier scarring of the lower penis to the testicles.

The patient underwent a scheduled surgery in which the suspensory ligament was released, preserving the dorsal neurovascular complex, with penile ascent and bilateral testicular descent (Fig. 2), in addition to anterior urethral plasty by primary closure in two planes, with foreskin closure in one plane and scrotum flap and terminal urethral plasty simultaneously (Fig. 3). The transurethral catheter was preserved for 4 weeks with subsequent spontaneous urination and no evidence of leakage in the ventral region of the penis. He presented an adequate transoperative and post-operative evolution with remission of urethrocutaneous fistula as well as adequate scarring and improvement of the appearance of the male external genitalia, in addition to preservation of erectile function, assessed by the International Index of Erectile Function-5 scale (Figs. 4 and 5).

Discussion

The reconstruction of the male genital area is complex due to its anatomy and the considerations that are made to preserve its functionality. Lesions after Fournier's gangrene represent a greater surgical challenge, which increases with the number of structures affected (decreases the success of the procedure). To increase the success rate of surgery, it is important that unfavorable factors such as ischemia, infection, and fibrosis are reduced.

Early and repeated debridement is a measure to treat Fournier's gangrene, adequate resection of non-viable tissues determines patient survival, and a window of adjacent healthy tissue should be included to limit infection[10]. Before reconstructive surgery, bacterial cultures should yield negative results, and if not, antibiotic therapy should be given depending on the microorganism that is colonizing the tissue[11]. It is also important to follow the basic principles of reconstructive surgery, such as tension-free, ischemia-free, and infection-free sutures. Moreover, maintaining the use of foreign bodies (transurethral catheter) for as little time as possible. Calderón in 2021[12] specified that for wounds with 2 cm involvement, it is more likely to achieve coverage by primary closure or partial skin grafts, while larger defects with 4-5 cm involvement will require fasciocutaneous or musculocutaneous flaps for coverage.

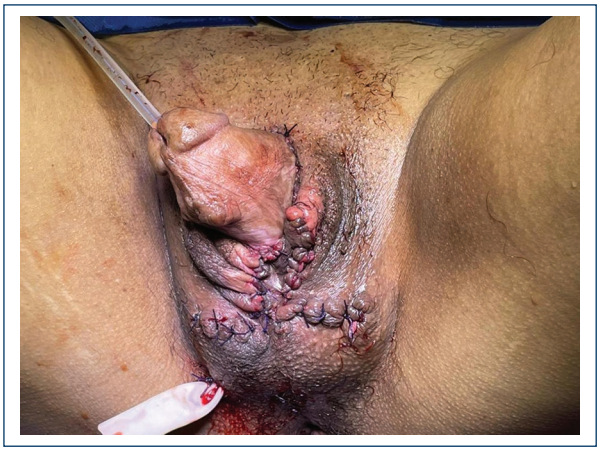

Figure 2. Release of the suspensory ligament preserving the dorsal neurovascular complex, with penile ascent and bilateral testicular descent.

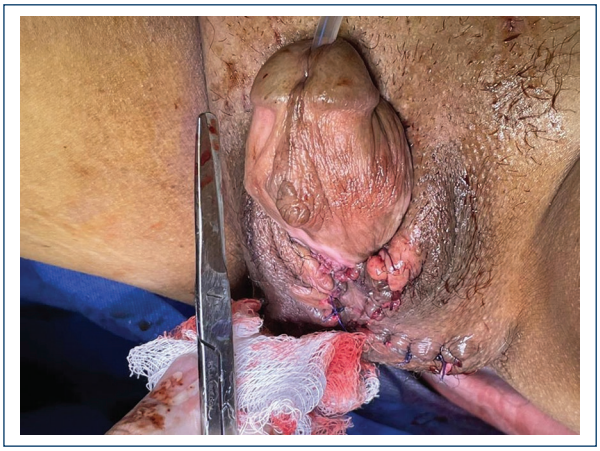

Figure 3. Urethral plasty, testicular descent, and Dartos flap.

Therapeutic procedures for Fournier syndrome cause esthetic and functional sequelae in the perineum area and even the abdomen. Reconstructive surgeries are chosen according to the properties of each case, considering: location, depth, size, function of the affected structures, and tissue arrangement[9,10,13]. Singh, in 2016, described the characteristics for the best results in a Fournier post-gangrene genital reconstruction surgery: a single procedure, preservation of function, natural appearance of the wound, minimal post-operative complications, and primary wound closure. The use of vacuum-assisted closure to increase the probability of graft engraftment demonstrated a positive effect on healing because it reduces the engraftment time and favors the vascularity of the lamina[12].

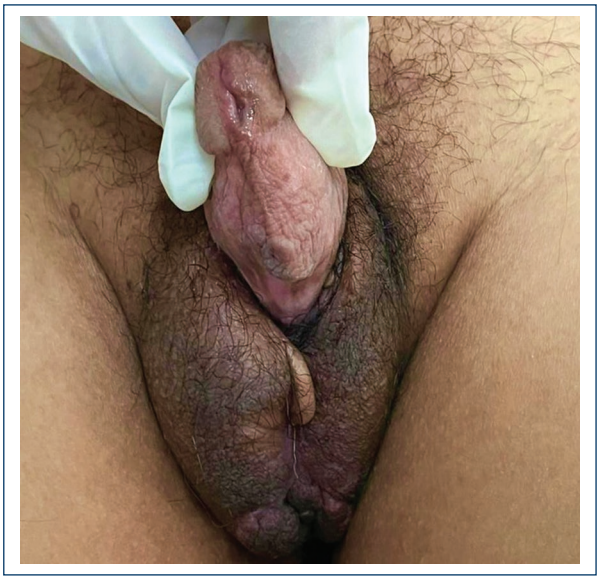

Figure 4. Penis after surgical reconstruction.

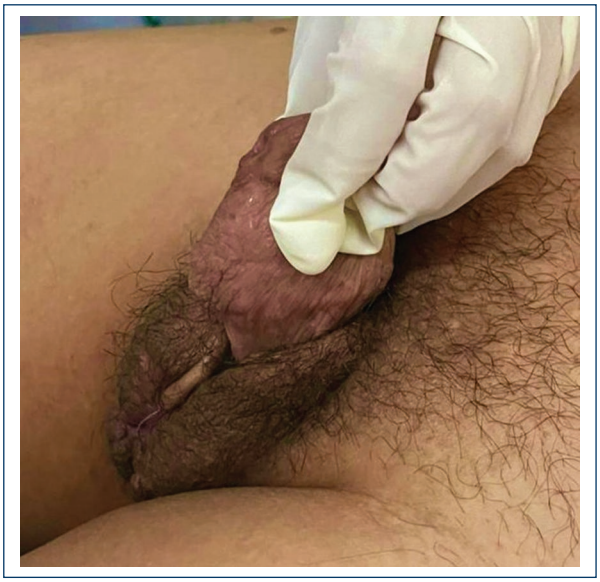

Figure 5. Adequate transoperative and post-operative evolution with remission of the urethrocutaneous fistula as well as adequate healing.

Conclusion

The information reported on reconstructive surgery of the external genitalia after Fournier's gangrene, associated with urethral lesions and its management, is insufficient to establish a standard approach since variables such as associated urethral lesions and patient comorbidities must be considered. In addition to considering that the characteristics of the tissue

make it an extremely complex intervention in which the surgeon's resources, skill, and experience have a great influence.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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CLINICAL CASES

Thoracoscopic esophagectomy with gastric pull-up in megaesophagus secondary to terminal achalasia

Rafael Rivera-Avalos, Verónica Rojas-Hernández, César G. Rojas-Benítez, Ernesto Castellanos-Flores, Francisco R. Higuera-Hidalgo, and Agustín Etchegaray-Dondé*

Upper Digestive Tract Clinic, Hospital General de México Dr. Eduardo Liceaga, Secretaría de Salud, Mexico City, Mexico

Abstract

In terminal achalasia, the presence of a megaesophagus with loss of axis in its distal third or persistence of symptoms despite multiple previous treatments, the esophagectomy by thoracoscopy with reconstruction by laparoscopic gastric ascent and cervical anastomosis (McKeown or 3-field esophagectomy) is a feasible and safe option that has managed to reduce morbimortality secondary to the intervention. We present the case of a 69-year-old patient with megaesophagus secondary to terminal achalasia and describe the surgical management and post-operative evolution.

Keywords: *Terminal achalasia. Megaesophagus. Thoracoscopic esophagectomy. Gastric pull-up. McKeown.*

Introduction

Achalasia is a chronic, progressive, idiopathic esophageal motor disorder characterized by the loss of primary peristalsis and the inability of the lower esophageal sphincter to relax in response to swallowing. A decrease in the number of ganglion cells in the myenteric plexuses has been observed in several surgical specimens, which preferentially affects the inhibitory neurons that produce nitric oxide that influences the relaxation of esophageal smooth muscle[1,2].

It has an estimated annual incidence of 1.6 cases/100,000/year. The most common symptoms are dysphagia, regurgitation, retrosternal pain, weight loss, and respiratory symptoms that can lead to aspiration pneumonia. An incidence of achalasia squamous cell carcinoma is estimated at 312.4 cases/100,000 patient-years[2].

Treatment aims to reduce the pressure gradient through the lower esophageal sphincter and improve gravitational esophageal emptying to alleviate symptoms. Pneumatic dilation and surgical myotomy are the first-line treatment modalities. In the absence of treatment or inadequate management, approximately 5% of patients develop terminal disease, which is characterized by progressive dilation with increased tortuosity of the esophagus[3,4]. Esophagectomy is indicated in patients with persistent or recurrent achalasia after the failure of less invasive treatments and who have developed a tortuous and dilated esophagus with deviation of its axis[5,6].

Case presentation

A 69-year-old woman was taken to the emergency room of our institution for presenting painless and

***Correspondence:**
Rafael Rivera-Avalos
E-mail: rafaelgaleano98@gmail.com

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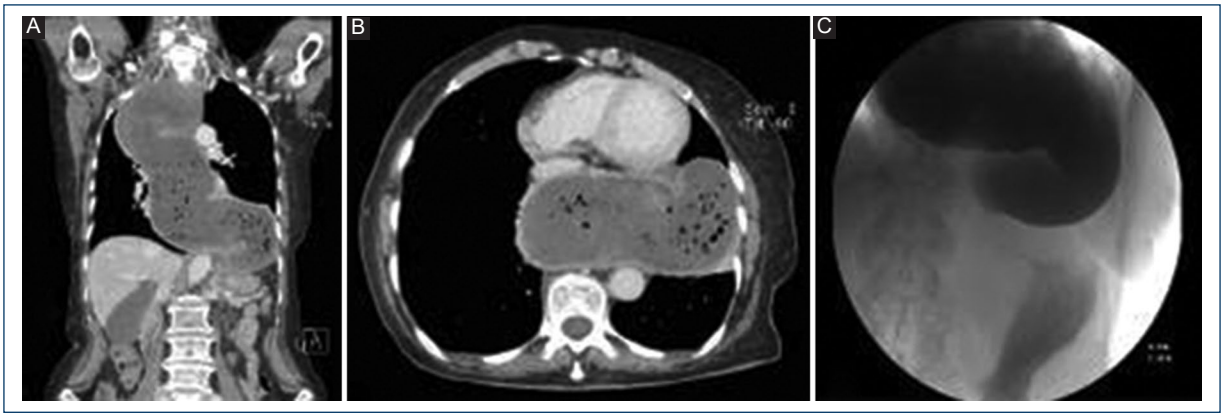

Figure 1. A: coronal section of computed tomography showing tortuous dilated esophagus with loss of axis with respect to the diaphragmatic hiatus and narrowing at the level of the esophagogastric junction. **B:** axial section showing markedly dilated megaesophagus occupying a large part of the left hemithorax. **C:** esophagogastric series with water-soluble contrast medium showing dilated esophagus of sigmoid aspect with filiform passage of the contrast medium into the stomach. Note the loss of the vertical axis.

progressive dysphagia to solid and liquid foods that began 11 years ago, which leaves her free evolution until total intolerance to the oral route. Dyspnea and unintentional weight loss of approximately 16 kg in 2 years were added, along with the appearance of a mass in the left cervical region, which is why she was evaluated by the otorhinolaryngology service, who requested a chest X-ray in which there was evidence of a mediastinal tumor with a hydro-aerial level. A thoraco-abdominal tomography is indicated in which a dilated esophagus with a diameter of up to 14.3 mm is observed at the retrocardiac level from the pharyngeal portion to the esophageal-gastric junction where its luminal diameter is abruptly reduced, the interior occupied with gastro-food residue throughout the trajectory causing anterior displacement and extrinsic compression of the trachea and anterior displacement of the cardiac silhouette. Corresponding to megaesophagus (Fig. 1A and B).

Physical examination showed oxygen saturation of 84% in room air, tachycardia, cachectic complexion with a body mass index of 18.6 kg/m^2 and at the left cervical level, a tumor of approximately 7 × 5 cm, soft, not painful. A 20 Fr nasogastric tube was placed for aspiration and emptying of food remains in the esophagus and to perform panendoscopy, however, after 3 attempts, it was not possible to complete the study due to the presence of pronounced angulation of the esophagus in its middle third that made it difficult for the endoscope to pass, observing significant esophageal dilation and esophagitis due to stasis.

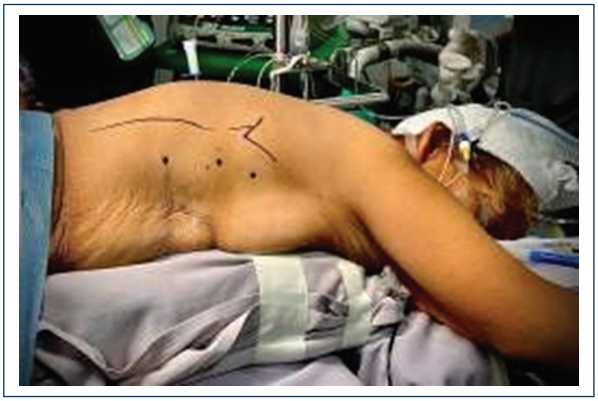

Figure 2. Semiprone decubitus position. Delimitation of the posterior axillary line and placement of the trocars in the 4th, 6th, and 8th intercostal spaces.

An esophagogastric series with water-soluble contrast was performed, where elongation of the esophagus was observed with a tortuous path (with a "sigmoid" appearance) and gradual luminal decrease at the level of its distal third, acquiring a bird's beak appearance that barely allowed the filiform passage of the contrast medium to the stomach, suggesting achalasia (Fig. 1C). Without the possibility of performing esophageal manometry, it was decided to perform a serological test to rule out Chagas disease, which was negative.

At the biochemical level, protein-calorie malnutrition and hydroelectrolyte imbalance were evident, so a central venous catheter was placed to initiate total parenteral nutrition for 2 weeks before the surgical procedure.

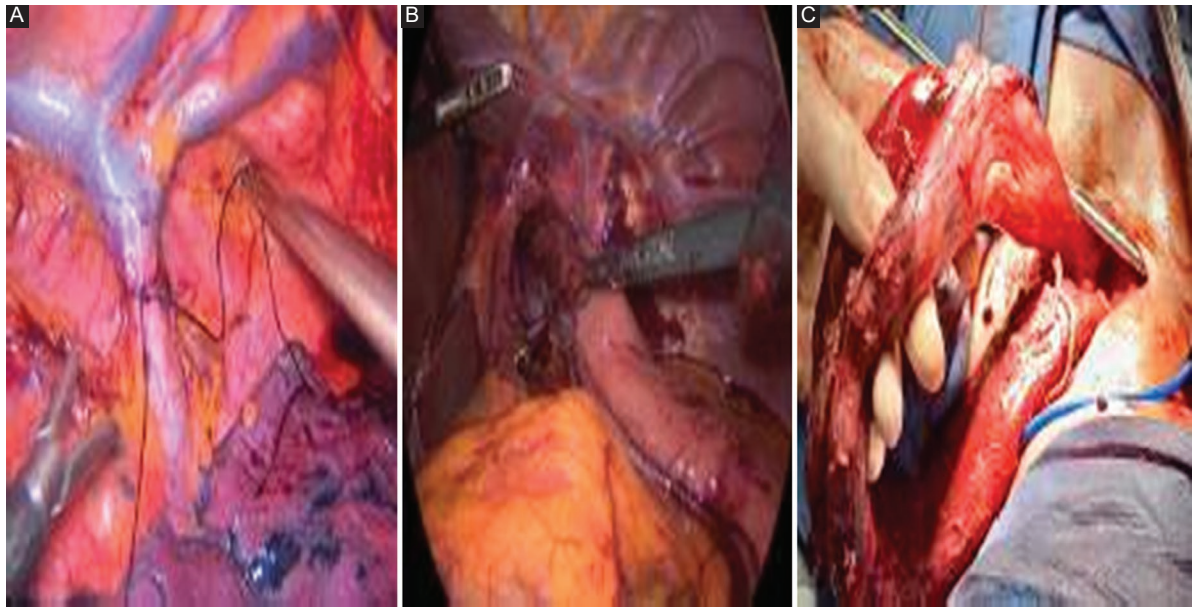

Figure 3. A: ligation of the azygos vein during thoracoscopy to allow complete dissection of the esophagus. **B:** formed gastric tube approximately 4 cm wide being directed toward the diaphragmatic hiatus. During the ascent, it must be ensured that the stapling line is kept on the right side avoiding its torsion. **C:** dilated esophagus exteriorized by left cervical incision.

In view of the imaging findings and having evaluated and ruled out other treatment alternatives, it was decided to proceed with esophagectomy and gastric ascent using a minimally invasive approach.

Initially, thoracoscopic esophagectomy was performed in the semi-prone position (Fig. 2) observing distortion of the anatomy at the thoracic level with an esophagus approximately 10 cm dilated with increased vascularity and periesophageal inflammation, as well as multiple adhesions to the right lung and mediastinal pleura. An adequate dissection was performed from the thoracic operculum to the diaphragmatic hiatus (Fig. 3A). During the second stage and after placing the patient in dorsal decubitus in a French position, laparoscopy was performed to begin with the dissection of the gastrocolic ligament, preserving the right gastroepiploic arch that will supply the gastric tube. By means of an articulated linear stapler, a gastric tube of approximately 4 cm wide with the greatest curvature is formed (Fig. 3B). At the same time, a left cervical incision of approximately 5 cm was made using a third approach to access and dissect the cervical esophagus (Fig. 3C). Once the gastric tube has been made and the abdominal hiatal dissection has been completed, the cervical esophagus is tractioned, externalizing the thoracic megaesophagus through the incision in the neck until the neoesophagus

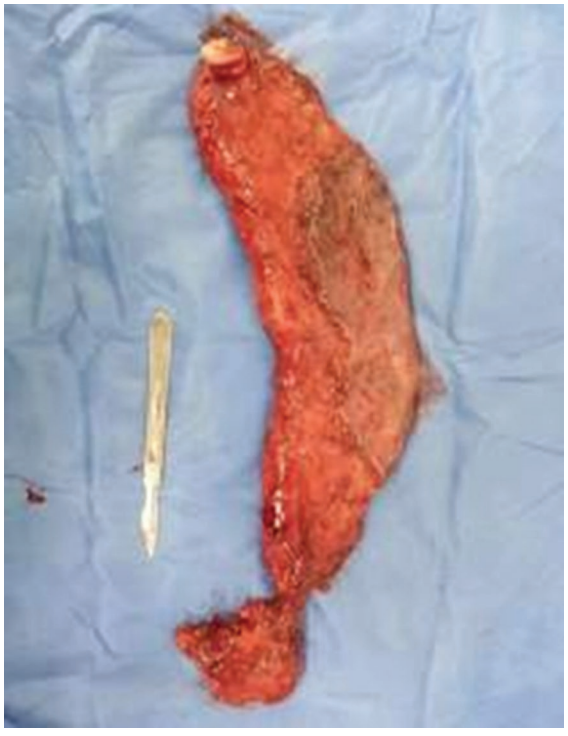

Figure 4. Surgical specimen.

and its gastric remnant, which had not yet been sectioned, are visible (Fig. 3C). Mechanical antiperistaltic lateral cervical esophagogastric anastomosis was

performed. Finally, a Penrose drain is placed leading to the mediastinum posterior to the cervical anastomosis. The resected specimen showed an esophagus dilated throughout its entire length (Fig. 4). The procedure lasted a total of approximately 7 h and 50 min with a bleed of 100 cc. The histopathological study was compatible with achalasia, revealing mild lymph node degeneration + acute ulcerated esophagitis with accentuated epithelial regenerative changes and histological data suggestive of acute esophagitis.

The patient remained in intensive care for 72 h, completing the post-operative period without complications. Total parenteral nutrition was continued until oral feeding was ensured, which was started with clear liquids on the 3rd day, with no evidence of leakage, a polymeric diet was started on the fourth day and progressed to porridge on the 11th post-operative day, having adequate tolerance. She was finally discharged on the 13th post-operative day. After 8 months of follow-up, the patient had adequate oral intake and a weight gain of 5 kg.

Discussion

Patients with achalasia have a 7-140 times higher risk than the general population of developing esophageal carcinoma[7]. It takes approximately 10-20 years from the onset of the first symptoms for a neoplastic transformation[2]. Esophagectomy in terminal achalasia is indicated in patients with a tortuous and dilated esophagus with axis deviation. Extrapolation from surgical series suggests that this process can last between 12 and 15 years[3,8]. Another indication is the persistence of long-term disabling symptoms despite multiple endoscopic and/or laparoscopic interventions. In a series of 385 patients with achalasia who underwent esophagectomy after having previously undergone unsuccessful Heller myotomy, the symptoms reported were regurgitation (100%), dysphagia (83%), chest pain (67%), and recurrent episodes of pneumonia and/or chronic cough (50%)[9]. In addition, the success of a myotomy is substantially reduced when the esophagus is tortuous in its supradiaphragmatic course, as is the case in the case presented[5,9].

The transhiatal approach can prevent the development of serious pulmonary complications and accelerate post-operative recovery; however, insufficient visualization of the posterior mediastinum, limited space for manipulation due to a large esophageal dilation, long operating time and great blood loss due to the difficulty in performing adequate hemostasis, are disadvantages that are considered to impact morbidity and mortality. The choice in favor of triple approach esophagectomy, also known as McKeown, is associated with fewer lethal complications in the event of anastomotic leakage because cervical exposure allows an anastomosis to be performed with less technical difficulty[10-12]. A dietary adjustment before surgery with a clear liquid diet for 2-5 days is recommended to reduce the amount of esophageal content retained[13]. Likewise, the anesthesiologist should perform the rapid sequence intubation technique with cricoid pressure or intubation in a semi-upright or fully upright position to avoid bronchoaspiration of the contents that could remain in the esophagus[14].

In a systematic review of patients undergoing esophagectomy for terminal achalasia, bringing together a total of 1307 patients, a post-operative morbidity was found between 19% and 50%, finding that the two most frequent complications were pneumonia and anastomotic leakage, a mortality of 0-5.4% and a hospital stay between 10 and 16 days. It was also observed that 27.5% of patients required endoscopic dilation of the anastomosis within 1 year[15]. The risk of respiratory infection after surgery can be reduced by three times if a minimally invasive approach is used. It has been seen that up to 40% of patients experience some type of cardiac arrhythmia after esophagectomy, most frequently atrial fibrillation, which is often asymptomatic, however, this can be a symptom of anastomotic leakage[14,15]. Chylothorax is a rare complication that can occur in 2% of all esophagectomies but can increase by up to 13% in achalasia, probably due to enlargement of the lymphatic ducts and their displacement due to distortion of the esophageal anatomy. Recurrent laryngeal nerve injury during cervical dissection may be greater in up to 20% of patients with achalasia and megaesophagus[8]. Up to 46% of patients may experience postoperative dysphagia, most of them due to stenosis of the anastomosis, which usually responds to endoscopic pneumatic dilations[15].

Regarding the choice of esophageal substitute, gastric interposition is considered to be of choice because it requires a single anastomosis and has a more constant pattern of blood supply to the stomach compared to the colon. In colonic interposition, three anastomoses are required, and long interpositions run a greater risk of ischemia, which can predispose to the formation of fistulas and stenosis. Duct redundancy can cause mechanical dysfunction and reoperation[3,15]. It is estimated that the majority of patients (75 and 100%) have managed to follow an unrestricted diet after the procedure. The success of surgery deteriorates progressively over time, with a failure rate of 20% at 10 years and up to 35% at 20 years[16].

In this case, the choice of esophagectomy by transhiatal approach is ruled out as an option due to the

formation of dense adhesions between the dilated esophagus and the mediastinum, as well as the presence of hypertrophied bronchial and aortic branches that would have hindered blind mobilization of the esophagus. Similarly, excessive dilation not only of the distal esophagus but also of the proximal esophagus would make its transhiatal mediastinal dissection extremely difficult with a higher rate of bleeding. For these reasons, the thoracoscopic approach turned out to be a feasible, safe option with a lower risk of complications for the patient.

Conclusion

Thoracoscopic esophagectomy can be performed safely, with acceptable morbidity, low mortality, and satisfactory dietary function. The results obtained by this minimally invasive approach for patients with megaesophagus are good when performed by experienced surgeons.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical declarations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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CLINICAL CASES

Well-differentiated primary pleural liposarcoma

*José F. Guerrero[1], Thelma Rizo-Pica[2], Javier M. Prado-Peredo[2], Jorge A. Ramírez-Arce[1], Romina Escobar-Paz[1], Andrea Hernández-de la Torriente[1], Yutzil M. Velázquez-Gachuz[3], and Alejandro Hernández-Solís[1]**

[1]Pneumology and Thoracic Surgery Service; [2]Anatomic Pathology Service. Hospital General de México Dr. Eduardo Liceaga, Secretaría de Salud; [3]Faculty of Higher Education Iztacala, Universidad Nacional Autónoma de México. Mexico City, Mexico*

Abstract

Primary pleural liposarcoma is a rare, slow-growing tumor, representing < 10% of pleural tumors, originating from residual remains of primitive mesenchymal tissue. We present the case of a 61-year-old male patient with chest pain and rapidly progressive dyspnea, observing in the imaging studies a hypodense tumor in the left hemithorax with Hounsfield units of –30 to –130 fatty tissue range with dimensions of 29.5 × 16.1 × 21.9 cm. Excision surgery together with chemotherapy and radiotherapy is the therapeutic alternative that has reported the greatest benefit in these patients.

Keywords: *Pleural liposarcoma. Mesenchymal tissue. Hypodense tumor.*

Introduction

Primary pleural liposarcoma (PPL) is an extremely rare malignant tumor, originating from mesenchymal cell remnants and very rarely from a pre-existing lipoma. A total of 43 cases have been reported in the literature worldwide, with the first case report being published by Ackerman and Wheeler in 1942. In the documented cases, it predominates in the male gender, being more frequent in the 5th decade of life (Table 1). The diagnosis should be suspected on images containing fat density with or without calcifications by chest computed tomography (CT) and confirmed by histopathological study. Surgical resection of the tumor is the therapeutic method of choice, although with risks of recurrence at 5 years[1].

Clinical case

A 61-year-old male presented with a history of systemic arterial hypertension of 25 years. Her condition began 2 months before hospitalization with asthenia, adynamia, non-productive cough, distal cyanosis, and rapidly progressive dyspnea. Physical examination included condensation syndrome in the left hemithorax. Laboratory studies Hb: 19, platelets: 118, leukocytes: 5.9, Dimer D: 4561. CT scan of the chest with image of hypodense tumor in the left hemithorax with Hounsfield units of –30 to 130 fatty tissue range and dimensions 29.5 × 16.1 × 21.9 cm, observing ovoid lesions with hyperdense walls with the presence of calcifications and hypodense centers near the posterior aspect of the hemithorax. Transthoracic biopsy was taken with an Abrams needle, obtaining samples of pearly tissue, histological sections identify neoplastic lesion composed of adipose tissue, with a solid growth pattern. Immunolabeling for MDM2 was performed, which was negative. During his hospital stay, the patient presented respiratory and hemodynamic deterioration and was admitted to the intensive care unit, where he later died due to complications secondary to the underlying diagnosis.

***Correspondence:**
Alejandro Hernández-Solís
E-mail: drhernandezsolis@yahoo.com.mx

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In the autopsy study, significant congestion was observed in the cephalic and cervical segments, jugular engorgement, and subclavian veins, with data of a superior vena cava syndrome. At the opening of the thoracic cavity, a tumor measuring 30 × 20 × 15 cm, well defined, with a lobed surface and adipose appearance, was observed in an anterior situation and occupying the entire left hemithorax (Fig. 1A). With collapse of the ipsilateral lung, displacement of the heart and mediastinal structures toward the right hemithorax (Fig. 1B). The appearance of the tumor was homogeneous with an adipose appearance, light yellow in color, with foci of necrosis and calcifications. Histologically, the tumor was composed of neoplastic adipocytes of mature appearance, with variation in their shape and size, accompanied by a fine vascular network with a characteristic chicken wire appearance (Fig. 1C). Nuclear atypia was demonstrated in both neoplastic adipocytes and stromal cells (Fig. 1D). Foci of sclerosis were observed, with dystrophic calcification, no evidence of dedifferentiation or heterologous elements was found. With the above, the diagnosis of well-differentiated liposarcoma, adipocytic subtype, was concluded. Immunohistochemical reactions were performed as a diagnostic adjunct, demonstrating diffuse cytoplasmic and nuclear positivity for S100 (Fig. 1E), and focal nuclear positivity for p16 in neoplastic adipocytes (Fig. 1F), as well as positivity for CD34 in blood vessels. Immunoreactions were performed for MDM2 and CDK4, which were negative; although it is expected to find positive these last markers since these oncogenes are molecularly amplified, their negativity does not rule out the diagnosis. In addition to what has already been mentioned, two previously unidentified lesions were found in the thyroid gland. A classic variant papillary thyroid carcinoma located in the left thyroid lobe, which measured 1.2 × 1.0 × 1.0 cm, and a clear cell follicular adenoma, located in the upper portion of the isthmus, which measured 1.5 × 1.3 × 1.2 cm.

Discussion

PPL is a rare tumor, accounting for 10% of tumors at the pleural level, other pleural lesions include benign lipomas, hemangioendotheliomas, hemangiopericytomas, angiomas, localized fibrous tumor of the pleura, and non-neoplastic cysts. PPL is usually slow-growing with an expansive rather than an infiltrative behavior, with non-specific clinical manifestations, leading to a delay in its diagnosis[2-4].

The World Health Organization classified this tumor into well-differentiated liposarcomas (40-50%), myxoid (20-30%), dedifferentiated subtype (15-20%), and pleomorphic (5-10%), depending on the histological components of the tumor. It occurs in adults in the fourth or fifth decade of life without gender predominance. Myxoid liposarcoma shows a specific and reciprocal chromosomal translocation that occurs in more than 95% of t(12; 16), (q13:p1), fusing the CHOP and FUS genes, causing a dysregulation in adipocyte differentiation and allowing the proliferation of immature forms. The round cell variant is characteristic and known for its worse prognosis[5]. Liposarcoma is thought to be derived from residual remnants of primitive mesenchymal tissue that may undergo a conformational change to malignant tissue, which later develops as a pleural liposarcoma[6,7].

In imaging studies it is described as a well-defined extrapulmonary mass that may have the presence of calcifications that can cause displacement of thoracic structures[8]. Color Doppler ultrasound can be useful in depicting the solid nature of these tumors and assessing the internal vascularity of the tumor. MRI is the study of choice for defining soft tissue tumors, delineating their location and planning the surgical procedure[9]. Atypical lipomatous tumor/well-differentiated liposarcoma, myxoid/round cell liposarcoma are S-100 protein positive and variably MDM2 positive. Pleomorphic liposarcoma is variably positive for both S-100 protein and MDM2, and well-differentiated liposarcoma is generally only positive for vimentin[5,10].

There are studies that suggest that p16 has greater sensitivity and specificity for the detection of well-differentiated liposarcoma and dedifferentiated liposarcoma; however, its diagnostic yield is higher in combination with MDM2 and CDK4. Although molecular confirmation of this tumor is desirable by demonstrating the amplification of MDM2 and/or CDK4, the morphological study and the clinical context of the tumor make the diagnosis. The treatment of choice is wide and complete resection, provided that adjacent structures allow it. Surgery is complemented by adjuvant radiation therapy, which has been shown to improve local control and survival rate, and sometimes with chemotherapy with doxorubicin, dacarbazine, and ifosfamide. Tumor recurrence is predominantly in the affected hemithorax; however, it can occur in the contralateral hemithorax and is in 70-90% of cases, with a 5-year survival of 71%[9,11,12].

Table 1. Global amount of pleural liposarcoma found since 1942, with a total of 43 cases reported until 2023

Author (year)	Age/sex	Pleura site	Tumor size (cm)	Histology	Therapy	Follow-up (months)
Ackerman and Wheeler (1942)	50/F	Left	Nt	Nt	Autopsy	FE/12 M
Gupta and Paolini (19767)	51/M	Right	21	POR	Autopsy	DN
Ambrosio (1974)	52/M	Left	Nt	Nt	C-Res	VSEE/66
Wouters et al. (1983)	19/F	Left	3.5	MYX	C-Res + Rad	Alive/55
Evans (1985)	61/M	Left	Nt	MYX	Autopsy	FE
Evans et al. (1987)	45/M	Left	Nt	MYX	Autopsy	MOE/0.07
Gregor et al. (1987)	54/M	Right	2-2.25	LPBD	C-Res	MCD/108
Munk and Muller (1988)	27/F	Left	Nt	Nt	Nt	DN
Carroll et al. (1992)	23/F	Left	29-21	MIXED	C-Res + RT	VSEE/16
Wong et al. (1994)	38/M	Right	Nt	MY	C-Res + RT	VSEE/5
Batouk (1995)	55/F	Right	10 × 7 and 1.5 × 0.5	LPBD	C-Res	VSEE/16
Okby and Travis (2000)	45/F	DN	16	MYX/RO	P/I-Res + QT	FE/7
Okby and Travis (2000)	73/M	Right	Nt	MYX	P/I-Res	FE/9
Okby and Travis (2000)	67/M	Right	18.5	LPBD	Nt	MCD/16
Okby and Travis (2000)	80/M	Right	20	MYX	C-or/I-Res	DN
Tosson and Krismann (2000)	51/M	2 Right/ 1 recurrent: left	18 × 12 × 7	MYX	C-Res/RAD	VSEE/5Y
Minniti et al. (2005)	50/M	Left	13	WDL	C-Res + Rad	VSEE/12
Takanami and Imamura (2005)	59/M	Right	12-5.3	LPD	C-Res	VSEE/6
Goldsmith and Papaguiamnopoulos (2007)	42/M	Left	Nt	MYX	C-Res + Rad	Alive/12
Papaguiamnopoulos and Goldsmith (2007)	80/F	Left	Nt	MYX	P/I-Res	FE/8
Benchetritt et al. (2007)	76/F	Left	18-11	LPD	C- o P/I-Res	MOE/0.1
Peng et al. (2007)	56/F	Left	Nt	LPBD	C-Res	VSEE/18
Dagli (2008)	56/F	Left	Nt	MYX	ND	DN
Alloubi et al. (2008)	58/M	Left	Nt	MYX	C-Res + Rad	VSEE/10
Elsayed (2010)	47/M	Right	18 × 12 × 10	LPBD	C-Res	VSEE
Chen et al. (2014)	19/M	DN	Nt	LPBD	C-Res	Alive/56
Chen et al. (2014)	30/F	DN	Nt	LPBD	C-Res	VSEE/48
Chen et al. (2014)	60/M	DN	Nt	LPBD	C-Res	VSEE/43
Chen et al. (2014)	20/F	DN	Nt	MYX	C-Res	Alive/90
Chen et al. (2014)	54/M	DN	Nt	MYX	C-Res	VSEE/26
Chen et al. (2014)	41/M	DN	Nt	LPD	C-Res	Died/15
Chen et al. (2014)	53/M	DN	Nt	LPD	C-Res	Died/11
Chen et al. (2014)	61/M	DN	Nt	LPBD	P/I-Res	VSEE/18

(Continues)

Table 1. Global amount of pleural liposarcoma found since 1942, with a total of 43 cases reported until 2023 *(continued)*

Author (year)	Age/sex	Pleura site	Tumor size (cm)	Histology	Therapy	Follow-up (months)
Chen et al. (2014)	DN/F	DN	DN	DN	DN	DN
Carrillo (2014)	49/F	Left	19×10	PL	C-Res	DN
Albujar Ching (2016)	56/M	Right	2 kg	MYX	C-Res	DN
Wang et al. (2017)	43/F	Left	21	MYX	C-Res	VSEE/8
Matsukumu (2018)	45/M	Left	10	LPD	P/I-Res	FE/4.2
Prabhakar (2019)	32/M	Right	20.8 × 13.6	MYX	QT-RT	VSEE
Kang (2020)	66/M	Left	4.5 × 3.3 × 3	C-Res	C-Res	VSEE
Layek (2022)	22/M	Left	23 × 18	DN	DN	VSEE
Palacios (2022)	46/M	Right	20 × 25	MYX	I-Res + QT	Alive

F: female; M: male; VSEE: alive with no evidence of disease; EF: died of disease; EOM: died of another disease; MCD: died of unknown causes; QT: chemotherapy; C-Res: complete resection; RT: radiotherapy; Nt: not size; P/Res: palliative and incomplete resection; By: poorly differentiated; Myx: myxoid; LPBD: well-differentiated liposarcoma; MYX/RO: myxoid and rounded type; LPD: dedifferentiated liposarcoma; PL: pleomorphic; DN: data not available.

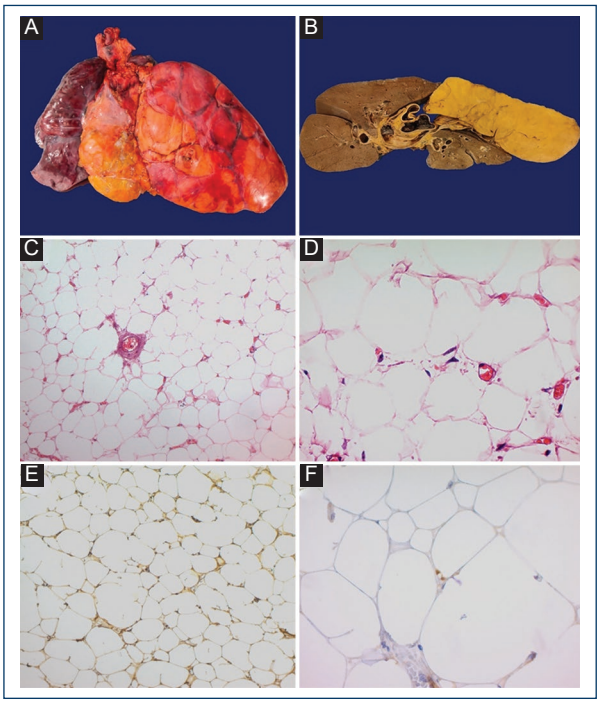

Figure 1. Liposarcoma. **A:** fresh cardiopulmonary block. **B:** tomographic section, piece fixed in formaldehyde. **C:** variation in cell size, vasculature in chicken wire, H&E, ×10. **D:** adipocytes with nuclear atypia, H&E, ×40. Immunoreactions: **E:** S100, positive in nucleus and cytoplasm of neoplastic adipocytes, ×10. **F:** p16 focal nuclear positive in neoplastic adipocytes, ×40.

Conclusion

Pleural liposarcoma is a rare tumor worldwide, the diagnosis is usually made late due to the presence of non-specific symptoms, being important to note that this entity should be suspected when a tumor with the presence of fat density in the thoracic cavity is found. However, there are no specific lesions, so the gold standard continues to be the histopathological study.

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Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

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Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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CLINICAL CASES

Left atrial myxoma debuting with ischemic stroke

Oscar E. Garmendia-Lezama

Cardiology Service, Hospital General de México Dr Eduardo Liceaga, Secretaría de Salud, Mexico City, Mexico

Abstract

The myxomas are the most common primary cardiac tumors. The majority of them are benign and can be an incidental finding or be almost asymptomatic. The symptoms depend on their location, with the most common being the left atrium, which carries an increased risk of clots. The main effects of the clots are on the central nervous system, but occasionally they can involve the respiratory, peripheral, or coronary system. The case of a 30-year-old patient without comorbidities with left atrial myxoma, which manifests with ischemic stroke, is presented.

Keywords: *Left atrial myxoma. Ischemic stroke.*

Introduction

Myxomas are the most common primary heart tumor[1]. It is estimated that more than 75% of myxomas originate in the left atrium, either in the mitral annulus or at the edge of the oval fossa of the interauricular septum; 20% arise from the right atrium, whereas 5% come from both the atrium and ventricle[2,3]. Atrial myxomas are associated with a triad of complications, including obstruction, embolisms, and constitutional symptoms (such as fever and weight loss)[2,4].

Due to the high systolic pressure and its location, left atrial myxomas were highly associated with an increased risk of systemic embolization, particularly in the central nervous system, retinal arteries, as well as viscera, spleen, kidneys, adrenal glands, abdominal aorta, iliac and femoropopliteal arteries[5]. Therefore, patients may have a variety of presentations, such as transient ischemic attack, hemiplegia, vision loss, chest pain, and dyspnea. The defects in neurological embolizations are probably the most serious complications of embolizations associated with left atrial myxomas[6].

Clinical case

A 30-year-old woman with no personal pathological history, who 5 h before admission presented a clinical picture characterized by loss of alertness of 5 min accompanied by dysarthria, right hemiparesis on cardiovascular examination presented a protodiastolic murmur “tumor plop” on the left parasternal border.

The computed tomography (CT) image of the simple skull shows that; ischemic cerebral infarction in the subacute phase located in the left hemisphere with involvement of the temporal lobe, inferior frontal gyrus, deep area of the semioval center, lenticular nucleus, dorsolateral portion of the head of the caudate nucleus, anterior arm and knee of the internal capsule, rostral area of the thalamus and short gyrus of the insula, exerts a slight effect on volume and obliterates the corresponding gyrus (Fig. 1).

Transthoracic echocardiogram is observed in the left atrium with diameters of 37 × 37 × 49 mm, left atrium volume 38 mL/m^2, multilobed and hypomobile tumor with the consistency of different echogenicities and

Correspondence:
Oscar E. Garmendia-Lezama
E-mail: oscar.garmendia@yahoo.com

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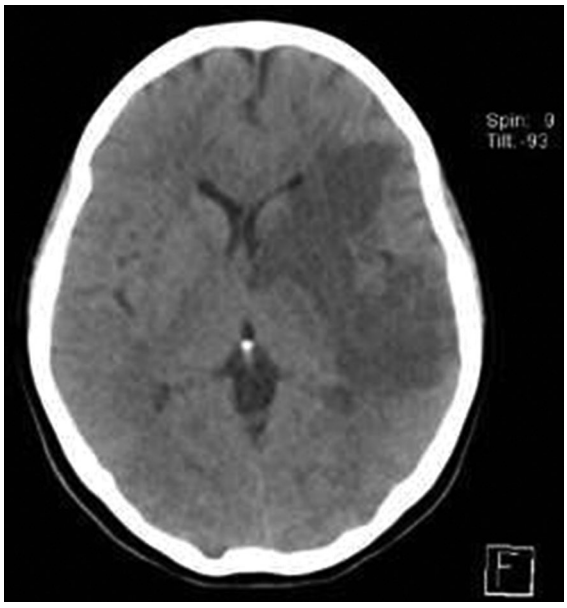

Figure 1. Ischemic cerebral infarction in the subacute phase located in the left hemisphere with temporal lobe involvement.

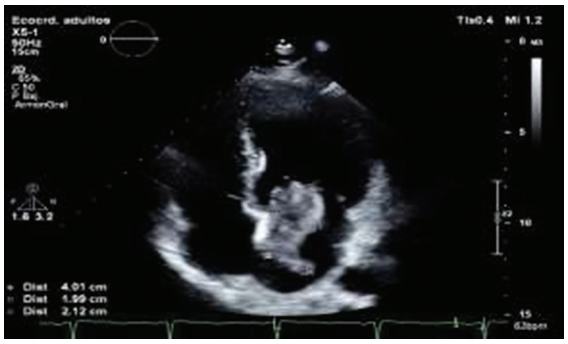

Figure 2. Apical axis four chambers are observed in the left atrium tumor is 40 × 20 mm and the larger lobe is 21 × 20 mm.

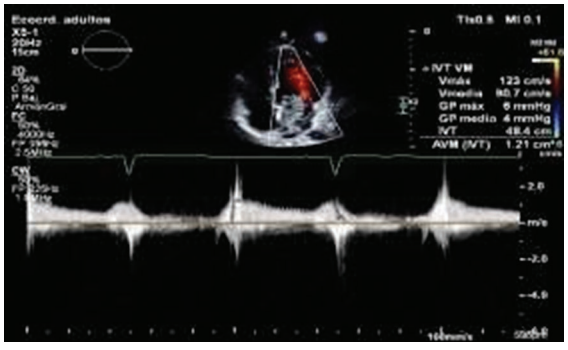

Figure 3. Continuous Doppler to the mitral valve presents functional stenosis of mild grade medium gradient 4 mmHG Maximum velocity of 1.2 m/s, insufficiency is mild with contracta vein of 2 mm.

cystic areas, of gelatinous consistency, adhered to the interatrial septum with a base of 25 × 27 mm very proximal at the anterior level of the septum and through it near the aortic valve. The size of the tumor is 40 × 20 mm and the larger lobe is 21 × 20 mm (Fig. 2), slides through the anterior leaflet of the mitral without being attached to it and interferes with the opening, causing functional stenosis of mild degree area by 3D planimetry 2.3 cm^2, mean gradient 4 mm Hg, maximum velocity of 1.2 m/s, the insufficiency is mild with a 2 mm contract vein (Fig. 3).

A right auriculotomy was performed, an interauricular septum was opened, finding a left atrial tumor with a pedicle attached to the middle third of the interatrial septum, so the septum was resected, obtaining a mucoid-like tumor exit of approximately 5 × 4 cm. (Fig. 4) A biopsy (2408739) is performed, which describes; a fragment of tissue of irregular shape and surface, measuring 4.3 × 3.8 × 1.2 cm., white with translucent areas and areas of hemorrhage, of soft consistency, serial cuts are made, observing solid and heterogeneous in which white areas are intermingled with dark brown. The presence of atrial myxoma is concluded.

Discussion

Cardiac myxoma is a neoplasm of uncertain histogenesis that occurs only on the endocardial surface, most often in the atrial location. Histological diagnosis is based on the finding of typical cells in a matrix rich in mucopolysaccharides. Cardiac myxoma cells are histologically and histogenetically different from the spindle cells of soft-tissue myxomas. It has been postulated that the cells that give rise to this tumor are the so-called "subendothelial reserve cells," which are totipotent and have the capacity to form vascular structures[7] and express endothelial and neural markers. The existence of a population of aneuploid cells in a tumor is generally considered to be evidence that the lesion is neoplastic[8]. The presence of aneuploidy, as well as the finding of chromosomal abnormalities in cases of myxomas, supports the neoplastic origin of this tumor.

The size and location of the myxomas determine the clinical manifestations of obstruction to intracardiac blood flow, with the simulation of valvulopathies of various types, especially mitral narrowing. The size of the

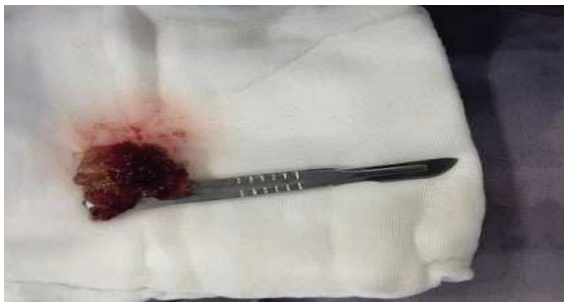

Figure 4. Mucoid tumor of approximately 5 × 4 cm.

tumor and also the different positions of the body can determine the severity of the obstruction and symptoms vary from dyspnea due to heart failure or syncope, to sudden death due to complete obstruction.

Embolization is a common manifestation, which is associated with small tumors (< 4.5 cm^2). Most emboli migrate to the central nervous system and cause strokes; however, they can migrate to any part of the arterial system and produce a variety of signs and symptoms. There are reported cases of embolism to the lower limbs or to the coronary limbs, among others. In some cases, cardiac and extracardiac manifestations may occur, including acute myocardial infarction, cerebrovascular events, pulmonary embolism, and fever of unknown origin; however, a classic triad has been established, consisting of obstructive and constitutional symptoms, as well as embolic events[5].

Cerebrovascular events associated with cardiac myxomas have been observed in up to 22% of cases, with a predominance in females[1]. The ideal imaging study is brain nuclear magnetic resonance imaging given the high rate of false negatives that CT of the skull yields. They have a low mortality rate and the ideal time for tumor resection is still unclear; despite this, it has been recommended that it be postponed until 4 weeks after the stroke event to reduce the risk of perioperative death[9].

Diagnosis is challenging; it is made through transthoracic, transesophageal echocardiogram, and cardiac magnetic resonance imaging, although it can sometimes be identified by cardiac CT. The echocardiogram can easily visualize the mass and describe the location, shape, size, number, and morphological characteristics; in addition, it assesses the hemodynamic consequences of the tumor[10]. On tomography, myxomas may be well-defined and appear lobed, smooth, mobile, round, or oval, with a narrow pedicle; they are generally heterogeneous and have patchy foci of calcification and enhancement[11].

As for treatment, expertise is required and will always be surgical. It is important to determine the origin and malignancy of these tumors in the pre-operative period. A well-known example is renal carcinoma with expansion to the right atrium, which can be mistaken for a primary tumor before being taken to surgery. In addition, not all of them are real tumors because there are "pseudotumors," thrombi, cysts, and tuberculomas[11]. Post-operative echocardiographic follow-up is recommended since the tumor recurrence rate after successful resection reaches up to 4-7%[12].

Conclusion

Atrial myxomas are the most common primary cardiac tumors, with embolization being one of their most frequent forms of presentation, most emboli migrate to the central nervous system, which is why atrial myxoma should be considered one of the main causes of cerebrovascular events in young patients without comorbidities.

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