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EDITORIAL

ORIGINAL ARTICLES

REVIEW ARTICLES

CLINICAL CASES

HOSPITAL GENERAL de MÉXICO
DR. EDUARDO LICEAGA

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Hospital General de México "Dr. Eduardo Liceaga"

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EDITORIAL

Acad. Dr. Rafael Romualdo Gutiérrez Vega. In memoriam

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Dr. Rafael Gutiérrez Vega, an outstanding medical surgeon, undergraduate and postgraduate professor, researcher, and manager at the Hospital General de México and at the Universidad Nacional Autónoma de México (UNAM), was born in Cuautla, Morelos, on October 15, 1955, in a middle-class family. He developed his first studies in his hometown and from an early age learned to collaborate, like his three brothers, in his father's business activities. When they reached the age to start their professional studies, first his older brother and later him, both had to separate from the family to move and live independently in Mexico City (Fig. 1).

In 1973, the Dr. Gutiérrez Vega began his medical career at the Faculty of Medicine of the UNAM and from the beginning, his commitment with himself and with his studies and continuous learning made him an outstanding student, receiving his degree in Medical Surgeon in 1979. He began his residency in General Surgery at the Hospital General de México, and was later invited as a surgeon of the staff, where he developed most of his patient care, teaching, and research work. It was not long before his outgoing personality, knowledge, and the quality of his studies made him stand out during patient visits, case discussions, and clinical sessions.

Shortly after finishing his postgraduate studies, he enthusiastically faced the beginning of laparoscopic surgery, performing, together with a group of fellow surgeons, the first cholecystectomy with this technique at the Hospital General de México[1]. In addition, he implemented the nutritional support clinic, observing that the nutritional status of hospitalized patients influenced the clinical evolution of the patients; for this, evaluated the prognostic nutritional index[2].

Showing a strong vocation for teaching, and shortly after finishing his residency, he began to collaborate as a professor in the Department of Surgery at the Faculty of Medicine (Fig. 2), UNAM and also began his phase as a researcher, developing various studies on the effects of renal and hepatic ischemia – reperfusion and the effect of free radicals on tissues, following the line of research initiated during his stay at Mount Carmel Mercy Hospital in Detroit, Michigan in 1989[3,4]. At the same time, he took on the task of integrating a multidisciplinary group to start, for the first time, a kidney transplant program at the Hospital General de México.

After being an adjunct professor of the postgraduate course in General Surgery for many years, the Dr. Gutiérrez Vega takes the direction of the course, where so many generations of young surgeons were trained in our hospital. His name was then proposed for the International Medical Knowledge Contest (CICoM), which is held among students from various national and international universities.

In 1994, he was invited to the Medical Directorate and later to the Medical Deputy General Director, Hospital General de México, as a manager, he had the opportunity to train in the field of medicine hitherto unknown to

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him: hospital administration. As was his custom, he overcame his inexperience with preparation, determination, and dedication. He used to be the first to arrive and the last to leave. The Dr. Gutiérrez Vega studied a master's degree in Senior Management, at the Pan-American Institute of Senior Business Management (IPADE).

Already more familiar with the structure and organization of the hospital, he had in mind to integrate a larger work group, that is why he created the Office of Assistants to the Director, non-existed until then, which, together with the hiring of more assistance personnel in the afternoon and evening favored the increase in patient care capacity. At the end of his term as Medical Deputy General Director, he returned fully to healthcare activities.

Later, he was General Director of Arbitration at the Comisión Nacional de Arbitraje Médico (CONAMED), where he used all his medical and professional experience to contribute to the solution of the medical problems that were presented to the Commission. During this period at CONAMED, he published the most significant clinical cases, in medical journals, to expose the importance of the doctor-patient relationship in the medical act, the constant improvement in medical care, the consideration of bioethical aspects by the health personnel and knowledge of the regulations for the medical and surgical care of patients[5,6].

In 2014, the Dr. Gutiérrez Vega accepts the position of editor in chief of the Medical Journal of the Hospital General de México; one of his first changes was to publish the medical journal in the English language; in the editorial of volume 77 of our journal he explains and justifies the reasons for this change; which consisted of making it more competitive in the international arena[7]. For 5 years, he encouraged researchers from the Hospital General de México and the UNAM School of Medicine, among other health institutions, to publish their work in our medical journal (Fig. 3), always with the idea to improve scientific quality and its impact factor.

He was a member of the Medical Society of the Hospital General de México, where he participated as President of the Honor and Justice Commission in the period 2015-2017 (Fig. 4). At the end of 2018, as editor of the Medical Journal of the Hospital General de México, he signed the agreement, to continue publishing the research work of health professionals, with the Permanyer Mexico publishing house (Fig. 5).

Still young, in his most productive years, in the midst of his tenacious work as an editor in chief, a severe blow to his health forced him to gradually abandon his activities to receive various treatments. When he visited the hospital during this time (the most difficult test he would face in his life), he did so with the best attitude, splendidly dressed, with the elegance that always characterized him. He published a large number of scientific articles, conferences, and presentations of scientific

Figure 1. Dr. Rafael Gutiérrez Vega, 1955-2022.

Figure 2. Seated from left to right: Dr. José Arturo Ortega Salgado, Dr. Rafael Gutiérrez Vega, Dr. Luis Padilla Sánchez. Standing from left to right: Dr. Carlos Agustín Rodríguez Paz, Dr. Eduardo E. Montalvo Jave, Dr. Adiola García Colín, Dr. Gregorio Quintero Beulo, Dr. Irma Carrillo Soto. Department of Surgery. Faculty of Medicine, UNAM.

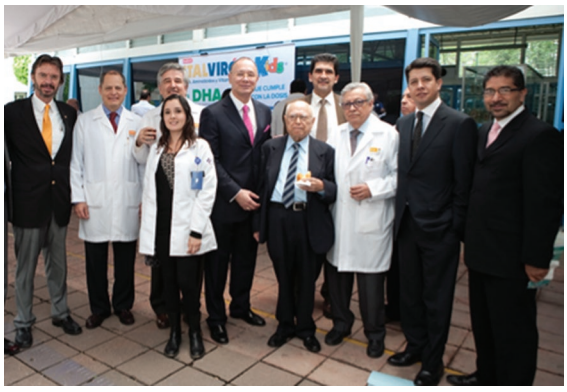

Figure 3. From left to right: Dr. Oscar Chapa Azuela, Dr. Alejandro Rodríguez Báez, Dr. José Humberto Garza Flores, Dr. Jimena Iberri, Dr. Rafael Gutiérrez Vega, Dr. Enrique Fernández Hidalgo, Dr. Luis Humberto Ortega León, Dr. Luis Miguel Cruz Melgar, Dr. Eduardo E. Montalvo Javé, Dr. Francisco Galindo González.

Figure 4. Dr. Rafael Gutiérrez Vega after rendering his report as editor of the Medical Journal of the General Hospital of Mexico, accompanied to his left by Dr. Sergio Cuevas Covarrubias President of the Medical Society of the General Hospital of Mexico, Dr. Eduardo Liceaga, 2020-2022 and to his right Dr. Octavio Amancio Chassin Treasurer of the Medical Society of the General Hospital of Mexico, Dr. Eduardo Liceaga, 2022-2023.

papers at national and international conferences, book chapters, and medical dissemination documents. In addition, he was a member of the most important medical and surgical associations and societies, including the Mexican Academy of Surgery, being an Emeritus member, also in the same category in the Mexican Association of General Surgery.

His last years were dedicated to enjoying the things, he was most passionate about: art in all its forms,

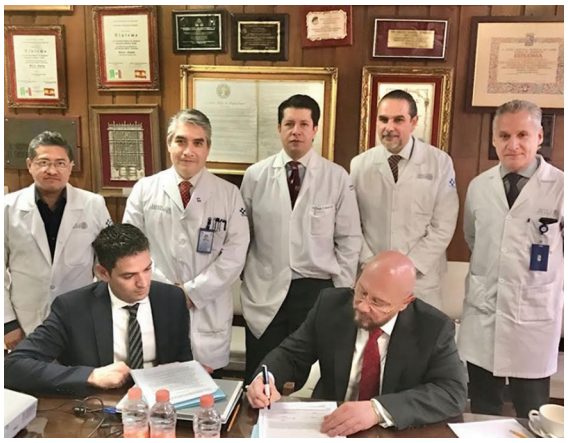

Figure 5. Signing of the agreement with the publishing house Permanyer México being president of the Medical Society of the General Hospital of Mexico, Dr. Eduardo Liceaga Dr. Arturo Larrazolo López (2019-2020) and editor in chief of the medical journal Dr. Rafael Gutiérrez Vega. With him at the signing from left to right: Dr. Marco Antonio Durán Padilla (2022-2023), Dr. Fiacro Jiménez Ponce, Dr. Eduardo Montalvo Jave (2015-2016), Dr. Adolfo Martínez Tovar and Frank García Lora representative of Permanyer México.

especially literature. He traveled a lot, strengthened family, and emotional ties; he enjoyed pleasant company and also enjoyed solitude; times of retreat and deep reflection. When the disease returned, he did too. He returned to the place and the family that saw him born. It seemed that when leaving, he wanted to take everything that he saw coming.

All of us who had the privilege of knowing Dr. Gutiérrez Vega will always remember him as a surgeon of excellence, with charisma and a deep humanitarian sense, but with a simple and cordial treatment, enthusiastic about knowledge and research and actively participating in academic exchanges. Inside and outside our hospital, he always contributes to reflection and improvement, with his point of view on excellence, surrounded by young people, students and doctors, whom he helped with their theses or accompanied them in their first steps in research and integrating them into their own projects.

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Ethical disclosures

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

Data confidentiality. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. Rafael GV, Francisco GG, Vicente GR, Octavio AC, Esteban MJ, Ignacio GM. Colecistectomía laparoscópica, una nueva alternativa y nuevos retos. análisis de una serie clínica de 94 enfermos. Rev Med Hosp Gen Mex. 1995;58:157-62.
2. Rafael GV, Erasto AL, Esteban MJ. Aplicabilidad del índice pronóstico de buzby en población Mexicana. Rev Med Hosp Gen Mex. 1997;60:66-70.
3. Rafael GV, Homero LM, Avissai AV, Octavio AC, Eduardo MJ, Renato ON, et al. Prevención de la lesión por isquemia reperfusión hepática en animales tratados con piroxicam. Modelo experimental en rata. Rev Med Hosp Gen Mex. 1994;57:102-9.
4. Gutiérrez-Vega R, Lazos-Ochoa M, Amancio-Chassin O, Montalvo-Jave E, Landetta-García J, Ortega-Salgado A, et al. Efecto protector de naloxona y piroxicam durante la lesión por isquemia reperfusión de intestino delgado. Rev Med Hosp Gen Mex. 1994;57:60-7.
5. Bustamante-Leija LE, Maldonado-Camargo VM, González-Anaya C, Gutiérrez-Vega R. Mecanismos alternativos de solución de controversias en la prestación de servicios de salud. Rev CONAMED. 2012;17:126-9.
6. Dubón-Peniche MD, Gutiérrez-Vega R, Pérez-Pérez JM, Castro-Hernández FI. La calidad de la atención y las controversias médico-paciente. Gaceta Mex Oncol. 2013;12:205-10.
7. Gutiérrez-Vega R. Impact factor; Its importance for authors and medical journals. Rev Med Hosp Gen Mex. 2014;77:151-2.

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ORIGINAL ARTICLE

Reconstructive management of total lower lip defects with a modified gate flap at the "Dr. Eduardo Liceaga" General Hospital of Mexico

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Abstract

Objective: *A surgical proposal is presented for the management of total lower lip defects based on the technique described in 1980 by Fujimori, called gate flap. The most common cause of total lip defects is oncological resections; likewise, epidermoid cancer represents more than 90% of the types of cancer in the lip. Reconstructive management after excisional treatment requires extensive anatomical knowledge of the area, and free flaps are currently the gold standard for total lower lip defects. It is for this reason that after a review of the surgical options described, we made modifications to the Fujimori gate flap.*
Materials and Methods: *The gate flap modified by us consists in a unilateral musculocutaneous flap, generating less donor site morbidity, and adding a palmaris longus tendon graft, performing a double pulley system for reconstruction of the oral sphincter, achieving adequate fluid continence. Three cases of elderly patients with total defects of the lower lip are presented.*
Results: *We found that Modified Gate Flap are superior to the gold standard (radial free flap). Achieving adequate skin coverage, restoration of the oral sphincter, shorter surgical time, they do not present complications associated with the procedure.*
Conclusions: *The ideal reconstruction should have not only an adequate aesthetic appearance, but also the restoration of function, associated with the lowest incidence of complications, with reproducible and constant results, which lead to a high degree of satisfaction of the patient and the surgical team; Same scenario we found with our therapeutic option.*

Keywords: *Lower lip reconstruction. Gate flap. Lip neoplasia. Lip diseases. Reconstructive surgical procedures.*

Introduction

Reconstruction of the lower lip in total defects or > 90% implies extensive knowledge of facial anatomy and surgical techniques in the reconstructive algorithm to preserve the sphincter function of the mouth.

The main cause of total defects of the lower lip is oncological resections, mainly caused secondary to the appearance of squamous cell cancer, which represents more than 90% of the types of lip cancer. Squamous cell cancer presents as ulcerated and exophytic lesions, slow-growing, with potential lymph node spread in the submandibular and submental regions. Its diagnosis is clinical and histopathological and should be complemented to the diagnostic approach with computed tomography images for lesions larger than 2 cm. The treatment is surgical resection with negative margins, and depending on the clinical stage, a lymphatic resection will be performed toward the corresponding lymph node replacement, and adjuvant chemotherapy and radiotherapy[1].

The classic reconstructive algorithm will depend on the size of the defect and location, with oral competence and plane reconstruction as its main objective[2].

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Figure 1. Patients diagnosed with clinical stage III epidermoid cancer, candidates for oncological resection and immediate reconstruction of the entire lower lip.

The reconstructive algorithm in lower lip defects is summarized in: small defects (< 30% or 1/3 part), intermediate (30-60% or up to 2/3 parts), and total defects (> 90%), and its management is with direct closure options, local flaps, and free flaps, respectively.

For intermediate defects (2/3 parts), the option is local flaps, the most used are those defects that involve the commissure: the Eastlander flap (interpolation flap, full thickness, triangular in shape, based on the labial arteries, and donor site the oral commissure), and in central lesions the Abbe flap (same characteristics as the Eastlander with a central donor site), including modifications thereof. In major central defects, the Karapandzic, Gillies, or Webster-Bernard flaps (Bernard[1]) are used.

The gold standard for total lower lip defects is the radial free flap with graft harvesting from the palmaris longus covered by it, providing internal and external coverage, and continuity of the orbicularis oculi muscle[3].

To present an alternative for total lower lip defects comparable to the gold standard, a review of reconstructive techniques is carried out. The technique described by Fujimori is optimized, in which internal and external coverage is achieved with preservation of oral continence and restoration of the continuity of the orbicularis oris muscle, providing less morbidity, and adequate functional and esthetic results.

Material and methods

Three elderly male patients recruited by the Head and Neck Surgical Oncology service of the General Hospital of Mexico “Dr. Eduardo Liceaga” with a clinical Stage III diagnosis of epidermoid cancer in the entire lower lip (It is the only inclusion criterion of the study). The patients were candidates for management by means of surgical resection and lymph node dissection and were recruited by the Plastic and Reconstructive Surgery service of the same Hospital, a reconstructive surgical plan was given.

Reconstruction is performed using a Gate flap or Fujimori flap with a modification to the original technique described by Ryosuke Fujimori (Fujimori[4]). An unilateral musculocutaneous flap based on the facial artery, with restoration of the oral sphincter, was performed. The same work team performs surgical procedure.

Results

Three elderly male patients are presented: 62, 60, and 70 years old, diagnosed with clinical Stage II epidermoid cancer, candidates for oncological resection, and immediate reconstruction of the entire lower lip (Fig. 1).

Surgical technique

Anatomical references are taken; the path of the facial artery is identified and marked, checking it with a portable 8 mHz Doppler. Subsequently, including the artery, the dimensions of the flap are drawn, taking into account the size of the defect resulting from the oncological resection in both axes, its upper limit will be the

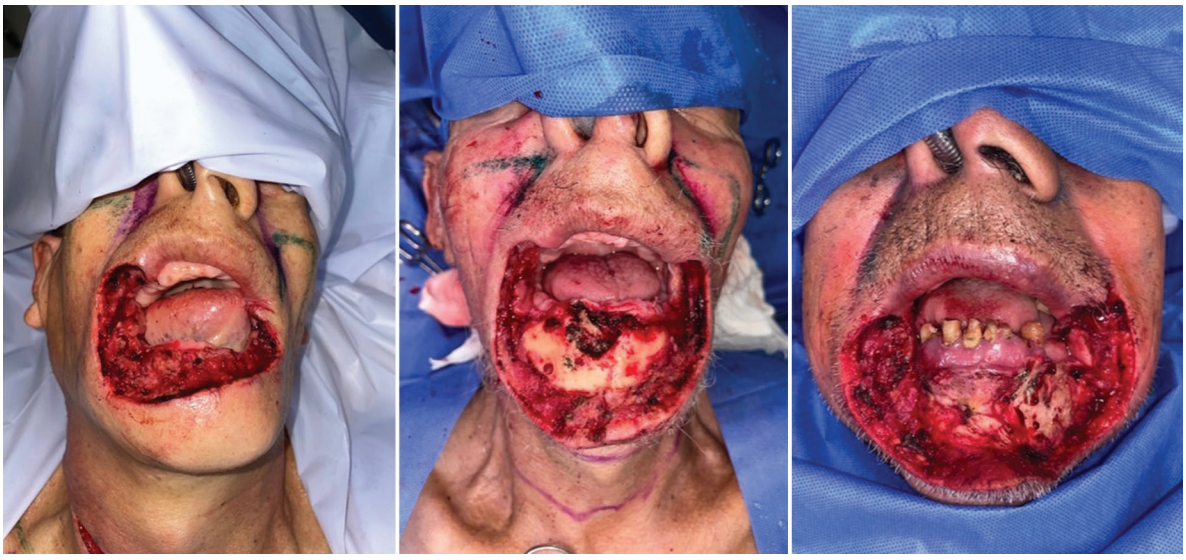

Figure 2. The surgical marking of the gate flap described by Fujimori in 1980 is shown. Bilateral marking is performed and intrasurgical, the decision is made as to which side to use at the expense of oncosurgical margins and vascularity of the donor site.

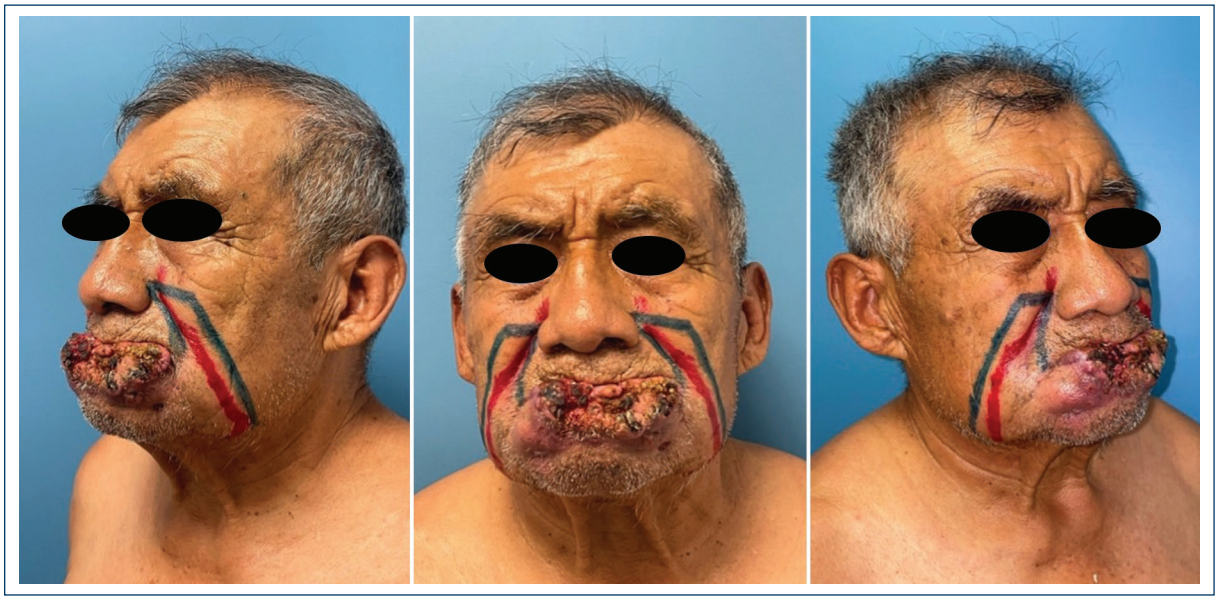

Figure 3. Patients in the immediate postoperative period of oncological resection showing defects involving the entire lower lip.

piriformis fossa and the lower one or pivot point even up to the mandibular ridge (Fig. 2). The oncosurgical team performs the tumor resection, in the first stage (Fig. 3). Subsequently, the second stage is performed, which consists of dissection in the cephalocaudal direction, performing a musculocutaneous flap, partially including the levator labii muscle and zygomaticus minor and major. The facial artery is ligated at the upper limit of the flap and included, preserving the buccinator muscle and oral mucosa. Along its course, the superior labial artery will be ligated and the flap is rotated 90° (Fig. 4).

Next, the Palmaris longus tendon is taken and sutured with two simple stitches with 3-0 nylon to the upper

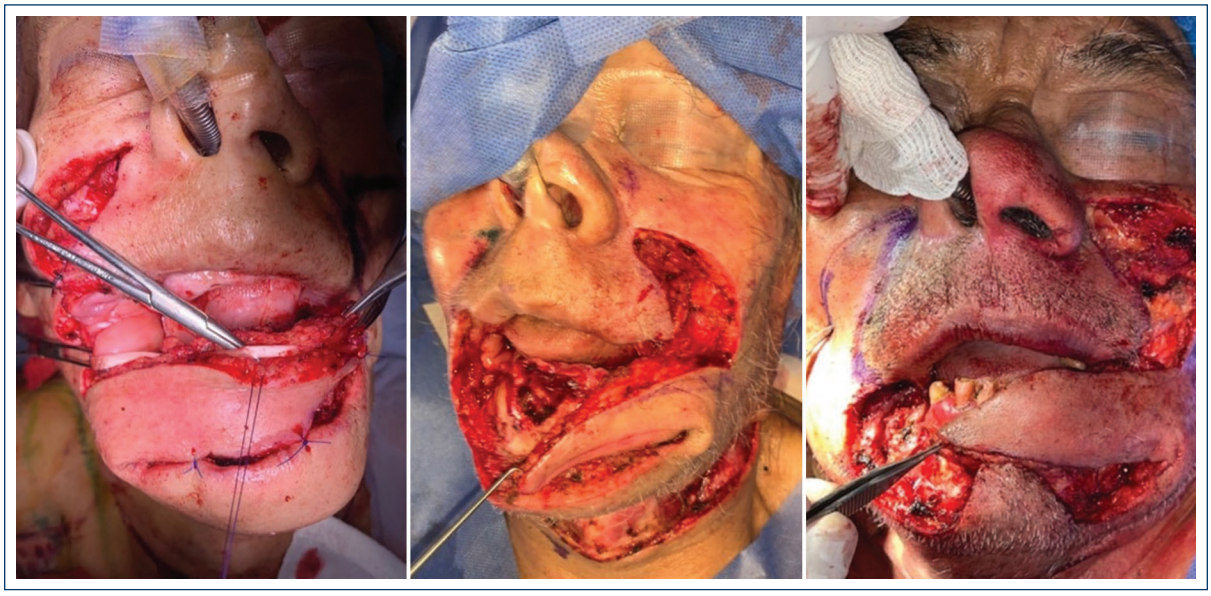

Figure 4. Trans-surgical images when performing a 90° rotation of the flap. Left image: the palmaris longus tendon can be seen passing through a bridge made subcutaneously in the flap.

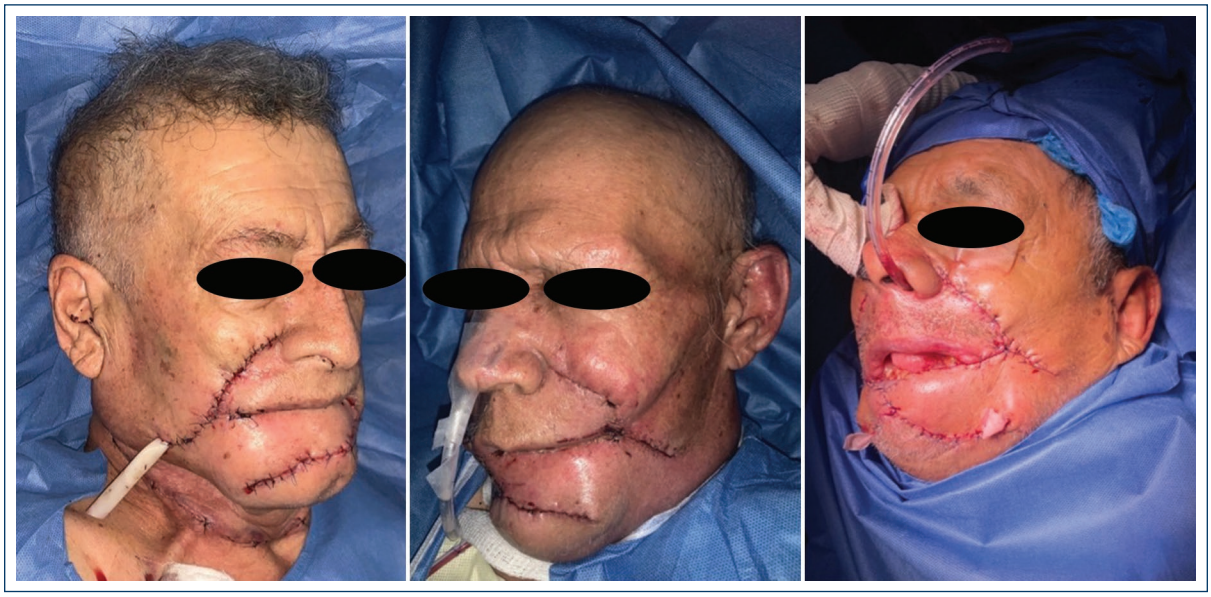

Figure 5. Immediate post-surgical result of the three patients.

portion of the ipsilateral orbicularis muscle and a pulley system is made in the modiolus, checking the traction of the orbicularis. Continuing, a bridge is made through the flap between the subcutaneous cellular tissue and its muscular portion until a new pulley system is created in the contralateral modiolus, and it is concluded by fixing it with 3-0 nylon to the contralateral orbicularis oculi muscle, with two points simple. Traction of the tendon graft is checked to ensure that the sphincter function of the mouth is adequate. The bloody area of muscle tissue in the oral cavity is covered with a full-thickness graft, taken in our case from the inguinal region, fenestrations are made to avoid seroma and hematomas, and it is fixed on the periphery with simple 4-0 polyglactin sutures. It is concluded by placing a nasogastric tube to protect the integrity of the graft in the oral mucosa (Fig. 5).

Figure 6. Post-surgical result of two patients at 6 months. Left image: the patient currently receiving radiotherapy and chemotherapy for tumor recurrence.

Surgical time for surgical resection and supraomohyoid neck dissection for oncosurgery was 90-120 min. Second surgical time modified gate flap is performed in 100 min with two surgical teams. Post-surgical management: a nasogastric tube is placed and oral fasting and enteral feeding are indicated for 7 days, then oral administration is restored with a soft consistency diet.

Follow-up

The first two patients progressed adequately and did not present complications associated with the flap or the graft and adequate oral competence (Fig. 6). The third patient (70 years old) died at the 4th month due to complications associated with oncological pathology.

Discussion

The gold standard for coverage of defects > 90% is free flaps, with the Chinese flap using the palmaris longus tendon being the main one[3].

Traditional local flaps for coverage of total or subtotal defects such as the Karapandzic flap[5] (bilateral lip advancement myocutaneous flap, with a design of continuation of the lip defect toward the nasolabial folds) Gillies flap[6] (or Fan-flap, which consists of advancing a full-thickness unilateral flap from the lip where the resection was performed, continuing the incision towards the labiomental sulcus and continuing over nasolabial fold) and Webster-Bernard[7] (modification of the Bernard flap, being a full-thickness flap, advanced, with excision of skin triangles based on the nasolabial fold, extending to the cheek, and moving them medially until they meet the contralateral flap, together with Webster's contribution with the excision of four triangles of cheek skin to allow advancement) provide adequate coverage of the defect, however, without preservation or partial preservation of the function, and obtaining as a result the main adverse effect: the microstoma.

The flaps described by Alic et al.[8] (modification of the Fujimori flap as it is unilateral full-thickness) and Gürel et al.[9] (carrying it out unilaterally or bilaterally as full-thickness Fujimori, with marking on the oral mucosa respecting papilla of the Stenon duct, in order not to injure it) with modifications of the original Fujimori technique, provide skin coverage without achieving oral continence or restoration of the sphincter of the mouth and represent a high risk of injury to the Stenon duct by including the mucosa oral, just as they do not give continuity to the oral sphincter.

There are reconstructive options with regional flaps such as the pectoral, deltopectoral, and mental flap for coverage of large defects; however, the esthetic and satisfaction result is affected from our point of view, as well as the impossibility of restoring oral competence.

This surgical proposal provides less morbidity of the donor site and less risk of complications associated with reconstruction, under the following premises: (1) it is unilateral, (2) the oral mucosa and buccinator muscle are respected, abolishing the risk of injury to the Stenon duct, (3) the length of the orbicularis muscle is restored by replacing it with a palmaris longus graft to preserve sphincter function, and (4) microstomia is avoided by not involving subunits of the lip for reconstruction.

Our technique is reproducible and requires an adequate knowledge of the anatomy of the face and neck, in addition to a close relationship with the oncosurgical team to preserve the facial artery.

It can be considered in results even superior to the current gold standard since it creates less donor site morbidity and provides the same oral competence with the use of the tendon graft, adding the pulley system.

Conclusion

The reconstructive gate flap option modified by the authors implies less morbidity as it is performed unilaterally, without presenting risk of injury to the Stenon duct; in addition, to recreating the oral sphincter through the pulley system with the palmaris tendon graft compared to the other techniques, where the main benefit is the coverage of the defect and not the oral competence that is achieved through this flap. In addition, we managed to avoid the most notorious adverse effect of the total reconstructions of the entire lip: the microstoma, by

respecting the integrity of our upper lip and the mucosa of our cheeks. The degree of satisfaction of the patients and the surgical team was favorable.

We consider the need to include a larger population to carry out an adequate statistical analysis of morbidities, complications, and evolution to have convincing evidence to support our surgical proposal as the gold standard for sequelae of this nature.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments have been performed on humans or animals for this research.

Data confidentiality. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

References

1. Neligan PC. Plastic Surgery. Craniofacial, Head and Neck Surgery and Pediatric Plastic Surgery. Lip Reconstruction. 4th ed., Vol. 3. Ch. 12. Netherlands: Elsevier Inc.; 2018. p. 305-28.
2. Roldan JC, Teschke M, Fritzer E, Dunsche A, Härle F, Wiltfang J, et al. Reconstruction of the lower lip: rationale to preserve the aesthetic units of the face. Plast Reconstr Surg. 2007l;120:1231-9.
3. Jeng SF, Kuo YR, Wei FC, Su CY, Chien CY. Total lower lip reconstruction with a composite radial forearm-palmaris longus tendon flap: a clinical series. Plast Reconstr Surg. 2004;113:19-23.
4. Fujimori R. "Gate flap" for the total reconstruction of the lower lip. Br J Plast Surg. 1980;33:340-5.
5. Karapandzic M. Reconstruction of lip defects by local arterial flaps. Br J Plast Surg. 1974;27:93-7.
6. Gillies HD, Frwde H, editors. Plastic Surgery of the Face. Vol. 40. London: Oxford University Press; 1920. p. 54-5.
7. Konstantinovi´c VS. Refinement of the fries and Webster modifications of the bernard repair of the lower lip. Br J Plast Surg. 1996;49: 462-5.
8. Alic B, Gürel M, Cilengir M, Seyhan A, Atlihan S. Unilateral gate flap for reconstruction of the lower lip. Plast Reconstr Surg. 1989;84: 814-9.
9. Gürel M, Alic B, Seyhan A, Cilengir M. Total lower lip reconstruction in advanced squamous carcinoma: application of the gate-flap technique. Ann Plast Surg. 1992;28:434-41.

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ORIGINAL ARTICLE

Association between lipid profile and gallbladder histopathology of post cholecystectomy patients

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Abstract

Introduction: *In cholelithiasis, lipid and histopathological alterations have been found and suggest the accumulation of lipids in the gallbladder tissue (cholesterolosis), due to the few existing reports a study was carried out to determine their association.* **Objectives:** *The aim of the study was to evaluate the association between the lipid profile and gallbladder histopathology in patients with cholelithiasis undergoing cholecystectomy.* **Methodology:** *An observational, cross-sectional, analytical, and prospective study was carried out in a group of patients from the Hospital General de México "Eduardo Liceaga" undergoing elective laparoscopic cholecystectomy from January 2015 to January 2020. With approval of the protocol by the ethics and research committee, the following variables were considered: age, sex, BMI, comorbidities (diabetes, dyslipidemia, hypertension, cirrhosis), LDL-C, HDL-C, total cholesterol, triglycerides, and histopathological findings (cholesterolosis, polyps, xanthogranulomatosis, acute cholecystitis, and cholecystitis chronicle). A descriptive and inferential analysis was performed with SPSS v.24. It was considered $p < 0.05$ as significant.* **Results:** *From a group of 302 patients, 133 cases (108 women and 25 men) were included in the study. They presented overweight (39%) and obesity (33%), the lipid profile with hypoalphalipoproteinemia (61%), hypertriglyceridemia (40%), hypercholesterolemia (17%), and elevated LDL-C (16%); and in histopathology chronic cholecystitis (70%), cholesterolosis (28%), and acute cholecystitis (7%).* **Discussion:** *Our sample is representative of the Mexican population (in physical characteristics and lipid profile). However, no significant association was found between dyslipidemia and histopathological findings.*

Keywords: *Lipid profile. Cholesterol, Cholesterolosis. Xanthogranulomatosis.*

Introduction

Cholelithiasis are hardened deposits (stones) of digestive fluid formed in the gallbladder, which are located within it or migrate to the main bile duct (MBD) and intrahepatic bile ducts. They are classified according to their composition and cholesterol stones are the most frequent with a prevalence of 10-15% in adults[1,2].

Its prevalence reaches its peak between 60-70 years (30% in women and 20% in men). However, studies indicate that its global prevalence is 64.1% in women and 29.5% in men[3]. It is a common problem in developed

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countries, representing a significant health burden, in the United States (EU) between 20 and 25 million adults have it[4], consuming up to $6.5 billion[5,6]. In Latin America, it occurs between 5 and 15%, and in Mexico 14.3% of adults present it (8.5% men and 20.5% women)[7].

More than 80% of cases are asymptomatic, only 10-20% will present symptoms within 5-20 years after diagnosis. Biliary colic occurs in 1-2% per year[8,9]. Its complications (cholecystitis, choledocholithiasis, pancreatitis due to gallstones, and cholangitis) occur with an annual rate of 0.1-0.3%[8]. Among its main risk factors are obesity, a diet rich in fat and a sedentary lifestyle[10,11].

Lipid profile abnormalities in patients with cholelithiasis

Altered serum lipids in cholelithiasis due to cholesterol stones suggest metabolic syndrome. More than half of patients with cholelithiasis could have a lipid disorder. It is accepted that the main event in the pathogenesis of cholesterol stones is altered lipid metabolism due to an increase in cholesterol levels compared to other lipids secreted by the liver into the bile[12].

Dyslipidemia is characterized by elevated levels of total cholesterol (TC), triglycerides (TG), low-density lipoproteins (LDL), and low levels of high-density lipoproteins (HDL). Studies have shown the association between dyslipidemia and stones, especially the increase in TG and LDL[13].

Channa et al. analyzed the serum lipid profile in patients with cholelithiasis and patients without cholelithiasis. They showed that elevated levels of TC, free cholesterol, LDL, TG, and reduced levels of HDL played an important role in the pathogenesis of gallstones in 45-year-old women with more than three children[14].

Acute/chronic cholecystitis is a chronic relapsing hepatobiliary disease, which can result from impaired metabolism of cholesterol, bilirubin, and bile acid. Many studies have shown an association between gallstones and abnormal lipids[15,16]. Due to cholelithiasis, various histopathological changes are produced in the mucosa of the gallbladder (acute, chronic and granulomatous inflammation, hyperplasia, cholesterolosis, dysplasia, and carcinoma). Being symptomatic, therapeutic intervention is necessary[17].

The objective of this study was to investigate the association between the histopathological finding of gallbladder lithiasis (secondary to an inflammatory process, hyperplasia, metaplasia, or carcinoma) and the lipid profile of patients undergoing laparoscopic cholecystectomy.

Material and methods

An observational, cross-sectional, analytical, and retrospective study was carried out. Records of patients over 18 years of age from the "Eduardo Liceaga" General Hospital of Mexico, who underwent laparoscopic cholecystectomy for cholelithiasis were analyzed in the period of January 2015 to January 2020. The pre-operative lipid profile was considered. Cases of patients older than 18 years of both sexes who underwent laparoscopic cholecystectomy for cholelithiasis were included in the study. Patients with incomplete clinical records were excluded from the study. The study was submitted for review by the Research Bioethics Committee of the General Hospital of Mexico "Eduardo Liceaga". Obtaining the following variables age, sex, BMI, comorbidities (diabetes, dyslipidemia, hypertension, cirrhosis, and other), LDL-c, HDL-c, TC, TG, cholesterolosis, polyps, xanthogranulomatosis, acute cholecystitis, chronic cholecystitis, and other finding histopathological. For the statistical analysis, the IBM SPSS version 24 software was used.

Results

Three hundred and two files were reviewed, of which 133 met the inclusion criteria. Twenty-five were men and 108 women, with an average age of 42.5 ± 13.86 years. The average weight in men was 77 ± 11.91 kg and 68.43 ± 12.03 kg for women. Height was 1.68 ± 0.08 m in men and 1.56 ± 0.06 m in women. The BMI in male patients was 27.86 ± 4.0 kg/m^2 and 27.92 ± 4.34 kg/m^2 in female patients.

Serum levels of LDL, HDL, cholesterol, and triglycerides of patients

TC levels were 172.5 ± 41.94 mg/dl, TG 165.1 ± 114.06 mg/dl, LDL-c 110 ± 42.67 mg/dl, and HDL-c 46.8 ± 12.82 mg/dl. In addition, the proportion of patients who presented abnormal values of these lipids was analyzed. It was found that 16.5% of the patients had hypercholesterolemia (values > 200 mg/dl), 39% hypertriglyceridemia (> 150 mg/dl), 16.5% high levels of c-LDL (> 130 mg/dl), and 57.8% low levels of c-HDL (< 50 mg/dl) (Fig. 1).

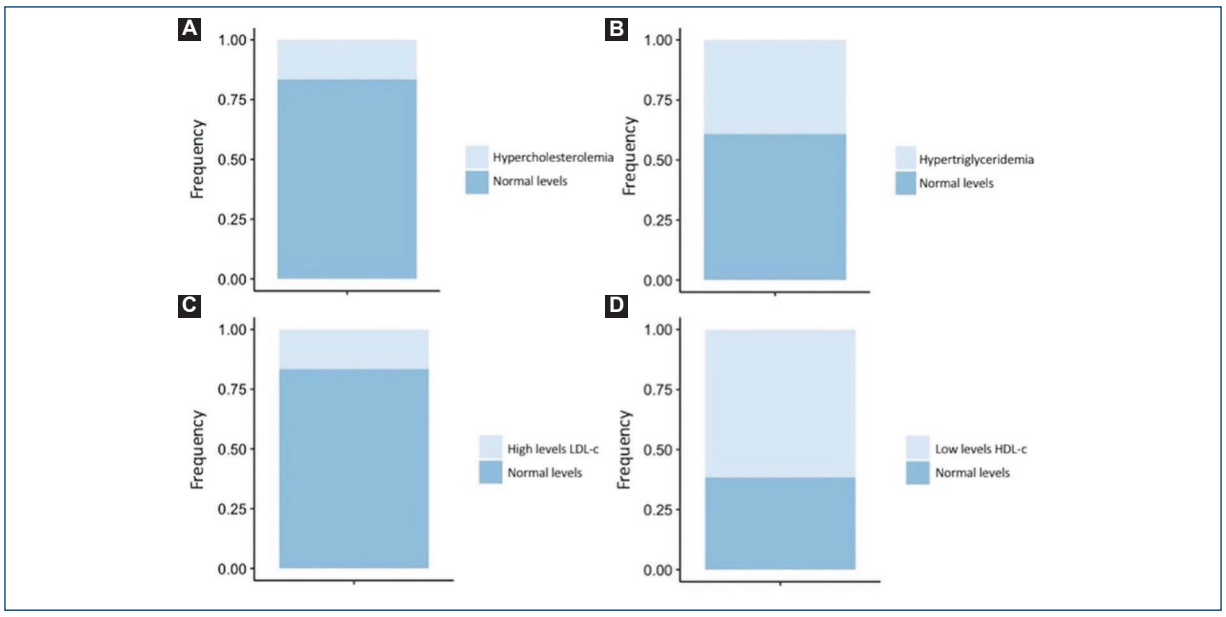

Figure 1. Proportion of patients with abnormal serum values. **A:** cholesterol. **B:** triglycerides. **C:** LDL-c. **D:** HDL-c.

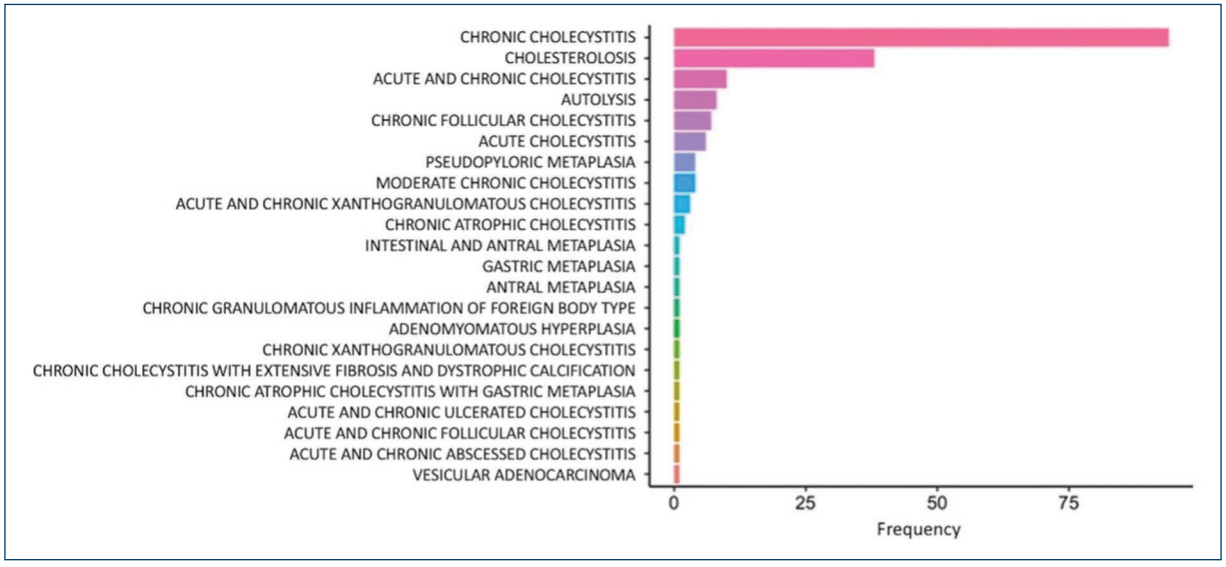

Figure 2. Frequency of pathologies in histopathological reports.

Frequency of cholesterolosis, polyps, xanthogranulomatosis, acute cholecystitis, chronic cholecystitis, and other histopathological findings

Chronic cholecystitis was found in 94 cases, cholesterolosis in 38, acute and chronic cholecystitis in 10, autolysis in 8, and adenocarcinoma in one case (Fig. 2).

Comparison between dyslipidemias and normal levels with reported pathologies

The Chi-square test was performed (CI 122-197) to evaluate the concordance between dyslipidemia with each reported pathology, without finding an association (Table 1). The four most common pathology reports were compared with dyslipidemia data, without finding an association (Table 2).

Table 1. Comparison of dyslipidemias with all pathology reports

Pathology	Total n (%)	p-value
Hypercholesterolemia	22 (16.54 %)	0.07
Hypertriglyceridemia	52 (39.09 %)	0.07
High levels of LDL	22 (16.54 %)	0.07
Low levels of HDL	77 (57.89 %)	0.08

Table 2. Comparison between main findings of pathology with dyslipidemia

Alterations in lipid profile	Total n (%)	p-value
Hypercholesterolemia	22 (21.35 %)	0.0614
Hypertriglyceridemia	52 (50.48 %)	0.18
High levels of LDL	22 (21.35 %)	0.17
Hypoalphalipoproteinemia	77 (74.75 %)	0.23

Discussion

In the sociodemographic characteristics of our patients, 33% presented obesity and 39% overweight, compared with the national characteristics where 39.1% presented obesity and 36.1% overweight. Regarding dyslipidemia, 17% had hypercholesterolemia, 40% hypertriglyceridemia, 16% high levels of LDL-c, and 61% low levels of HDL-c (hypoalphalipoproteinemia). In Mexico, 31% have hypercholesterolemia, 47% hypertriglyceridemia, and 55.2% hypoalphalipoproteinemia[18]. Histopathological reports coincide with the three phases of gallbladder inflammation from cystic duct obstruction (edema, hemorrhage, and gallbladder wall necrosis and leukocyte infiltration with subsequent wall necrosis and perforation)[5].

Among the international studies with the largest number of patients is the one of Yaylak et al., who reported 429 cases. The most common report was cholesterolosis (18%), followed by acute cholecystitis (10.7%). Battha and Singh reported 287 cases demonstrating chronic cholecystitis in 73.3% of cases. In our study, the most common finding was chronic cholecystitis (70%), cholesterolosis (28%), and acute cholecystitis (7%). No significant correlation between dyslipidemia and histopathological findings was found in comparison with the study by Battha and Singh[19,20]. However, we highlight the findings of gastric metaplasia and adenomyomatous hyperplasia in patients with altered lipid profile.

Conclusions

Alterations in the lipid profile were not associated with the following histopathological findings: Chronic cholecystitis, cholesterolosis, and xanthogranulomatosis in patients after elective laparoscopic cholecystectomy. However, the association of dyslipidemia with gastric metaplasia and adenomyomatous hyperplasia can be studied in a larger population. It should be noted that there are few reports that list all the histopathological findings of the gallbladder in the Mexican population, despite the fact that it is a very common pathology in our country, as we have already described. This, together with the characteristics of our population (overweight, obesity, and dyslipidemia) represents an area of opportunity in studies with a greater number of cases.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments have been performed on humans or animals for this research.

Data confidentiality. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. Tanaja J, Lopez RA, Meer JM. Cholelithiasis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
2. Lammert F, Gurusamy K, Ko CW, Miquel JF, Méndez-Sánchez N, Portincasa P, et al. Gallstones. Nat Rev Dis Prim. 2016;2:16024.
3. Payen JL, Muscari F, Vibert E, Ernst O, Pelletier G. [Biliary lithiasis]. Presse Med. 2011;40:567-80.

4. Shaffer EA. Gallstone disease: epidemiology of gallbladder stone disease. Best Pract Res Clin Gastroenterol. 2006;20:981-96.
5. Gallaher JR, Charles A. Acute cholecystitis. Clinical review. JAMA. 2022;327:965-75.
6. Shaffer EA. Epidemiology and risk factors for gallstone disease: has the paradigm changed in the 21st century? Curr Gastroenterol Rep. 2005;7: 132-40.
7. Almora CL, Prado YA, González TP, Ferro YP, Hernández ZH. Diagnóstico clínico y epidemiológico de la litiasis vesicular. Revisión bibliográfica. Rev Cien Méd Pinar Río. 2012;16:200-14.
8. Pedersen G, Hoem D, Andrén-Sandberg A. Influence of laparoscopic cholecystectomy on the prevalence of operations for gallstones in Norway. Eur J Surg. 2002;168:464-9.
9. Yoo KS. Management of gallstone. Korean J Gastroenterol. 2018;71:253-9.
10. Casper M, Lammert F. Gallstone disease: basic mechanisms, diagnosis and therapy. Praxis (Bern 1994). 2011;100:1403-12.
11. Ruhl CE, Everhart JE. Gallstone disease is associated with increased mortality in the United States. Gastroenterology. 2011;140: 508-16.
12. Batajoo H, Hazra NK. Analysis of serum lipid profile in cholelithiasis patients. J Nepal Health Res Counc. 2013;11:53-5.
13. Wang J, Shen S, Wang B, Ni X, Liu H, Ni X, et al. Serum lipid levels are the risk factors of gallbladder stones: a population-based study in China. Lipids Health Dis. 2020;19:50.
14. Channa NA, Ghanghro AB, Soomro AM. Quantitative analysis of serum lipid profile in gallstone patients and controls. Pak J Anal Environ Chem. 2010;11:7.
15. Hayat S, Hassan Z, Changazi SH, Zahra A, Noman M, Ul Abdin M, et al. Comparative analysis of serum lipid profiles in patients with and without gallstones: a prospective cross-sectional study. Ann Med Surg (Lond). 2019;42:11-3.
16. Shabanzadeh DM. Incidence of gallstone disease and complications. Curr Opin Gastroenterol. 2018;34:81-9.
17. Sing A, Singh G, Kaur K, Goyal G, Saini G, Sharma D. Histopathological changes in gallbladder mucosa associated with cholelithiasis: a prospective study. Niger J Surg. 2019;25:21-5.
18. ENSANUT. Encuesta Nacional de Salud y Nutrición 2018-19. SS México: ENSANUT.
19. Bhatta S, Singh S. Study of gallbladder lesions and its relationship with serum lipid profile. Int J Adv Med. 2018;5:1245-9.
20. Yaylak F, Deger A, Ucar BI, Sonmez Y, Bayhan Z, Yetisir F. Cholesterolosis in routine histopathological examination after cholecystectomy: what should a surgeon behold in the reports? Int J Surg. 2014;12:1187-91.

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ORIGINAL ARTICLE

Frequency and clinical association of *NY-ESO-1* gene expression in diffuse large B-cell lymphoma

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Abstract

Objective: *Our objective was to evaluate the frequency of expression and determine the expression levels of the NY-ESO-1 gene in patients with DLBCL as well as to examine its relationship with clinical parameters and survival.* **Methods:** *We analyzed NY-ESO-1 gene expression levels using real-time quantitative RT-PCR (RT-qPCR) in 112 patients with DLBCL. The associations between the expression of the NY-ESO-1 gene and the clinical variables were evaluated using the Chi-square test and Fisher's exact test. Overall survival (OS) was determined using the Kaplan–Meier method.* **Result:** *The results showed that the NY-ESO-1 gene was expressed in 46.4% (52/112) of patients with DLBCL, and NY-ESO-1 gene expression was associated with clinical parameters such as LDH, clinical stage, and International Prognostic Index (IPI) ($p \leq 0.05$). High levels of NY-ESO-1 gene expression were associated with advanced disease stages, and the survival rates after 5.3 years of tracking were lower in the patients expressing the NY-ESO-1 gene (66.4%) than in those not expressing the gene (23.1%).* **Conclusion:** *The expression levels of the NY-ESO-1 gene in patients with DLBCL may be of great utility for diagnosing and determining the prognosis of this disease.*

Keywords: *DLBCL. NY-ESO-1. Lymphoma.*

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma, and it is responsible for approximately 30-50% of all new cases[1,2]. DLBCL represents a heterogeneous group of tumors with highly variable genetic abnormalities, clinical characteristics, responses to treatment, and prognosis[3-5]. The diagnosis of DLBCL is accomplished through histopathological studies and immunophenotyping. The following clinical criteria are currently used for determining the prognosis of this disease: clinical stage, functional state (ECOG), International Prognostic Index (IPI), LDH levels, and β2 microglobulin levels. Despite advances in immunotherapy (anti-CD20 therapy) as well as the incorporation of new cytotoxic agents (bendamustine), a select group of patients continues to have an unfavorable prognosis[6].

The subdivision of DLBCL into two major biological categories based on their presumed cell of origin: germinal center B cell (GCB), and activated B cell (ABC)[7].

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Several molecular alterations have been identified in DLBCL, such as the expression of the *NY-ESO-1* gene (New York esophageal squamous cell carcinoma-1), which is part of the group of cancer-testis antigen (CTA)[8-9]. This gene encodes a protein that is overexpressed in many cancers, but absent in normal tissue except for testicular[10-11]. This gene is found in a duplicated region of the X-chromosome and, therefore, has a neighboring gene of identical sequence. It has been used to diagnose and assess the prognosis of various types of cancer[11-12], and its expression is restricted solely to immune-privileged germinal cells, which are the most immunogenic of this family[13-14]. It is abnormally expressed in a variety of cancers and is associated with the unfavorable evolution of cancer of the cervix and breast, as well as multiple myeloma and non-small cell lung cancer[15-19].

Levels of expression of the *NY-ESO-1* gene were analyzed in patients with DLBCL using quantitative RT-PCR (RT-qPCR) in real time and relationship between the clinical parameters and survival rate, the detection of *NY-ESO-1* by RT-qPCR could be useful for disease prognosis and follow-up.

Materials and methods

Type of study

This was a prospective, descriptive observational, clinical study between April 2018 and June 2020.

Study population

This was a prospective clinical study with 112 patients with DLBCL who had previously provided signed informed consent forms. The histological diagnosis was established according to the World Health Organization (WHO) classification (SH, 2020). Approval for the present study was provided by the Ethics Committee of the Hospital General de Mexico "Dr. Eduardo Liceaga." The informed written consents were collected from all enrolled patients and the entire study was performed based on the Declaration of Helsinki.

The study population was characterized according to their clinical parameters, including prior medical history, disease stage, and levels of lactate dehydrogenases (LDHs). The average age was 45 years (range 18-69), and 46.4% were male and 53.5% female. The patients were treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Patients who showed a partial response to treatment were treated with dexamethasone, etoposide, and cisplatin as second-line chemotherapy at the discretion of the treating doctor. The survival global analysis was conducted after 5.3 years.

Lymph node biopsies

Lymph nodes from the patients were frozen in liquid nitrogen immediately after surgical excision and stored until RNA extraction.

Testicular tissue

Testicular tissue from a 60-year-old patient with prostate cancer was used to determine the levels of relative expression basal of the *NY-ESO-1* gene.

RNA extraction and cDNA preparation

Total cellular RNA was extracted from the frozen tissue and the controls using TRIzol® Reagent (Life Technologies, Paisley, UK). The RNA was stored at –80°C until needed. A total of 2 μg of RNA was used for the synthesis of cDNA by means of the reverse transcriptase M-MLV (Life Technologies, Paisley, UK).

Quantitative real-time PCR assay

The mRNA expression levels of the *NY-ESO-1* (Hs00265824_m1)[19] and glyceraldehyde 3-phosphate dehydrogenase (GAPDH; Hs00985689) genes were measured using the TaqMan® gene expression assay (Applied Biosystems, Foster City, CA, USA). The *GAPDH* gene was used as an endogenous control, and each sample was analyzed in triplicate.

The relative gene expression levels were calculated by the $2^{-\Delta\Delta Ct}$ method. We used the median as cutoff between high and low expression.

Statistical analysis

The analyses between *NY-ESO-1* gene expression and the clinical variables were performed using Chi-square test and Spearman test. The survival data were analyzed using the Kaplan–Meier method and compared with the log-rank test, considering $p \leq 0.05$ to be statistically significant. The statistical program S.P.S.S. version 20 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, USA) was used for the analyses.

Results

Frequency of NY-ESO-1 expression at the mRNA level in DLBCL patients

The frequency of *NY-ESO-1* gene expression was 46.4% (52/112). The levels of relative expression with respect to control (testicular tissue) were 0.2 times in Stages I/II, while in Stages III/IV, they were 1.5 times and 2.2 times, respectively, (Fig. 1). The expression levels were significantly different between Stages III and IV in comparison with Stage I/II, revealing a relation hip between the level of expression and advanced-stage disease (p = 0.007).

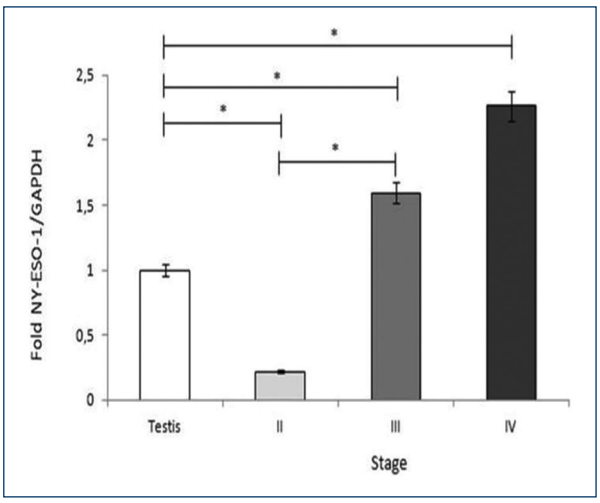

Figure 1. mRNA expression levels of *NY-ESO-1* in DLCBL stages. The expression results were obtained from four samples from Stages I and II, 48 from Stages III and IV. Significant differences between results ($p \leq 0.5$) were obtained means of parametric test. T, testicular tissue.

Association of NY-ESO-1 expression with clinical variables

The statistical analysis showed significant values for the parameters of LDH, clinical stage, and IPI ($p \leq 0.05$). Elevated LDH levels in serum and a high IPI were associated with gene expression in 39.2% (p = 0.001) and 32.1% (p = 0.019) of the patients, respectively. In addition, 42.8% of the positives were associated with clinical Stage III or IV (p = 0.001) (Table 1).

Expression of NY-ESO-1 and its relation to the survival rate

The study was performed over 5.3 years, and survival median at 3 years was 23.1% for the positive patients and 66.4% for the negative patients (Fig. 2). During this period, we observed that 76.9% (40/52) of the patients expressing *NY-ESO-1* died. In contrast, 33.3% (20/60) of the negative patients died. In the statistical analysis, a log-rank value of p = 0.001 was calculated.

Discussion

Patients with DLBCL exhibit heterogeneous clinical characteristics, as well as variability in their responses to treatment and prognoses[20-22]. Although survival can be estimated based on clinical parameters (age, LDH levels in serum, extranodal site involvement, disease stage, and immunophenotype B), as well as molecular abnormalities (*p53, BCL-2, BCL6, MUM.1, and Ki67*), controversy exists regarding their utility as prognostic and survival markers[23]. As a result, it is of paramount importance to find new markers that could be incorporated to determine the prognosis of this disease.

We evaluated the clinic pathological relevance of *NY-ESO-1* gene expression in patients with DLBCL at diagnosis who were admitted to the hematology service of the Hospital General de México. We decided to examine the expression of the *NY-ESO-1* gene in patients with lymphoma, as it is a CTA present in various types of cancer and is associated with clinical factors such as poor prognosis and lower survival[24-25]. We confirmed that *NY-ESO-1* gene expression is associated with the advanced stage of the disease, changes in the levels of LDH and the IPI, and survival rates. In DLBCL, there are no reports of an association between the expression of this gene and clinical parameters. Hudolin et al.[26] analyzed the expression of the *NY-ESO-1* gene in 24 samples of testicular tissue with DLBCL; expression was observed in 54.1% and was not correlated with clinical parameters or survival. We observed that the percentage of expression of the *NY-ESO-1* gene in the stages of the disease in patients with DLBCL was 3.5% in Stages I-II and 42.8% in Stages III-IV. These results are consistent with the previous reports on melanoma in which a percentage of 3.34% was observed in Stage I and 9.52% in Stage II, and up to 45% in Stage III[27]. Similar results were reported in bladder and prostate cancer, where the frequency of expression increases with respect to the stage of the disease[28-30].

Only two studies have measured the expression levels in metastatic esophageal squamous cell carcinoma

Table 1. Associations between clinical characteristics and NY-ESO-1 expression in DLBCL patients

	Expression	No expression
Median (range)	58 (18-69)	37 (19-65)
Sex Male Female	 (%) 20 (17.8) 32 (28.5)	 (%) 32 (28.5) 28 (25)
More than 1 extra nodal site Yes No	 32 (28.5) 20 (17.8)	 20 (17.85) 40 (35.7)
ECOG performance status greater 0 1 2 3 4	 0 28 (25) 24 (21.4) 0 0	 4 (3.5) 48 (42.8) 8 (7) 0 0
Serum LDH level > normal Yes No	 44 (39.2) 8 (7)	 12 (10.7) 48 (42.8) 0.001*
IPI Low Low-intermediate High	 4 (3.5) 12 (10.7) 36 (32.1)	 28 (25) 20 (17.8) 12 (10.7) 0.019*
Stage I-II III-IV	 4 (3.5) 48 (42.8)	 40 (35.7) 20 (17.8) 0.001*

*Chi-square value significance level $p \leq 0.05$.
LDH: lactate dehydrogenase.

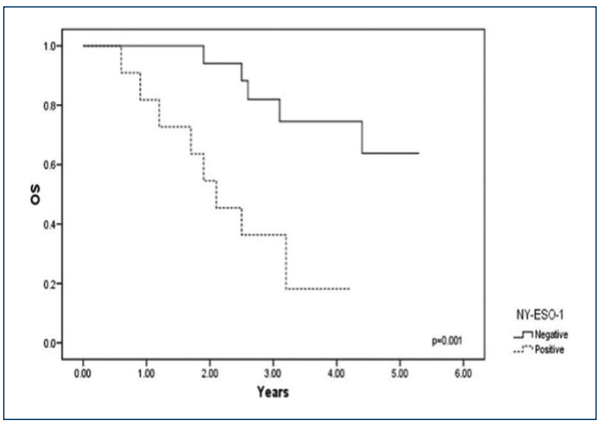

Figure 2. Overall survival in DLCBL patients based on the *NY-ESO-1* expression. The 5.3 years overall survival rate is analyzed in patients. Survival median at 3 years was 23.1 for the positive and 66.4% for the negative patients ($p = 0.001$).

and non-small-cell lung cancer using RT-qPCR, and elevated transcription levels were associated with advanced disease stages[31-32].

The increase in the level of *NY-ESO-1* gene transcription in patients with DLBCL is a finding of great importance; it could be a prognostic marker for this disease. In addition, the increase in advanced stages of the disease may explain its oncogenic role and the proliferative advantage it confers to tumor cells[33-34].

Global survival is lower in patients who express *NY-ESO-1*, and these results concur with those reported for lung cancer, demonstrating that the expression of *NY-ESO-1* is significantly associated with an adverse prognosis[35]. Similar data associating the expression of this gene with decreased disease-free survival have been reported for gastrointestinal and bladder cancer[36]. Other reports have examined the associations between the expression of the *p53, bcl-2, and ki67* genes and global survival in patients with DLBCL and did not observe an association[37]. Rearrangements of the *BCL-6* gene have been associated with 50% survival at 5 years in patients treated with R-CHOP, although the reported expression frequency was only 19%[38]. We have reported that the *MAGE-A3* gene is associated with a decrease in survival in patients with DLBCL[39].

NY-ESO-1 gene expression in patients with DLBCL may be helpful for identifying and stratifying risk groups, with other molecular marker of this disease that may benefit from new or intensified therapies.

Conclusion

Our results demonstrate that expression of the *NY-ESO-1* gene is associated with a poor prognosis of patients with DLBCL, and it is highly important to incorporate this gene into panels of existing molecular markers.

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Conflicts of interest

The authors declare that do not exist conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments have been performed on humans or animals for this research.

Data confidentiality. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

References

1. Humberto BC, Omar RP, Carlos MM, Horacio MF, Juan CJ. Quimioterapia en linfoma no Hodgkin: 17 años de experiencia en el hospital general de México. Rev Med Hosp Gen Mex. 2010;73:213-8.
2. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jafee ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. 2011;117:5019-32.
3. Hernandez-Ruiz E, Alvarado- Ibarra M, Juan Lien-Chang LE, Banda-Garcia L, Aquino-Salgado JL, Barragan-Ibanez G, et al. Epidemiology and clinical characteristics of Non-Hodgkin Lymphoma in Mexico. World J. Oncol. 2021;12(1):28-33.
4. Hartmann EM, Ott G, Rosenwald A. Molecular biology and genetics of lymphomas. Hematology Oncol Clin North Am. 2008;22:807-23.
5. Harris NL, Stein H, Coupland SE, Hummel M, Favera RD, Pasqualucci L, et al. New approaches to lymphoma diagnosis. Hematology Am Soc Hematol Educ Program. 2001;1:194-220.
6. Brenner H, Gondos A, Pulte D. Ongoing improvement in long-term survival of patients with Hodgkin disease at all ages and recent catch-up of older patients. Blood. 2008;111:2977-83.
7. Velazquez EF, Jungbluth AA, Yancovitz M, Gnjatic S, Adams S, O'Neill D, et al. Expression of the cancer/testis antigen NY-ESO-1 in primary and metastatic malignant melanoma (MM)-correlation with prognostic factors. Cancer Immun. 2007;12:11.
8. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. N Engl J Med. 2002;346:235-42.
9. Hofmann M, Ruschenburg I. mRNA detection of tumor-rejection genes BAGE, GAGE, and MAGE in peritoneal fluid from patients with ovarian carcinoma as a potential diagnostic tool. Cancer. 2002;96:187-93.
10. Yakirevich E, Sabo E, Lavie O, Mazareb S, Spagnoli GC, Resnick MB. Expression of the MAGE-A4 and NY-ESO1 cancer-testis antigens in serous ovarian neoplasms.Clin Cancer Res. 2003;9:6453-60.
11. Gnjatic S, Nishikawa H, Jungbluth AA, Güre AO, Ritter G, Jäger E, et al. NY-ESO-1: review of a immunogenic tumor antigen. Adv Cancer Res. 2006;95:1-30.
12. Chen YT, Scanlan MJ, Sahin U, Türeci O, Gure AO, Tsang S, et al. A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening. Proc Natl Acad Sci U S A. 1997; 94:1914-8.
13. Napoletano C, Bellati F, Tarquini E, Tomao F, Taurino F, Spagnoli G, et al. MAGE-A and NY-ESO1 expression in cervical cancer: prognostic factors and effects of chemotherapy. Am J Obstet Gynecol. 2008;198:99.e1-7.
14. Bandi- D, Jureti- A, Sarcevi- B, Separovi- V, Kujundzić-Tiljak M, Hudolin T, et al. Expression and possible prognostic role of MAGE-A4, NY-ESO1, and HER-2 antigens in women with relapsing invasive ductal breast cancer: retrospective immunohistochemicalstudy.Croat Med J. 2006;47:32-41.
15. Krüger S, Ola V, Feller AC, Fischer D, Friedrich M. Expression of cancer-testis antigen CT7 (MAGE-C1) in breast cancer: an immunohistochemical study with emphasis on prognostic utility.Pathol Oncol Res. 2007;13:91-6.
16. Andrade VC, Vettore AL, Felix RS, Almeida MS, Carvalho F, Oliveira JS, et al. Prognostic impact of cancer/testis antigen expression in advanced stage multiple myeloma patients. Cancer Immun. 2008;8:2.
17. Li J, Yin J, Zhong J, Yang Z, Tang A, Lis S. Clinicopathological and Pronostic Significance of PRAME overexpression in Human cancer: A Meta-Analysis. Biomed Res Int.2020;2020:8828579.
18. John T, Starmans MH, Chen YT, Russell PA, Barnett SA, White SC, et al. The role of cancer-testis antigens as predictive and prognostic markers in non-small cell lung cancer. PLoS One. 2013;8:e67876.
19. Cerón-Maldonado R, Martínez-Tovar A, Ramos-Peñafiel CO, Miranda-Peraltaa E, Mendoza-Salasa I, Mendoza-Garcíac E. Detection and analysis of tumour biomarkers to strengthen the diagnosis of acute and chronic leukaemias. Rev Med Hosp Gen Mex. 2015;78:78-84.
20. Larouche J, Berger F, Chassagne-Clement C, Sebban C, Ghesquieres H, Salles G, et al. Lymphoma recurrence 5 years or more following diffuse large B-cell lymphoma: clinical characteristics and outcome. J Clin Oncol. 2009;27:8562.
21. Alonso-Alvarez S, Redondo-Guijo A, Blanco Ó, Alcoceba M, Balanzategui A, Caballero JC, et al. Lymphoma heterogeneity: threedifferenthistologicalpictures and oneunique clone. Case Rep Hematol. 2016;2016:3947510.
22. Van Rhee F, Szmania SM, Zhan F, Gupta SK, Pomtree M, Lin P, et al. NY-ESO1 is highly expressed in poor-prognosis multiple myeloma and induces spontaneous humoral and cellular immune responses. Blood. 2005;105:3939-44.
23. Küçükzeybek BB, Bener S, Çallı AO, Paksoy TD, Payzin B. Prognostic significance of Bcl-2 and p53 protein expressions and Ki67 proliferative index in diffuse large B-cell lymphoma. Turk J Haematol. 2013;30:275-82.
24. Bujas T, Marusic Z, Balja MP, Mijic A, Kruslin B, Tomas D. MAGE-A 3/4 and NY-ESO-1 antigens expression in metastatic esophageal squamous cell carcinoma. Eur J Histochem. 2011;55:e7.
25. Endo M, De Graaff M, Ingram DM, Lim S, Lev DC, Bruijn IH, et al. NY-ESO-1 (CTAG1B) expression in mesenchymal tumors. Mod Pathol. 2015;28:587-95.
26. Ok CY, Li L, Xu-Monette ZY, Visco C, Tzankov A, Manyam GC, et al. Prevalence and clinical implications of epstein-barr virus infection in de novo diffuse large B-cell lymphoma in western countries. Clin Cancer Res. 2014;20(9):2338-2349.
27. Hudolin T, Kastelan Z, Ilic I, Levarda-Hudolin K, Basic-Jukic N, Rieken M, et al. Immuno histochemical analysis of the expression of MAGE-A and NY-ESO1 cancer/testi antigens in diffuse large cell testicular lymphoma. J Transl Med. 2013;11:123.
28. Dyrskjot L, Zieger K, Lildal TK, Reinert T, Gruselle O, Coche T, et al. Expression of MAGE-A3, NY-ESO1, LAGE-1 and PRAME in urothelial carcinoma. Br J Cancer. 2012;107:116-22.
29. Nakada T, Noguchi Y, Satoh S, Ono T, Saika T, Kurashige T, et al. NY-ESO1 mRNA expression and immunogenicity in advanced prostate cancer. Cancer Immun. 2003;3:10.
30. Kurashige T, Noguchi Y, Saika T, Ono T, Nagata Y, Jungbluth A, et al. NY-ESO1 expression and immunogenicity associated with transitional cell carcinoma: correlation with tumor grade. Cancer Res. 2001;61:4671-4.
31. Szender JB, Papanicolau-Sengos A, Eng KH, Miliotto AJ, Lugade AA, Gnjatic S, et al. NY-ESO-1 expression predicts an aggresive phenotype of ovarian cancer. Gynecol Oncol. 2017;145(3):420-425.
32. John T, Starmans MH, Chen YT, Russell PA, Barnett SA, White SC, et al. The role of cancer-testis antigens as predictive and prognostic markers in non-small cell lung cancer. PLoS One. 2013;8:e67876.
33. Olarte I, Martinez A, Ramos-Peñafiel C, Castellanos-Sinco H, Zamora J, Collazo-Jaloma J, et al. MAGE-A3 expression is an adverse prognostic factor in diffuse large B-cell lymphoma. Hematology. 2011;16:368-72.
34. Mendoza-Salas I, Olarte-Carrillo I, Miranda-Peralta E, Ramos-Peñafiel C, García-Laguna A, Cerón-Maldonado R, et al. Frequency of cancer testis antigens in chronic myeloid leukemia. Rev Med Hosp Gen Mex. 2016;79:46-5.
35. Gure AO, Chua R, Williamson B, Gonen M, Ferrera CA, Gnjatic S, et al. Cancer-testis genes are coordinately expressed and are markers of poor outcome in non-small cell lung cancer. Clin Cancer Res. 2005;11:8055-62.
36. Perez D, Hauswirth F, Jager D, Metzger U, Samartzis EP, Went P, et al. Protein expression of cancer testis antigens predicts tumor recurrence and treatment response to imatinib in gastrointestinal stromal tumors. Int J Cancer. 2011;128:2947-52.
37. Shustik J, Han G, Farinha P, Johnson NA, Ben Neriah S, Connors JM, et al. Correlations between BCL6 rearrangment lymhoma treated with CHOP or RCHOP. Hematologica. 2010 Jan;95(1):96-101.
38. Monte M, Simonatto M, Peche LY, Bublik DR, Gobessi S, Pierotti MA, et al. MAGE-A tumor antigens target p53 transactivation function through histone deacetylase recruitment and confer resistance to chemotherapeutic agents. Proc Natl Acad Sci U S A. 2006;103:11160-5.
39. Kawano R, Karube K, Kikuchi M, Takeshita M, Tamura K, Uike N, et al. Oncogene associated cDNA microarray analysis shows PRAME gene expression is a marker for response to anthracycline containing chemotherapy in patients with diffuse large B-cell lymphoma. J Clin Exp Hematop. 2009;49:1-7.

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REVIEW ARTICLE

Gastrointestinal symptoms and disorders related to COVID-19. Lessons learned from gastroenterologists

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Abstract

COVID-19 is mainly a respiratory illness caused by the SARS-CoV-2 but can also lead to GI symptoms. The primary host receptor which mediates the mechanism as SARS-CoV-2 enters the cell is the ACE2 receptor. Therefore, GI symptoms can be common in COVID-19, and in some cases, they are the first manifestation even before fever and respiratory symptoms. In addition, the liver function tests alteration often is related to a worse prognosis. The exact incidence of GI symptoms is a matter of debate. Moreover, wide variation concerning GI symptoms frequency exists, but the predominant ones seem to be diarrhea, anorexia, nausea, vomiting, and abdominal pain or discomfort. This review summarizes the most relevant findings of COVID-19 on the digestive system, including the liver, biliary tract, pancreas, the most common GI symptoms, and the atypical clinical GI manifestations.

Keywords: *Coronavirus disease 2019. Severe acute respiratory syndrome coronavirus 2. Gastrointestinal symptoms. Pancreatitis. Liver injury. Gastrointestinal bleeding.*

Introduction

Coronavirus disease 2019 (COVID-19) is mainly a respiratory disorder due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. However, more recent evidence now considers it a multisystemic infectious disease, and the digestive tract is one of the systems that could be affected[2]. This disease is characterized by fever, dry cough, fatigue, and lymphopenia, in some cases leading to severe acute respiratory syndrome (SARS), organ dysfunction, and death[3]. Fever is the most common symptom of COVID-19, which occurs in 83-98% of patients followed by cough in 46-82% of patients. Overall, 80% of those infected in Hubei Province, China, were described as mild cases, 13.8% were severe cases warranting hospitalization, and 6.1% needed intensive care unit (ICU) care. COVID-19 may progress to severe bilateral pneumonia and acute respiratory distress syndrome requiring prolonged mechanical ventilation[4].

Many extrapulmonary manifestations of COVID-19 have been described, suggesting that the hematologic, cardiovascular, renal, gastrointestinal (GI), hepatobiliary, endocrinologic, neurologic, ophthalmologic, reproductive, and dermatologic systems can all be affected[5,6].

SARS-CoV-2 belongs to the beta coronavirus genus and enters cells through the angiotensin-converting enzyme 2 (ACE2) receptor[7]. A virus surface spike protein mediates SARS-CoV-2 binds to its receptor ACE2

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through its receptor-binding domain (RBD) and is proteolytically activated by human proteases[8]. ACE2 is highly expressed in many cells from various human organs[9]; particularly lungs, vascular endothelial cells, kidneys, gastrointestinal tract, liver, and arterial smooth muscle cells. Thus, all of these organs might be susceptible to SARS-CoV-2 infection[6].

More attention has been paid to the GI manifestations of SARS-CoV-2 since SARS-CoV-2 RNA was first detected in the stool of the first reported COVID-19 case in the United States, who also presented with diarrhea, nausea, and vomiting[10,11]. GI manifestations are common in patients with COVID-19. A study from China has reported that 50.5% of COVID-19 patients have at least one GI manifestation[12]; among GI manifestations of COVID-19, diarrhea seems to be the most commonly reported in children and adults[13].

Methods

This is a narrative review. We searched PubMed, EMBASE, MEDLINE, and Web of Science up to January 2021 to identify all studies documenting the presence of gastrointestinal symptoms in patients with a confirmed diagnosis of COVID-19. The following search terms alone or matched with the Boolean operators “AND” or “OR” were used: “COVID-19,” “SARS-CoV-2,” “coronavirus,” “pandemic,” “diarrhea,” “gastrointestinal symptom(s),” “stool,” “feces,” “pancreas,” “pancreatitis,” “liver injury,” “hepatitis,” “biliary tract,” and “gastrointestinal bleeding.” No temporal, study design, or language restrictions were applied. We focused on full-text articles, but abstracts were considered if relevant (Fig. 1).

Overview of SARS-CoV-2 viral infection

SARS-CoV-2 binds its envelope homotrimeric spike protein to the membrane-bound form of angiotensin-converting enzyme 2 (ACE2) at the host cell membrane to enter the host target cell[14]. The union of the virus with its ACE2 cellular receptor triggers internalization of the complex into the cell, leading to the down-regulation of the ACE2[15] and favoring the interruption of angiotensin II (AngII) metabolism; causing an increase in its plasma concentration. AngII is responsible for a prothrombotic effect, endothelial and platelet activation, vasoconstriction, and inflammation[16].

Specific ACE2 expression in extrapulmonary tissues and its relation to gastrointestinal symptoms

SARS-CoV-2 contagiousness and pathogenicity mostly depend on the interactions, including virus attachment, receptor recognition, protease cleaving, and membrane fusion[17]. Cell entry is a key component of cross-species transmission, mainly for the beta coronaviruses. All coronaviruses encode a surface spike protein, which binds to the host cell receptor and mediates viral entry[18]. The primary host receptor that mediates the mechanism as the SARS-CoV-2 enters the cell is the ACE2 receptor, which regulates the virus’s cross-species and human-to-human transmissions[18-20]. The broad distribution of ACE2 receptors in the venous and arterial endothelial cells, arterial smooth muscle cells, biliary tract, cardiovascular, renal, and GI tissues predisposes to the involvement of multiple organs, which may also explain the various extrapulmonary symptoms[3].

The ACE2 cell surface receptor in the liver was more highly expressed in cholangiocytes (near to 60%) than hepatocytes (less than 3%). The level of ACE2 expression in cholangiocytes was similar to that in type 2 alveolar cells of the lungs; thus, the liver and biliary tract could be infected for SARS-CoV-2, causing dysfunction[21]. In the liver, immunohistochemistry stains for ACE2 were negative on T and B lymphocytes, Kupffer cells, as well as the sinusoidal endothelium[22].

Zhang et al. revealed that ACE2 mRNA and protein are importantly expressed in small intestinal enterocytes but not on intestinal immune cells or goblet cells. ACE2 may mediate the invasion, amplification, and activation of GI inflammation in the GI tract, leading to GI symptoms susceptibility[3]. Furthermore, SARS-CoV-2 RNA can be detected in the stool of patients; thus, the virus could replicate in the enterocytes of the small intestine[3,23]. Among 20% of COVID-19 patients, viral RNA has been detected in the stool even after the nasopharyngeal swabs become negative[24-26]. Viral RNA can be detected in the stool of more than 50% of the COVID-19 patients with GI symptoms[27]. Chen et al. studied 42 laboratory-confirmed patients with COVID-19; 67% of these patients tested positive for SARS-CoV-2 RNA in stool samples; 64% of them remained positive during 7 (6-10) days for viral RNA in the stool after the pharyngeal swabs became negative[28]. Moreover, Wu et al. have shown that SARS-CoV-2 viral RNA may be present in fecal samples for nearly 5 weeks after the respiratory samples tested negative for the virus[29].

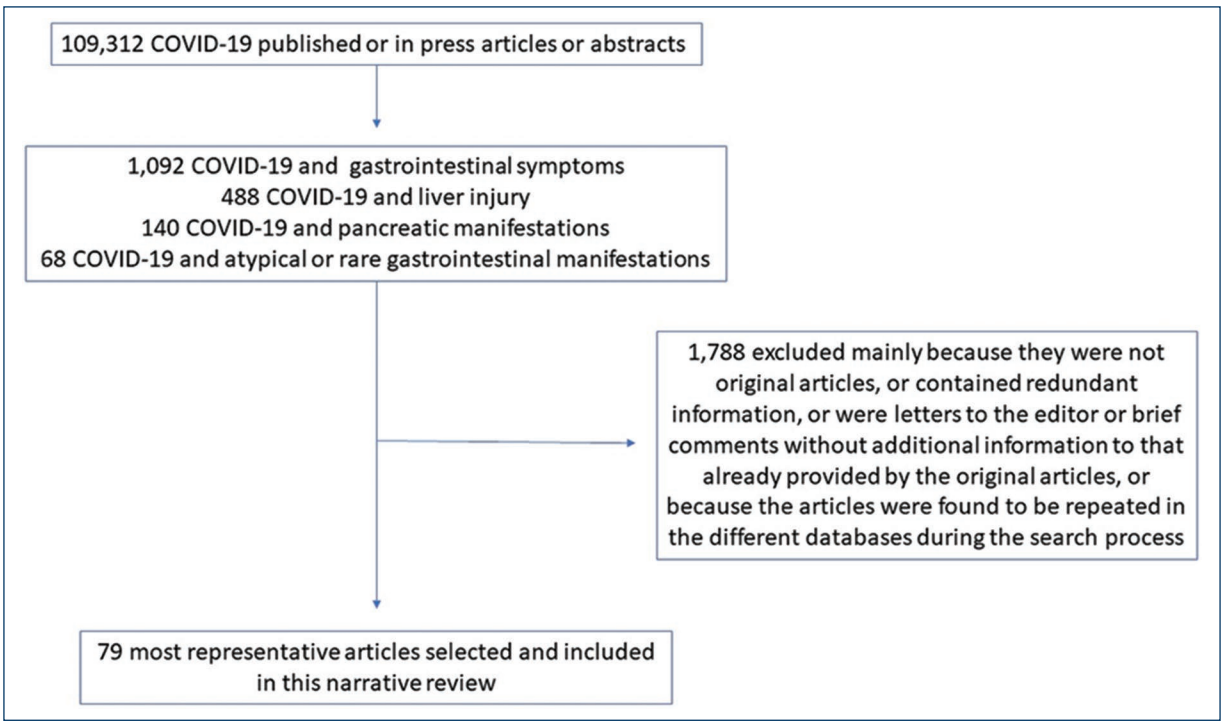

Figure 1. Criteria of search and selection of the most representative articles.

Positivity for SARS-CoV-2 RNA in stool specimens was not always related to GI symptoms or the severity of the disease since only 19% of patients in the case series of Chen Y had any GI clinical manifestation[28].

The high expression of ACE2 protein, as a functional receptor for SARS-CoV-2 in the enterocytes, and the finding of the virus in the stool of patients indicate that fecal-oral transmission may also exist[23-29].

Frequency of gastrointestinal manifestations

There are two main phases in SARS-CoV-2 infection. The early or viral phase occurs shortly after infection. It is characterized by low inflammatory activity and a high viral load, with scarcely any symptoms, but also associated with GI symptoms[30]. Then, in the progressive or late infection phase, patients develop the most severe symptoms such as respiratory distress and fever[31].

GI symptoms can be frequent in COVID-19 and, in some cases, be the first manifestation even before respiratory symptoms and fever[10,32] (Table 1). The exact incidence of GI symptoms is a matter of debate[33]. Furthermore, wide variation regards the frequency of GI symptoms exists, but taking in count, cohort studies with at least 99 patients or more included, the frequency of any GI symptom ranges from as low as 2.0%[34] to as high as 50.5%[12]. Most of the available data come from China, where a large cohort, including 1099 patients reported a frequency of any GI symptom of 5.0%[4]. Another large cohort study conducted in China by Luo et al. found that of 1141 confirmed COVID-19 cases, 183 (16%) presented with GI symptoms[35].

In a systematic review with meta-analysis by Cheung et al. including 60 studies comprising 4243 patients, the pooled prevalence of all GI symptoms was 17.6% (95% confidence interval [CI], 12.3-24.5); 11.8% of patients with non-severe COVID-19 had GI symptoms (95% CI, 4.1-29.1), and 17.1% of patients with severe COVID-19 had GI symptoms (95% CI, 6.9-36.7). Likewise, in this study, the pooled prevalence of stool samples that were positive for virus RNA was 48.1% (95% CI, 38.3-57.9); of these samples, 70.3% of those collected after the loss of virus from respiratory specimens tested positive for the virus (95% CI, 49.6-85.1)[36].

The most common GI reported symptoms in several studies are diarrhea, anorexia, nausea, vomiting, and abdominal pain or discomfort[36,37]. Of all these GI symptoms, only the presence of abdominal pain seems to be associated with a more severe course of the disease (odds ratio [OR] 7·10; 95% CI: 1·93-26·07)[37].

Table 1. Frequency of the most common gastrointestinal manifestations reported in COVID-19 patients

GI manifestation	Estimated frequency (%)	Source of information	n	Relevant comments
Any GI symptom	2.0 5.0 11.5 16 17.6 22.2 25 50.5	[34] [4] [42] [35] [36] [49] [38] [12]	99 1099 4434 1141 4243 293 892 204	– Wide variability across the studies. – Most relevant information from large cohort studies comes from China.
Diarrhea	2.0 4.5 6.5 7.4 7.8 10.4 19.8 31.9	[34] [48] [49] [40] [42] [39] [38] [56]	99 132 293 4805 4434 NA 892	– Seems to be the most common GI manifestation from COVID-19
Nausea/vomiting	1.0 1.5 2.4 3.6 4.6	[34] [48] [49] [42] [40]	99 132 293 4434 4805	– Unspecific clinical manifestation
Hypoxia	2.4 12.1 15.2	[42] [48] [49]	4434 132 293	– Unspecific clinical manifestation
Abdominal pain	0.7 0.8	[49] [42]	293 4434	– Related to a severe clinical course of COVID-19
Liver injury ALT (elevation) AST (elevation) ALT (elevation) AST (elevation) AP (elevation) TBIL (elevation) LFT (altered) Liver enzymes (increased) ALT (elevation) AST (elevation) TBIL (elevation) Albumin (decreased) Pre-albumin (decreased) ALT (elevation) AST (elevation) ALT (elevation) AST (elevation) AP (elevation) TBIL (elevation) GGT (elevation) LFT (altered)	 14.6 20 61.6 83.4 22.7 16.1 62.4 24.2 13.8 18.8 6.3 27.5 38.8 2.1 2.5 29.7 25.7 6.7 16.2 27 45.2	 [40] [44] [45] [48] [46] [49] [50] [54]	 4805 1827 100 132 80 293 74 1611	– Extremely variability though the different available studies according to if the studied population was constituted by an ambulatory, hospitalized, or intensive care patients. – Related to a worse prognosis, need for intensive care, and higher mortality rate. – Controversy if it is SARS-CoV-2 direct injury or drug-induced liver injury, or due to acute systemic inflammatory response.

ALT: alanine aminotransferase; AP: alkaline phosphatase; AST: aspartate aminotransferase; COVID-19: coronavirus disease 2019; GGT: gamma-glutamyl transferase; GI: gastrointestinal; LFT: liver function test; SARS-CoV-2: severe respiratory acute syndrome coronavirus-2; TBIL: total bilirubin.

In a large cohort from New York, which included 892 patients, 25% of patients had any GI symptom, the most common was diarrhea in 19.8%[38]. Furthermore, D'Amico et al. performed a pooled analysis of the available studies until March 2020, founding an overall diarrhea rate of 10.4%[39].

In a systematic review with a meta-analysis conducted from November 2019 to March 2020 by Parasa et al.,

including a total of 4805 patients extracted from 23 published and six preprint studies, the pooled rate reported 7.4% (95% CI, 4.3%-12.2%) of cases presenting diarrhea and 4.6% (95% CI, 2.6%-8.0%) of cases with nausea or vomiting. Fecal tests positive for SARS-CoV-2 were reported in eight studies, and viral RNA shedding was detected in the stool of 40.5% (95% CI, 27.4%-55.1%) of patients[40].

In a recent systematic review by Almeida et al., the prevalence of GI symptoms ranged from 6.8% to 61.3%, including diarrhea (8.14% to 33.7%), nausea/vomiting (1.53%-26.4%), anorexia (12.1%-40.0%), and abdominal pain (0%-14.5%). The presence of viral RNA in stools was rarely tested but positive in 0%-48.1%[41]. Likewise, Merola et al. identified 33 studies that were included in a meta-analysis. Out of 4434 COVID-19 patients, GI manifestations' pooled prevalence was 11.51% (95% CI: 8.16-15.35). Similar to other studies, they found that the most frequent GI symptom was diarrhea (7.78% of cases; 95% CI: 5.05-11.04), followed by nausea/vomiting (3.57%; 95% CI: 1.87 to 5.80), hypoxia (2.39%; 95%CI: 0.55-5.46), and abdominal pain (0.78%; 95% CI: 0.26-1.57). Positivity for COVID-19 in stool samples was observed in 41.5% (95% CI: 17.70-67.65) of cases[42].

GI symptoms are of particular significance in COVID-19 patients because, in contrast to other coronaviruses, they appear early and may worsen during the disease, whereas in some cases may be solitary. In patients presenting solely with GI symptoms, there is usually a delay in disease diagnosis and time to first respiratory symptoms, rendering them a source of viral dissemination[33]. In these times, the presence of diarrhea should generate awareness of a possible SARS-CoV-2 infection[31] (Fig. 2).

Adequate rehydration and potassium monitoring are recommended in all COVID-19 patients with diarrhea. There is not enough evidence about the safety and efficacy of antidiarrheal drugs in this context[31].

Intestinal dysbiosis and COVID-19

Significantly few studies have addressed the link between COVID-19 and intestinal dysbiosis. Zuo et al. performed shotgun metagenomic sequencing analyses of fecal samples from 15 patients with COVID-19. These patients had significant alterations in fecal microbiomes compared with controls, characterized by enrichment of opportunistic pathogens and depletion of beneficial commensals. The baseline abundance of *Coprobacillus, Clostridium ramosum,* and *Clostridium hathewayi* correlated with COVID-19 severity; there was an inverse correlation between the abundance of *Faecalibacterium prausnitzii* (an anti-inflammatory bacterium) and disease severity. During hospitalization, *Bacteroides dorei, Bacteroides thetaiotaomicron, Bacteroides massiliensis,* and *Bacteroides ovatus,* which downregulate the expression of angiotensin-converting enzyme 2 (ACE2) in the murine gut, correlated inversely with SARS-CoV-2 load in fecal samples from patients[43]. From these results, we must remember that strategies to alter the intestinal microbiota might reduce COVID-19 severity, but further investigation is required in this field.

Liver and biliary tract involvement

Several observational studies have reported liver function test abnormalities in COVID-19 patients[40,44-51] (Table 1).

Liver injury in COVID-19 patients is mainly characterized by a mild elevation of aspartate transaminase (AST) and alanine transaminase (ALT) with a rare incidence of cholestasis[52,53]. However, bilirubin levels are usually more than double in those with severe infection when compared to those with milder disease[24], the incidence of elevated ALT and AST is widely variable, ranging from 2.5%-50.0% to 2.5%-61.1%, respectively[53]. In a study by Parasa et al., the pooled rate for AST levels outside reference ranges was 20% (95% CI, 15.3%-25.6%) of patients, and the pooled rate for ALT levels outside reference ranges was 14.6% (95% CI, 12.8%-16.6%) of patients[40]. Hundt et al. conducted a study including 1827 COVID-19 patients admitted to hospital, where abnormal liver tests were commonly seen, both at admission. At admission, most patients with abnormal liver tests had minimal elevation 1-2× the upper limit of normal (ULN). Abnormal liver tests are mainly related to the severe course of COVID-19. Medications used to treat COVID-19 (lopinavir/ritonavir, hydroxychloroquine, remdesivir, and tocilizumab) are also associated with liver transaminases rising >5× ULN during hospitalization[44].

In the study by Lenti et al., liver function tests were altered in 62.4% of COVID-19 patients and improved during follow-up. Altered liver function tests were associated with worse outcomes in those who developed SARS. In patients with altered liver function tests, PaO_2/FiO_2 < 200 was associated with more significant mortality and needed intensive care[45]. In the study by Li et al., liver function test abnormalities were seen most commonly in severe COVID-19 cases compared with mild cases[48]. Higher AST levels and lower levels of albumin and pre-albumin were significantly associated with mortality[46]. Furthermore, the elevation of ALT

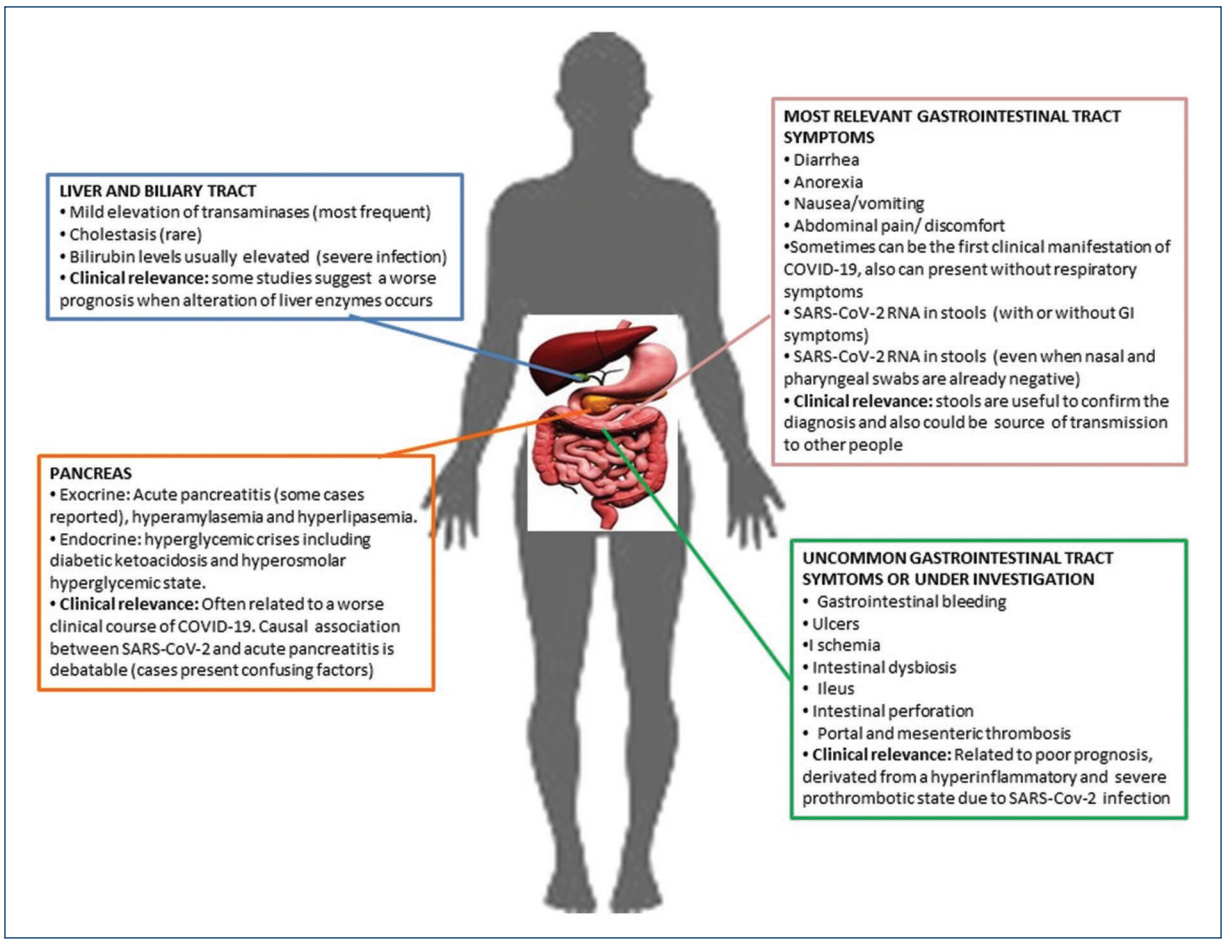

Figure 2. Gastrointestinal clinical manifestations of COVID-19.

and AST correlated with the development of coagulopathy[50]. In severe COVID-19 pediatric patients, a high percentage (50%) of liver function tests abnormalities were also reported[51].

Recently, our group published the data of a prospective Latin American cohort of 1611 patients with COVID-19. On admission, abnormal liver function tests were present in 45.2% (95% CI 42.7-47.7) patients. Overall, 15.1% of patients died. Patients with abnormal liver tests on admission had higher mortality compared to those with normal liver biochemistries. After excluding patients with a history of chronic liver disease, abnormal liver tests on admission were independently associated with death [OR 1.5 (95% CI 1.1-2.0); p = 0.01] and severe COVID-19 (2.6 [2.0-3.3], p < .0001), both adjusted by age, gender, diabetes, pneumonia, and body mass index > 30[54].

Abnormal liver function tests have consistently shown to be more prevalent in severe COVID-19[55]. Elevated liver enzymes are more common in those with a severe disease course (40-60%) than those who are asymptomatic or have a mild disease (18-25%)[24].

In a cohort study, factors at admission predicting the requirement for invasive mechanical ventilation during hospitalization for COVID-19 were AST ≥ 250 IU/L and D-dimer ≥ 3500 ng/mL[56].

In addition, it is important to mention that preexisting CLD is a condition with low reported prevalence (2.5%) in COVID-19 patients[57]. Nevertheless, this coexistence has been associated with a worse outcome[57,58]. The patients with cirrhosis are at increased risk of death from COVID-19, particularly those with more advanced cirrhosis and alcohol-related liver disease. A study found that the mortality rate was 32% in cirrhosis patients compared to 8% in those without cirrhosis (p < 0.001). Acute hepatic decompensation occurred in 46% of patients with cirrhosis, of whom 21% had no respiratory symptoms. Near 50% of those with decompensation had acute-on-chronic liver failure[59].

Current data are limited, and it is difficult to ascertain whether the liver injury could be due to direct viral infection, though there is no evidence of active replication of the SARS-CoV-2 in hepatocytes[24]; or drug-induced liver injury; or may be due to complications such as ischemic hepatitis driven for hypoxemia[52,53]. The elevated transaminases are often accompanied by high creatine kinase and lactate dehydrogenase, suggesting viral myositis[60]. In addition, the activation of the immune system and "cytokine storm" may contribute to an immune-mediated liver injury process in COVID-19[61].

Pancreas

The possible association between SARS-CoV-2-related infection and pancreatic disorders remains uncertain and not well defined[47,62]. Whether SARS-CoV-2 plays a role in acute pancreatitis (AP), etiology remains controversial since the main evidence is based on some reports of clinical cases[63].

Hadi et al. described two female clinical cases of AP due to SARS-CoV-2 (other causes of AP were exhaustively excluded). The main finding in both cases was the rapidly increasing value of amylase during the disease[64]. Gadiparthi et al. also reported a case of severe AP[63]. Kataria et al. also reported a case of AP related to COVID-19 in a woman without other risk factors for AP[65]. A systematic review conducted on May 15, 2020, including six case reports and two retrospective cohorts, found 11 COVID-19 patients with AP. Most cases were considered SARS-CoV-2 induced, but the authors were able to identify other possible causes in most of them that could explain the development of AP[66].

In a case series of 52 patients admitted for COVID-19, Wang et al. found evidence of pancreatic injury, defined as elevated amylase and lipase, in up to 17% of these patients[67]. Similarly, in a descriptive study including 71 patients, McNabb-Baltar et al. found that 9 (12.1%) developed hyperlipidemia, with 2 (2.8%) greater than 3 times the upper limit stock. However, nobody developed acute pancreatitis, and the presence of hyperlipidemia was not associated with poor outcomes or symptoms[62]. The endocrine pancreas seems altered too. In a South Korean report of two patients, COVID-19 infection was implicated in severe acute hyperglycemic crises[68].

GI bleeding as an atypical manifestation of COVID-19

GI bleeding as the first symptom of COVID-19 is a scarce report. It seems to affect mainly older men, and it was more frequently reported in severe COVID-19 cases; most of them required a blood transfusion, and the source of bleeding was not detected or was related to GI ulcers affected upper, middle, and lower GI tract[69-75].

Guotao et al. described the case of an 83-year-old man with hematochezia as the initial symptom of SARS-CoV-2 infection, in whom no source of bleeding was identified by colonoscopy or abdominal computed tomography (CT) scan[69]. Amarapurkar et al. also reported the case of a 63-year-old man who presented with acute abdomen and was diagnosed as hemorrhagic enteritis without any predisposing conditions but positive for SARS-CoV-2[70]. Another interesting case was reported by Carvalho et al., a 71-year-old woman with hemorrhagic colitis due to SARS-CoV-2. The main findings, in this case, were the endoscopic evaluation to 40 cm from the anal verge, which revealed patchy areas of focal erythema without ulceration in the descending colon, sigmoid colon, and rectum; and the histological examination of the colon and rectal biopsies showing a slight expansion of the lamina propria with edema with normal cellularity and intact crypts[71]. Gulen et al. also reported a case of a 53-year-old man with GI bleeding with COVID-19 and the absence of other major risk factors for GI bleeding[72].

Gadiparthi et al. reported three cases of GI bleeding in patients with severe SARS-CoV-2. In these cases, the source of bleeding was mainly attributed to GI ulceration. In this case series, two out of three patients had a higher Glasgow-Blatchford bleeding score of 7 and 11 on admission, which translates to high-risk GIB with a need for intervention >50% two patients died due to respiratory failure although GIB resolved[73].

A 77-year-old man, without previous gastrointestinal disease, was diagnosed with SARS-CoV-2 infection, which progressed rapidly, requiring mechanical ventilation. The endoscopy revealed multiple round herpetic erosions and superficial ulcers (4-6 mm in size) covered with white exudates and blood clots located on the proximal esophagus. The tissue specimens from these lesions tested positive for SARS-CoV-2 RNA, with lymphocytic infiltration typical of viral esophagitis[74].

Barrett et al. described six patients who tested positive for SARS-CoV-2 and had self-limited hematochezia or melena. The range of age in these cases was 66-77 years old, most of them (4/6) were men, most of them were African-Americans (4/6), just two of them were taking anticoagulation after COVID-19 diagnosis, most of them had no history of GI diseases (one had

a history of internal hemorrhoids, large and small diverticular disease, and small hiatal hernia)[75].

Barberis et al. presented a rare case of a 71-year-old woman hospitalized for COVID-19 pneumonia, which presented recurrent severe intestinal bleeding; the patient underwent a colonoscopy which showed severe inflammation associated with pseudopolyps, ulcerations, and diffuse bleeding; subsequently, she developed hemorrhagic shock and a subtotal colectomy with terminal ileostomy was performed; a swab for SARS-CoV-2 was made on the abdominal fluid in which the presence of the virus was demonstrated within the abdominal cavity[76]; other authors have performed studies on the peritoneal fluid in COVID-19-positive patients, but without finding the virus[77].

Other atypical gastrointestinal manifestations of SARS-CoV-2 infection

Paralytic ileus and intestinal perforation are also rare manifestations of SARS-CoV-2 infection. Ibrahim et al. recently published two cases; both were 33-year-old men, first hospitalized for severe COVID-19 pneumonia requiring mechanical ventilation support. He developed significant bowel dilatation and perforation of the mid-transverse colon and needed laparotomy and colonic resection. Histopathology of the resected bowel specimen showed acute inflammation, necrosis, and hemorrhage, supporting a role for COVID-19-induced microthrombosis, leading to perforation. The second patient also had severe COVID-19 pneumonia, renal failure, and acute pancreatitis. His hospital course was complicated with paralytic ileus, but he improved with conservative management[78].

Ischemic GI complications, although uncommon, also have been reported in the literature. A systematic literature review performed from January 2020 to June 2020 identified 22 studies and 31 patients with the mean age of 59 ± 12.7 (age range: 28-80) years old; most of them (74.2%) were male. The significant GI imaging findings include mesenteric, arterial, or venous thromboembolism followed by small bowel ischemia. Nine patients (29%) presented with arterial compromise due to superior mesenteric thromboembolism, resulting in bowel ischemia. Besides, 6 patients (19.3%) demonstrated occlusive thrombosis of the portal and superior mesenteric veins. A 64.5% required laparotomy and bowel resection, and the mortality rate was high since 40% of patients died[79].

Conclusions

The GI clinical manifestations of SARS-CoV-2 are heterogeneous, with widely variable incidence, prevalence, and frequency among the different cohorts and case series reported worldwide. The binding of the viral spike glycoprotein to ACE2 and its receptor on the target cell plays a crucial role as an entry pathway to the cells that express it, which is, in the first place, the most popular mechanism that seems to explain more reliably the occurrence of GI symptoms in COVID-19 patients.

In addition, the systemic inflammatory response and the secondary prothrombotic state developed in the most severe cases of COVID-19, which seems to be mechanisms involved in the presentation of uncommon GI clinical manifestations, such as ulceration, bleeding, ischemia, or intestinal perforation.

Concerning hepatopancreatobiliary organs, it remains to be established whether the injury to these tissues is due to a direct viral effect, or is somewhat secondary to the systemic inflammatory process, endothelial vascular damage prothrombotic phenomena. Specifically, about the liver injury seen in COVID-19 patients, another hypothesis is the occurrence of idiosyncratic drug-induced liver injury possibly related to the polypharmacy with which these patients are usually treated.

Finally, in terms of primary prevention, maybe the most important to consider is that in almost half of COVID-19 patients with GI symptoms, viral RNA can be detected in their stool for determining the diagnosis. The possibility of fecal-oral transmission of SARS-CoV-2 must be considered.

It is already known that COVID-19 is a systemic disease with the involvement of many organs, including the digestive system. This article adds to the literature a comprehensive summarized review of all reported most common GI, liver, biliary, and pancreatic manifestations of COVID-19 and included rare or atypical ones that must not be forgotten.

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References

1. Li H, Liu SM, Yu XH, Tang SL, Tang CK. Coronavirus disease 2019 (COVID-19): current status and future perspectives. Int J Antimicrob Agents. 2020;55:105951.
2. Temgoua MN, Endomba FT, Nkeck JR, Kenfack GU, Techie JN, Essouma M. Coronavirus disease 2019 (COVID-19) as a multisystemic disease and its impact in low- and middle-income countries (LMICs). SN Compr Clin Med. 2020;2:1377-87.
3. Zhang H, Li HB, Lyu JR, Lei XM, Li W, Wu G, et al. Specific ACE2 expression in small intestinal enterocytes may cause gastrointestinal symptoms and injury after 2019-nCoV infection. Int J Infect Dis. 2020;96:19-24.
4. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-20.
5. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26:1017-32.
6. Zheng KI, Feng G, Liu WY, Targher G, Byrne CD, Zheng MH. Extrapulmonary complications of COVID-19: a multisystem disease? J Med Virol. 2021;93:323-5.
7. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579:265-9.
8. Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A, et al. Cell entry mechanisms of SARS-CoV-2. Proc Natl Acad Sci U S A. 2020;117:11727-34.
9. Agarwal A, Chen A, Ravindran N, To C, Thuluvath PJ. Gastrointestinal and liver manifestations of COVID-19. J Clin Exp Hepatol. 2020;10:263-5.
10. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382:929-36.
11. Xu Y, Liu P, Gu J. Gastrointestinal and liver involvement in patients with COVID-19. Lancet Gastroenterol Hepatol. 2020;5:798-9.
12. Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol. 2020;115:766-73.
13. Tian Y, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. Aliment Pharmacol Ther. 2020;51:843-51.
14. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. 2020;581:215-20.
15. Mahmudpour M, Roozbeh J, Keshavarz M, Farrokhi S, Nabipour I. COVID-19 cytokine storm: the anger of inflammation. Cytokine. 2020;133:155151.
16. Franchini M, Marano G, Cruciani M, Mengoli C, Pati I, Masiello F, et al. COVID-19-associated coagulopathy. Diagnosis (Berl). 2020;7:357-63.
17. Cleary SJ, Pitchford SC, Amison RT, Carrington R, Cabrera CL, Magnen M, et al. Animal models of mechanisms of SARS-CoV-2 infection and COVID-19 pathology. Br J Pharmacol. 2020;177:4851-65.
18. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B beta coronaviruses. Nat Microbiol. 2020;5:562-9.
19. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci. 2020;63:457-60.
20. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol. 2020;94:e00127.
21. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. bioRxiv. 2020.
22. Jothimani D, Venugopal R, Abedin MF, Kaliamoorthy I, Rela M. COVID-19 and the liver. J Hepatol. 2020;73:1231-40.
23. Lei H, Ding Y, Nie K, Dong Y, Xu J. Potential effects of SARS-CoV-2 on the gastrointestinal tract and liver. Biomed Pharmacother. 2021;133:111064.
24. Matthai J, Shanmugam N, Sobhan P. Coronavirus disease (COVID-19) and the gastrointestinal system in children. Indian Pediatr. 2020;57:533-5.
25. Kopel J, Perisetti A, Gajendran M, Boregowda U, Goyal H. Clinical insights into the gastrointestinal manifestations of COVID-19. Dig Dis Sci. 2020;65:1932-9.
26. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology. 2020;158:1831-3.
27. Segura PS, Lázaro YA, Tapia SM, Chaves TC, Domingo JJ. Involvement of the digestive system in covid-19. A review. Gastroenterol Hepatol. 2020;43:464-71.
28. Chen Y, Chen L, Deng Q, Zhang G, Wu K, Ni L, et al. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. J Med Virol. 2020;92:833-40.
29. Wu Y, Guo C, Tang L, Hong Z, Zhou J, Dong X, et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. Lancet Gastroenterol Hepatol. 2020;5:434-5.
30. He X, Lau EH, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med. 2020;26:672-5.
31. Villapol S. Gastrointestinal symptoms associated with COVID-19: impact on the gut microbiome. Transl Res. 2020;226:57-69.
32. Schmulson M, Dávalos MF, Berumen J. Beware: gastrointestinal symptoms can be a manifestation of COVID-19. Rev Gastroenterol Mex. 2020;85:282-7.
33. Galanopoulos M, Gkeros F, Doukatas A, Karianakis G, Pontas C, Tsoukalas N, et al. COVID-19 pandemic: pathophysiology and manifestations from the gastrointestinal tract. World J Gastroenterol. 2020;26:4579-88.
34. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-13.
35. Luo S, Zhang X, Xu H. Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). Clin Gastroenterol Hepatol. 2020;18:1636-7.
36. Cheung KS, Hung IF, Chan PP, Lung KC, Tso E, Liu R, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: systematic review and meta-analysis. Gastroenterology. 2020;159:81-95.
37. Mao R, Qiu Y, He JS, Tan JY, Li XH, Liang J, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020;5:667-8.
38. Ferm S, Fisher C, Pakala T, Tong M, Shah D, Schwarzbaum D, et al. Analysis of gastrointestinal and hepatic manifestations of SARS-CoV-2 infection in 892 patients in Queens, NY. Clin Gastroenterol Hepatol. 2020;18:2378-9.
39. D'Amico F, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention, and management. Clin Gastroenterol Hepatol. 2020;18:1663-72.
40. Parasa S, Desai M, Chandrasekar VT, Patel HK, Kennedy KF, Roesch T, et al. Prevalence of gastrointestinal symptoms and fecal viral shedding in patients with coronavirus disease 2019: a systematic review and meta-analysis. JAMA Netw Open. 2020;3:e2011335.
41. Almeida JFM, Chehter EZ. COVID-19 and the gastrointestinal tract: what do we already know? Einstein (Sao Paulo). 2020;18:eRW5909.
42. Merola E, Armelao F, De Pretis G. Prevalence of gastrointestinal symptoms in coronavirus disease 2019: a meta-analysis. Acta Gastroenterol Belg. 2020;83:603-15.
43. Zuo T, Zhang F, Lui GC, Yeoh YK, Li AY, Zhan H, et al. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. Gastroenterology. 2020;159:944-55.
44. Hundt MA, Deng Y, Ciarleglio MM, Nathanson MH, Lim JK. Abnormal liver tests in COVID-19: a retrospective observational cohort study of 1,827 patients in a major U.S. hospital network. Hepatology. 2020;72:1169-76.
45. Lenti MV, De Andreis FB, Pellegrino I, Klersy C, Merli S, Miceli E, et al. Impact of COVID-19 on liver function: results from an internal medicine unit in Northern Italy. Intern Emerg Med. 2020;15:1399-407.
46. Li T, Guo Y, Zhuang X, Huang L, Zhang X, Wei F, et al. Abnormal liver-related biomarkers in COVID-19 patients and the role of prealbumin. Saudi J Gastroenterol. 2020;26:272-8.
47. Zippi M, Hong W, Traversa G, Maccioni F, De Biase D, Gallo C, et al. Involvement of the exocrine pancreas during COVID-19 infection and possible pathogenetic hypothesis: a concise review. Infez Med. 2020;28:507-15.
48. Li HY, Wang JW, Xu LW, Zhao XL, Feng XJ, Xu YZ. Clinical analysis of 132 cases COVID-19 from Wuhan. Medicine (Baltimore). 2020;99:e22847.

49. Wang Z, Ye D, Wang M, Zhao M, Li D, Ye J, et al. Clinical features of COVID-19 patients with different outcomes in Wuhan: a retrospective observational study. Biomed Res Int. 2020;2020:2138387.
50. Chen S, Liu H, Li T, Huang R, Gui R, Zhang J. Correlation analysis of coagulation dysfunction and liver damage in patients with novel coronavirus pneumonia: a single-center, retrospective, observational study. Ups J Med Sci. 2020;125:293-6.
51. Sun D, Li H, Lu XX, Xiao H, Ren J, Zhang FR, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. World J Pediatr. 2020;16:251-9.
52. Cheong J, Bartell N, Peeraphatdit T, Mosli M, Al-Judaibi B. Gastrointestinal and liver manifestations of COVID-19. Saudi J Gastroenterol. 2020;26:226-32.
53. Garrido I, Liberal R, Macedo G. Review article: COVID-19 and liver disease-what we know on 1st May 2020. Aliment Pharmacol Ther. 2020;52:267-75.
54. Mendizabal M, Piñero F, Ridruejo E, Anders M, Silveyra MD, Torre A, et al. Prospective Latin American cohort evaluating outcomes of patients with COVID-19 and abnormal liver tests on admission. Ann Hepatol. 2021;21:100298.
55. Cha MH, Regueiro M, Sandhu DS. Gastrointestinal and hepatic manifestations of COVID-19: a comprehensive review. World J Gastroenterol. 2020;26:2323-32.
56. Higuera-de la Tijera F, Servín-Caamaño A, Reyes-Herrera D, Flores-López A, Robiou-Vivero EJ, Martínez-Rivera F, et al. Impact of liver enzymes on SARS-CoV-2 infection and the severity of clinical course of COVID-19. Liver Res. 2021;5:21-7.
57. Islam MZ, Riaz BK, Islam AN, Khanam F, Akhter J, Choudhury R, et al. Risk factors associated with morbidity and mortality outcomes of COVID-19 patients on the 28th day of the disease course: a retrospective cohort study in Bangladesh. Epidemiol Infect. 2020;148:e263.
58. Ibáñez-Samaniego L, Bighelli F, Usón C, Caravaca C, Carrillo CF, Romero M, et al. Elevation of liver fibrosis index FIB-4 is associated with poor clinical outcomes in patients with COVID-19. J Infect Dis. 2020;222:726-33.
59. Marjot T, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: an international registry study. J Hepatol. 2021;74:567-77.
60. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020;5:428-30.
61. Alqahtani SA, Schattenberg JM. Liver injury in COVID-19: the current evidence. United Eur Gastroenterol J. 2020;8:509-19.
62. McNabb-Baltar J, Jin DX, Grover AS, Redd WD, Zhou JC, Hathorn KE, et al. Lipase elevation in patients with COVID-19. Am J Gastroenterol. 2020;115:1286-8.
63. Gadiparthi C, Bassi M, Yegneswaran B, Ho S, Pitchumoni CS. Hyperglycemia, hypertriglyceridemia, and acute pancreatitis in COVID-19 infection: clinical implications. Pancreas. 2020;49:e62-3.
64. Hadi A, Werge M, Kristiansen KT, Pedersen UG, Karstensen JG, Novovic S, et al. Coronavirus disease-19 (COVID-19) associated with severe acute pancreatitis: case report on three family members. Pancreatology. 2020;20:665-7.
65. Kataria S, Sharif A, Ur Rehman A, Ahmed Z, Hanan A. COVID-19 induced acute pancreatitis: a case report and literature review. Cureus. 2020;12:e9169.
66. Juhász MF, Ocskay K, Kiss S, Hegyi P, Párniczky A. Insufficient etiological workup of COVID-19-associated acute pancreatitis: a systematic review. World J Gastroenterol. 2020;26:6270-8.
67. Wang F, Wang H, Fan J, Zhang Y, Wang H, Zhao Q. Pancreatic injury patterns in patients with coronavirus disease 19 pneumonia. Gastroenterology. 2020;159:367-70.
68. Kim NY, Ha E, Moon JS, Lee YH, Choi EY. Acute hyperglycemic crises with coronavirus disease-19: case reports. Diabetes Metab J. 2020;44:484-5.
69. Guotao L, Xingpeng Z, Zhihui D, Huirui W. SARS-CoV-2 infection presenting with hematochezia. Med Mal Infect. 2020;50:293-6.
70. Amarapurkar AD, Vichare P, Pandya N, Deshpande S. Haemorrhagic enteritis and COVID-19: causality or coincidence. J Clin Pathol. 2020;73:686.
71. Carvalho A, Alqusairi R, Adams A, Paul M, Kothari N, Peters S, et al. SARS-CoV-2 gastrointestinal infection causing hemorrhagic colitis: implications for detection and transmission of COVID-19 disease. Am J Gastroenterol. 2020;115:942-6.
72. Gulen M, Satar S. Uncommon presentation of COVID-19: gastrointestinal bleeding. Clin Res Hepatol Gastroenterol. 2020;44:e72-6.
73. Gadiparthi C, Perisetti A, Sayana H, Tharian B, Inamdar S, Korman A. Gastrointestinal bleeding in patients with severe SARS-CoV-2. Am J Gastroenterol. 2020;115:1283-5.
74. Li X, Huang S, Lu J, Lai R, Zhang Z, Lin X, et al. Upper gastrointestinal bleeding caused by SARS-CoV-2 infection. Am J Gastroenterol. 2020;115:1541-2.
75. Barrett LF, Lo KB, Stanek SR, Walter JW. Self-limited gastrointestinal bleeding in COVID-19. Clin Res Hepatol Gastroenterol. 2020;44:e77-80.
76. Barberis A, Rutigliani M, Belli F, Ciferri E, Mori M, Filauro M. SARS-Cov-2 in peritoneal fluid: an important finding in the Covid-19 pandemic. Br J Surg. 2020;107:e376.
77. Emile SH. Should we continue using laparoscopy amid the COVID-19 pandemic? Br J Surg. 2020;107:e240-1.
78. Ibrahim YS, Karuppasamy G, Parambil JV, Alsoub H, Al-Shokri SD. Case report: paralytic ileus: a potential extrapulmonary manifestation of severe COVID-19. Am J Trop Med Hyg. 2020;103:1600-3.
79. Keshavarz P, Rafiee F, Kavandi H, Goudarzi S, Heidari F, Gholamrezanezhad A. Ischemic gastrointestinal complications of COVID-19: a systematic review on imaging presentation. Clin Imaging. 2020;73:86-95.

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REVIEW ARTICLE

Helical tomotherapy: advanced radiotherapy technology

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Abstract

Nowadays, technology has evolved considerably, and has made radiotherapy a sophisticated treatment due to it use high-precision equipment and advanced imaging techniques that guarantee an exact treatment that is reflected in the control of the disease with decrease in the toxicity that was previously present, and this is important because 60-70% of cancer patients will require this treatment at some point in the evolution of the disease. Among the new equipment to provide radiotherapy, there is the helical tomotherapy, which is a linear accelerator with many dosimetric advantages for the administration of treatment. To carry out this procedure, a series of steps are required from the assessment consultation by the radiation oncologist until the end of the treatment.

Keywords: *Radiotherapy. Tomotherapy. Oncology. Hypofractionated radiation therapy.*

Introduction

Technological advances have allowed radiation to be applied precisely to the desired site, managing to administer higher doses to the tumor, avoiding, or minimizing unnecessary radiation to nearby organs. It is understood that radiotherapy is a little known discipline, hence the importance of showing how it works and what is the process that is followed to achieve successful treatments since both malignant and benign tumors are treated and it is important that other medical specialties know this.

What is radiotherapy?

Radiotherapy is a treatment that consists of the emission of high-energy radiation that originates from a machine (linear accelerator), and goes to a certain area; it is considered that 60-70% of patients diagnosed with cancer will require treatment with radiotherapy at some point in the course of their disease[1]. It is also useful in benign pathologies such as: keloid scar, Graves' ophthalmopathy, and arteriovenous malformations to name a few[2].

Ionizing radiation is used to forms ions (electrically charged particles) and deposits energy in the cells of the tissues, this energy damages the genetic material (DNA) of the cells, causing them to lose their ability to divide and proliferate[3]. Radiation does not immediately destroy cancer cells, so it takes days or weeks of treatment for the DNA to be damaged enough for these cells to die[4].

To give this treatment, a machine (linear accelerator) is used that generates high-energy photons (X-rays) that point to the site to be treated. A linear accelerator is a piece of equipment that uses microwave technology to accelerate electrons located in a waveguide. These electrons collide with a metal target to produce high-energy X-rays, which are shaped as they exit the

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machine to form a beam that resembles the shape of the patient's tumor using a multileaf collimator. The beam exits from a part of the accelerator called a gantry, which can be rotated around the patient[5].

The technology available is extraordinary and radiation oncology has evolved to become a highly sophisticated specialty due to the incorporation of computer tools, managing to obtain and transfer digital medical images, in addition to the development of planning systems in such a way that it evolved from a 2D radiotherapy based on X-ray to 3D radiotherapy based on volumetric images such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET-CT)[6,7].

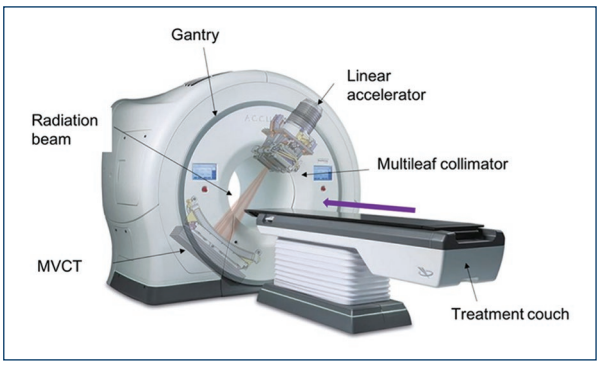

Figure 1. Basic diagram of a tomotherapy unit showing how the radiation beam exits through multileaf collimators that give it the shape of the tumor while the table moves longitudinally and the gantry rotates.

What is tomotherapy?

Tomotherapy is a charged particle linear accelerator that is specialized in rotational radiotherapy treatments using a fan-shaped radiation source and uses a table that moves at a constant speed during treatment. Its design reminds us more of a computerized axial tomography equipment, it has a donut-shaped gantry and inside is the compact linear accelerator that can rotate around the patient, and this helical linear accelerator generates an X-ray beam with energy of 6 megavolts (MV). The beam exits through primary collimators and generates a fan-shaped beam, the width of this beam is 1.0, 2.5, or 5.0 cm and laterally it reaches 40 cm. The fluence of this beam is modulated by a binary multileaf collimator, composed of 64 tungsten plates with a width of 6.25 mm each. Intensity modulation is achieved by varying the fraction of time that the different blades are open or closed. It has a mega voltage computed tomography (MVCT) detector mounted in front of the source that has the purpose of control and verification of treatments, in this way image-guided radiotherapy (IGRT) is performed in each treatment. The accelerator rotates at a constant speed while the table together with the patient moves longitudinally until completing the volume to be radiated[8] (Fig. 1).

The advantages of tomotherapy over other linear accelerators are that the patient can be treated up to a length of 135 cm without repositioning and two or more volumes can be treated at the same time due to the characteristics of the equipment already mentioned, making the treatment faster and more comfortable for the patient, example: patients diagnosed with medulloblastoma, ependymoma grade II-III, leukemia, and embryonic tumors of the central nervous system (CNS) in whom the treatment field is required to include the skull and the entire bone marrow spinal. It has a high precision because all the treatments are guided by image, and verified in each fraction, this allows to carry out treatments with hypofractionation (higher dose in fewer fractions), for example: breast cancer[9], also with this precision it allows the radiation dose to be reduced to the organs surrounding the tumor, thus reducing the toxicity that was experienced with other radiotherapy equipment (cobalt 60). It is a versatile piece of equipment, because we can perform intracranial and extracranial radiotherapy and radiosurgery techniques[10].

Radiotherapy process

To carry out a treatment with radiotherapy, a set of procedures must be determined that are carried out from the assessment in the doctor's appointment until the end of the treatment.

Medical office

As part of the multidisciplinary oncology team, an initial evaluation is carried out, where according to the diagnosis and staging of the disease, it is decided whether the patient is a candidate for this treatment, what is the sequence to follow (either neoadjuvant, concomitant or adjuvant) and the intention of treatment (curative or palliative).

Simulation

Administering multiple doses of radiation to exactly the same site requires immobilization of the patient, which must be easily reproducible throughout their

treatment, this is achieved with the support of special fixation devices, such as thermoplastic masks (head and neck), breast ramp, and immobilizers (abdomen and extremities) (Fig. 2), these devices are placed on the simulator table that consists of a conventional CT scanner identical to those used for diagnosis, once the patient is positioned and immobilized, a volumetric acquisition and an image that is clear enough to define the area to be irradiated, then these images are sent to a special computer for planning.

At the end of the acquisition of the tomography, with the help of lateral and medical laser beams (arranged in the same way in the treatment bunker) marks or tattoos are made on the skin, with these marks we specify the isocenter and define our coordinate system that will be a reference in the linear accelerator that will allow to position and align the patient in all his treatments.

Figure 2. Fixation devices used in simulations and treatments, depending on the site to be radiated, the device used to completely immobilize and be reproducible in each treatment.

Planning

The computed tomography obtained in simulation is merged with MRI, PET CT, and/or contrast-enhanced CT to improve visualization of the organs.

With these images, the radiation oncologist defines the site to be radiated, in case of macroscopic disease, a Gross Total Volume (GTV) is outlined, a margin that includes subclinical disease, the possible routes of dissemination (based on the location and the histological type), lymphatic drainage and recurrence patterns, the sum of all this is known as CTV (Clinical Target Volume), and a margin that considers the variations due to the internal movement of the patient as well as the variations that it may have from a fraction to another, this is called the PTV (Planning Target Volume). The PTV is the volume at which radiation treatment is given[11,12] (Fig. 3).

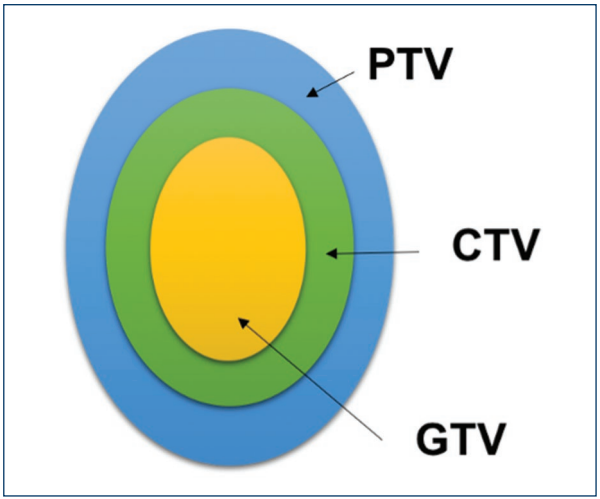

Figure 3. GTV: Gross Tumor Volume, defined as the tumor visible on images; CTV: Clinical Target Volume: Defined as GTV + subclinical disease (invisible invasion); PTV: Target Planning Volume: Defined as the CTV + margin that considers the variations between fractions.

In addition, the organs at risk are defined, that is, healthy organs that are close to the tumor (PTV) and whose function must be preserved as far as possible. The radiation oncologist also prescribes the total dose, fractionation, organs to be protected and their dose limits, later the medical physicist, who uses the simulated CT images to calculate the dose distribution, makes a treatment plan (according to physician specifications) that is optimized with a treatment planning system. The final treatment plan is presented to the doctor graphically and by means of a dose-volume histogram with the distribution of the dose both in the site to be irradiated and in the organs at risk. The radiation oncologist evaluates the treatment plan made by the medical physicist and verifies that it is appropriate for the treatment.

Quality control

Once the plan is approved by the radiation oncologist, the medical physicist verifies that the linear accelerator is capable of "mechanically" delivering the planned treatment, that it can reproduce head positions and movements of the multileaf collimator, position of the table, among others. And, in addition, verify that what is delivered "dosimetrically" is correct, that is, that the energy (dose) is that which comes out of the linear accelerator[13].

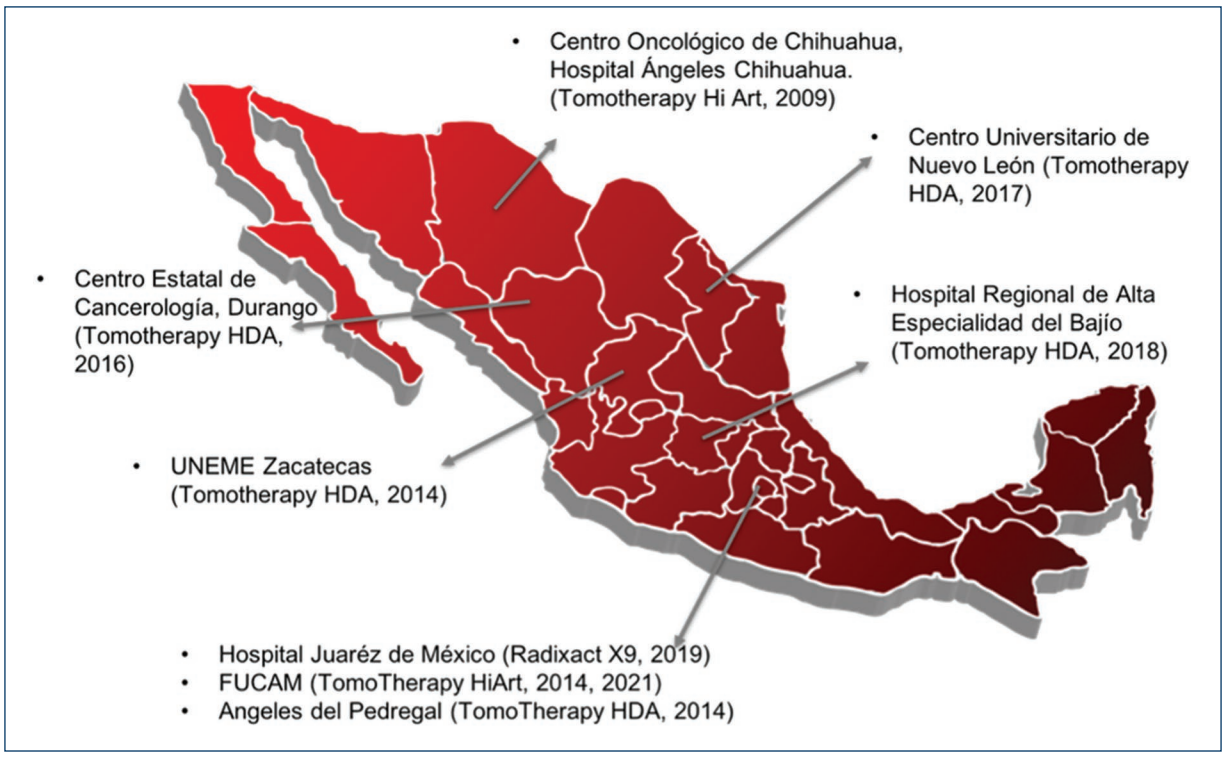

Figure 4. Centers that have a tomotherapy in Mexico.

Treatment

Once the quality control has been carried out, the procedure for starting treatment is as follows: the patient is positioned on the table of the tomotherapy team as simulated in the CT scan, using the tattoos made in the simulation as support, an image acquisition is performed with kilovoltage to what we know as mega voltage computed tomography (MVCT) to assess that it is correctly positioned when comparing the initial CT with the MVCT; with this information, the radiotherapy technicians make the necessary modifications to ensure the proper positioning of the patient. Once the radiation oncologist approves this verification, the treatment proceeds. These verifications are made to each patient before each of their treatment sessions.

Patient control

During treatment, the patient is evaluated in consultation by the radiation oncologist to find out if the treatment is being carried out according to what was estimated, to treat adverse effects if they occur, evaluate the result and once it is finished the patient is scheduled periodically to assess the chronic effects of radiotherapy.

All these steps are performed sequentially in each of the patients who are candidates to receive radiotherapy in the tomotherapy team. The time that this entire process takes is varied and depends on the workload of each institution. It generally takes 1-2 weeks, in the event of an oncological emergency (hemorrhage, spinal cord compression syndrome, etc.), this entire process is accelerated so that the patient receives treatment on the same day.

Tomotherapy in Mexico

According to the Accuray Latam & Worldwide database, 591 tomotherapy equipment (of this brand) are installed in the world; 18 are in Latin America, 13 are TomoTherapy model, 5 are RadiXact model. In Mexico there are 8 tomotherapy teams that are in: Centro Oncologico of Hospital Angeles de Chihuahua, Centro Universitario de Nuevo León, Centro de Cancer in Durango, Unidad de Especialidades Medicas in Zacatecas, Hospital Regional de Alta Especialidad del Bajio, Hospital Angeles del Pedregal, Fundacion de Cancer de Mama and Hospital Juarez de México[14] (Fig. 4).

There are two ways to give radiation treatment with this equipment; Helical radiotherapy; in which the

Figure 5. Tomotherapy.

radiation is given in a continuous rotational way with a helical pattern, and Direct radiotherapy; where the gantry is fixed at a certain angle while the radiation is delivered, both forms of treatment are carried out while the table moves continuously longitudinally (Fig. 5).

Due to the new technologies and quality control that are available today, radiotherapy schemes have been modified, passing in some cases from conventional treatment to hypofractionation, that is, high doses of radiation are given in few fractions in selected patients and in this way the shifts in the team are optimized to be able to treat a greater number of patients, but the greatest advantage is for the patient because the overall treatment time is reduced and thus the costs of transportation, lodging, etc., are reduced.

The patients who are considered candidates for hypofractionation are mainly those with a diagnosis of breast cancer, both early clinical stages and locally advanced, and patients with rectal cancer (candidates for preoperative radiotherapy), since there are published studies that have shown that there is no difference in oncological outcomes (overall survival, disease-free survival, and locoregional recurrence) or toxicity[15-17]. It is important to mention that patients must be perfectly selected to carry out this type of treatment, since the success of the final result depends on it.

Conclusion

Tomotherapy is a helical linear accelerator that is installed throughout the world. Thanks to the ability of the team to perform image-guided radiotherapy, we have high precision in treatments, being able to take a technological leap that allows higher doses to be given to tumors and reducing the dose that reaches organs at risk, consequently, the patients have less morbidity and safe treatment is guaranteed even in benign pathologies. It is recommended to have trained personnel with well-defined activities to optimize the workflow.

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Conflicts of interest

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Ethical disclosures

Protection of people and animals. The authors declare that no experiments have been performed on humans or animals for this research.

Data confidentiality. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article.

References

1. Abshire D, Lang MK. The evolution of radiation therapy in treating cancer. Semin Oncol Nurs. 2018;34:151-7.
2. Meyer JL. The radiation therapy of benign diseases. Current indications techniques. Front Radiat Ther Oncol Basel Karger. 2001;35:1-17.
3. Jackson SP, Bartek J. The DNA-damage response in human biology and disease. Nature. 2009;461:1071-8.
4. Minniti G, Goldsmith C, Brada M. Radiotherapy. Handb Clin Neurol. 2012;104:215-28.
5. Anderson R, Lamey M, MacPherson M, Carlone M. Simulation of a medical linear accelerator for teaching purposes. J Appl Clin Med Phys. 2015;16:359-77.
6. Grégoire V, Guckenberger M, Haustermans K, Lagendijk JJW, Ménard C, Pötter R, et al. Image guidance in radiation therapy for better cure of cancer. Mol Oncol. 2020;14:1470-91.
7. Chetty IJ, Martel MK, Jaffray DA, Benedict SH, Hahn SM, Berbeco R, et al. Technology for innovation in radiation oncology. Int J Radiat Oncol Biol Phys. 2015;93:485-92.
8. Saw CB, Katz L, Gillette C, Koutcher L. 3D treatment planning on helical tomotherapy delivery system. Med Dosim. 2018;43:159-67.
9. Chitapanarux I, Nobnop W, Tippanya D, Sripan P, Chakrabandhu S, Klunklin P, et al. Clinical outcomes and dosimetric study of hypofractionated Helical tomo therapy in breast cancer patients. PLoS One. 2019;14:e0211578.

10. Saw CB, Gillette C, Peters CA, Koutcher L. Clinical implementation of radiosurgery using the Helical tomotherapy unit. Med Dosim. 2018;43:284-90.
11. Landberg T, Chavaudra J, Dobbs J, Hanks G, Johansson KA, Möller T, et al. Report 50. J Int Comm Radiat Units Meas. 1993;26:1.
12. Landberg T, Chavaudra J, Dobbs J, Gerard JP, Hanks G, Horiot JC, et al. Report 62. J Int Comm RadiatUnits Meas. 1999;32:1.
13. Miften M, Olch A, Mihailidis D, Moran J, Pawlicki T, Molineu Q, et al. Tolerance limits and methodologies for IMRT measurement-based verification QA: recommendations of AAPM task group No. 218. Med Phys. 2018;45:e53-83.
14. Available from: https://www.accuray.com/es/centros-de-tratamiento/
15. Ohri N, Haffy BG. Alternatives to standard fractionation radiation therapy after lumpectomy. Surg Oncol Clin N Am. 2018;27:181-94.
16. Liu L, Yang Y, Guo Q, Ren B, Peng Q, Zou L, et al. Comparing hypofractionated to conventional fractionated radiotherapy in postmastectomy breast cancer: a meta-analysis and systematic review. Radiat Oncol. 2020;15:17.
17. Swedish Rectal Cancer Trial, Cedermark B, Dahlberg M, Glimelius B, Påhlman L, Rutqvist LE, et al. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med. 1997;336:980-7.

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CLINICAL CASES

Percutaneous balloon valvuloplasty in a pregnant patient with pulmonary bioprosthetic valve stenosis

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Abstract

The pulmonary valve's anomalies can lead to the obstruction of the right ventricle's outflow tract. This leads to the right ventricle's pressure overload, dilation, hypertrophy and eventually his malfunction. Balloon angioplasty or valve replacement surgery is indicated in cases of severe pulmonary stenosis. Often, the insertion of bioprosthetic pulmonary valves is required; however, after several years these patients often require a second surgery due to the valve's malcfunction. We report the case of a pregnant patient with a bioprosthetic pulmonary valve who required a ballon angioplasty due to this valve's stenosis.

Keywords: *Percutaneous valvuloplasty. Bioprosthesis. Pulmonary valve. Pregnancy.*

Introduction

The most common form of the right ventricular outflow tract obstruction (RVOTO) is pulmonary valve stenosis. Pulmonary valve stenosis (PE) occurs remotely in 8-10% of congenital cardiopathies but is often associated with other congenital lesions. Valvular, subvalvular and supravalvular stenosis tend to be congenital and can be associated with genetic syndromes including Noonan, Alagilole and Williams syndrome as well as congenital rubella. Pulmonary stenosis can also be an acquired infection, for example, in cases of rheumatic heart disease, carcinoid heart disease, lumps, infectious endocarditis, or secondary to traumatism[1].

Case presentation

A 40-year-old female patient with a history of congenital complex heart disease: Ventricular septal defect (VSD) and infundibular stenosis both of them corrected with VSD closure and biological pulmonary valve bioprosthesis placement when she was 8 years old. The patient mentions a diseased sibling who died 7 days after being born due to a non specified congenital cardiopaty. Within her gynecologic history we find three pregnancies, one vaginal delivery, one cesarean section, and one current pregnancy of 25 gestation weeks. Her condition began within the previous 5 months with fatigue and dyspnea associated with lesser than usual activities, which is why she attended a prenatal care appointment from where she was referred to the cardiology service. During the physical cardiovascular exploration, she presented with rhythmical arterial pulses of adequate intensity and amplitude. Thorax malformations nonexistent, apex in the fifth intercostal space, anterior axilary line, 2.5 cm area with low left paraesternal lift. During cardiac auscultation: S_1 normal, S_2 split at the

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expense of P_2, no S_3 or S_4. Holosystolic murmur in tricuspid area, intensity III/VI, regurgitant, augmented with Rivero Carvallo's maneuver. Pulmonic area with mesotelesystolic murmur, intensity IV/VI, ejective, increasing-decreasing, as well as an early diastolic murmur. An EKG was requested, it showed complete. An EKG was requested, it showed complete right bundle branch block blockage (RBBB) and data of hypertrophy in the right ventricle (Fig. 1). A transthoracic EKG was taken which reported a left ventricle with a FEV1 of 53%, systolic flattening of the interventricular septum due to the overload of the right ventricle, Grade III diastolic dysfunction, dilated and hypertrophic right ventricle with preserved systolic function. No data of residual VSD. Right atrium severely dilated. Moderate tricuspid insufficiency, pulmonary artery systolic pressure (PASP) of 7 mmHg with low ecocardiographical probability of pulmonary hypertension. In the pulmonary valve an endoprosthesis with Vmax 5.5m/s was observed, peak gradient 124 mm Hg, mid gradient 68 mm Hg, valvular area by 3D planimetry of 1 cm^2 compatible with severe pulmonary stenosis, in addition with Color Doppler jet area pulmonary insufficiency can be observed, classified as moderate because of a vena contracta of 4mm and a vena contracta's area of 0.9 cm^2 (Fig. 2). Due to findings compatible with bioprothesic pulmonary valve stenosis and because of her current pregnancy, she was scheduled for a plasty with baloon of said valve.

Said procedure was done un the hemodynamic ward with the presence of the clinical and interventional cardiology services along with echocardiography, vascular surgery, cardiovascular anesthesiology, obstetrics and gynecology and the maternal-fetal medicine department of our hospital. With previous placement of a protection lead apron over the patient's abdomen, a right femoral approach was made with modified Seldinger thecnic, a right catetherism was made with 5 Fr pigtail cathether and multipurpose 5 Fr MPB. Subsequently with a Super-Stiff 0.035 × 260 mm guide a femoral introducer was exchanged by a 12 Fr and a PTA MAXI LD 20 mm balloon was moved forward, positioning itself within the ring of the pulmonary prosthesis and dilating itself in three occasions until the disappearance of the balloon's groove for the amplification of the infundibulum and the pulmonary bioprosthesis (Fig. 3).

A measurement of the pulmonary gradient was ade pre and post valvuloplasty (93 mm Hg and 26 mm Hg, respectively), showing a reduction grater tan 50%, finalizing the procedure successfully. A control transthoracic echocardiogram was made in the room, without any evidence os acute complications, corroborating the

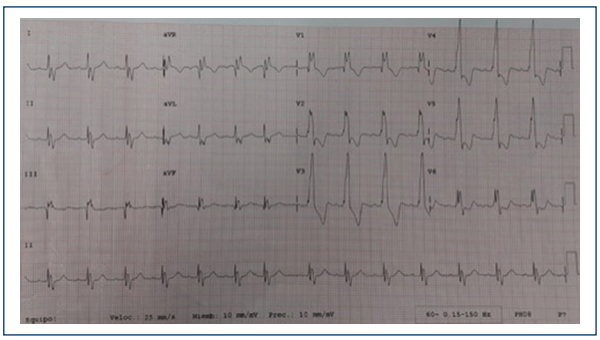

Figure 1. Electrocardiogram, 12 derivations, synus rythm, cardiac frecuency of 100 bpm. P 80 ms, PR 160 ms, rSR in V1-V6 to QR +120°, QRS 120 ms, no ischemia, lesion or necrosis.

reduction of the pulmonary gradient with V. maxim 3.2 m/s, maxim gradient 42 mm Hg and mid gradient 22 mm Hg, continuing with moderate pulmonary insufficiency (Fig. 4). A fetal ultrasound was also made by the maternal-fetal medicine service without any evidence of complications for the binomy. The patient was released with an appointment at external consultation for monitoring and a cesarean section was programmed at 37 weeks of gestation without any complications. At present, the patient has satisfied parity and is scheduled for a mechanical pulmonary valve replacement, awaiting procedure.

Discussion

The pulmonary valve anomalies, the subvalvular area or supravalvular area can lead to the obstruction of the TSVD. PS can be valvular, subvalvular (infundibular) or supravalvular, being the valvular PS, the most common form conforming the 7-10% of congenital heart diseases. There is a slight predominance in the female gender and 2% of familiar cases do not have a genetic cause. The main consequence of PS is the overload of pressure of the right ventricle. Whose grade is dependent on the gravity of the stenosis. The overload of pressure of the right ventricle results in the increase of contractility and dilation, which leads to an increase in the tension of the wall and compensatory hypertrophy of the right ventricle[2,3]. The increase of the muscle mass allows the right ventricle to keep a normal cardiac output. The long-term volume load can cause diastolic dysfunction of the right ventricle with elevation of the end-diastolic pressure of said ventricle. The dilation of the right ventricle and the tricuspid ring form the substrate for the functional tricuspid regurgitation which aggravate the volume overcharge and is the cause of the symptomatology in patients. Said

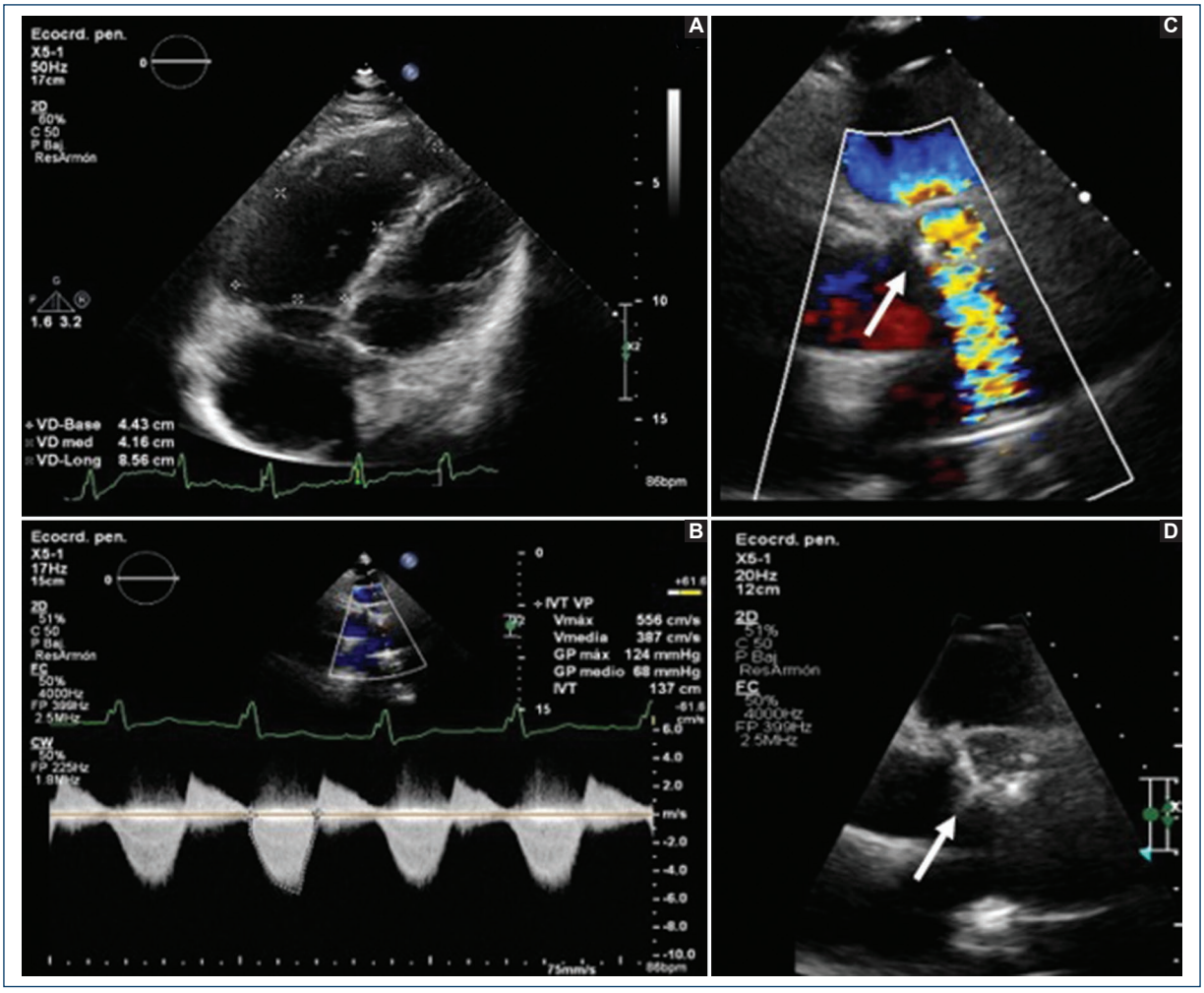

Figure 2. Transthoracic echocardiogram **A:** apical proyection 4 cameras. A dilated and hypertrofic right ventricle is observed **B:** continues Doppler. V max 5.5, G max 124 mm Hg, G mid 68 mm Hg. **C** and **D:** short axis projection at great vessels level. Here can be observed a bioprosthetic pulmonary thickened valve with turbulent flow by Doppler color (arrow).

symptoms can be developed in patients with moderate to severe stenosis and mainly include dyspnea and fatigue with any effort like it happened with the patient of our case. In severe stenosis cases, the right ventricle cannot increase the cardiac output, which can cause thoracic pain by effort, syncope and sudden death. Right cardiac insufficiency is uncommon in adults but can happen if the severe disease remains untreated. For the diagnosis, the echocardiogram is the most common image technic and allows the evaluation of the location of the obstruction, the morphology of the valve and the degree of stenosis. Furthermore, information can be obtained about the TSVD, the pulmonary ring, the pulmonary arteries and the size and function of the right ventricle. The definition of severe PS according to the guidelines of the American Heart Association (AHA)/ American College of Cardiology (ACC) from 2014 for the treatment of patients with valvular heart disease is a V. maxim over 4 m/s or a maximum gradient superior to 64 mm Hg. In this case, the patient had a V. maxim of 5.5 m/s and a maximum gradient of 124 mm Hg. In the guidelines of ACC/AHA of 2008 for the handling of adults with congenital heart disease, severe pulmonary stenosis is defined as a maximum gradient superior to 50 mm Hg, moderate when the gradient is from 30-50 mm Hg and minor when is inferior to 30 mmHg[4]. The balloon valvuloplasty can provide a certain degree of relief for the dysplastic pulmonary valves and is a reasonable first line option[5]. When the balloon valvuloplasty is not enough, a surgical intervention can be considered or a transcatheter pulmonary valve replacement if it is available. After the repair of complex cardiac defects,

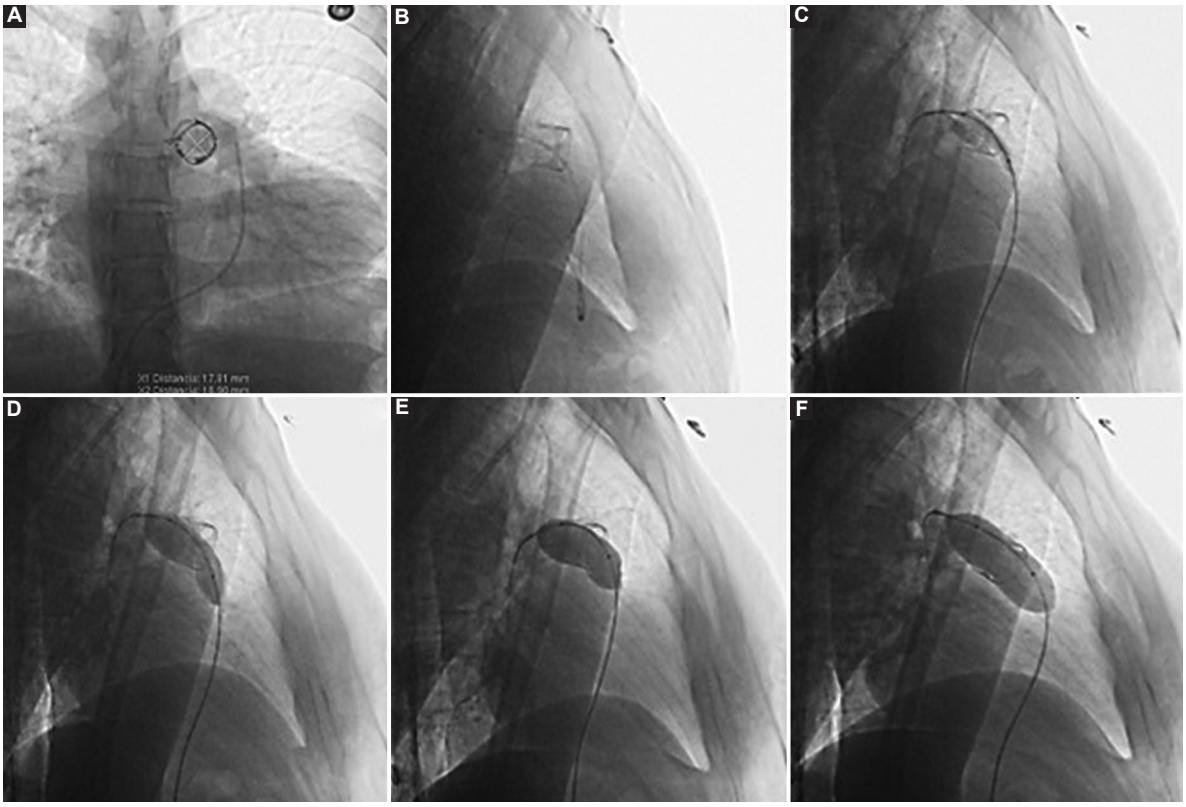

Figure 3. Right catheterization. **A-C:** a pulmonary bioprosthesis can be observed and passage of the balloon catheter trough the ring of the pulmonary bioprosthesis. **D-F:** dilation with balloon within pulmonary bioprosthesis with disappearance of the balloon's groove due to its total expansion.

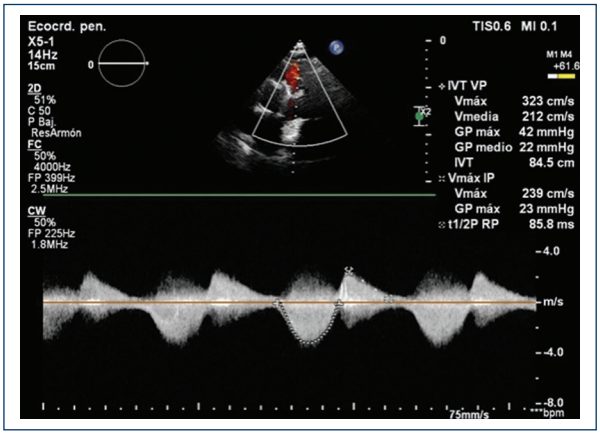

Figure 4. Transthoracic echocardiogram posterior to valvuloplasty. Continues Doppler. Diminution of the pulmonary stenosis gradient, with persistency of moderate pulmonary insufficiency.

bioprosthetic pulmonary valves are often needed to maintain the function of the pulmonary valve. Many patients with bioprosthetic pulmonary valves require another surgery due to the inevitable failure of the valve[6]. The balloon valvuloplasty is a highly effective and safe method for the treatment of acute and chronic congenital pulmonary diseases. The balloon valvuloplasty of a bioprosthetic stenotic pulmonary valve can be an effective palliative procedure to delay the future valvular replacement. However, the balloon valvuloplasty of bioprosthetic valves in pulmonary positions has rarely been done. There have been some cases that reported successful dilations and better posterior clinics[7,8]. The American Heart Association and the American College of Cardiology recommended the following handling plans in their 2008 guidelines:

- Asymptomatic patients with a Doppler maximum gradient > 30 mm HG can be monitored every 5 years with electrocardiogram and Doppler echocardiography.
- Asymptomatic patients with a Doppler maximum gradient > 30 mm HG can be subjected to monitoring every 2-5 years with Doppler echocardiography.
- A valvulotomy with balloon is recommended for asymptomatic patients with a Doppler maximum gradient > 60 mm Hg.

– A valvulotomy with balloon is recommended in symptomatic patients with a Doppler maximum gradient > 50 mm Hg and a Domingo pulmonary valve.
– A surgical intervention is recommended for severe valvular stenosis with severe pulmonary insufficiency, hypoplastic pulmonary ring, subvalvular stenosis, or supravalvular stenosis[9].

Due to the fact that the patient had subvalvular pulmonary stenosis as a kid, she required a replacement with bioprosthetic pulmonary valve. Unfortunately, the valvulotomy with balloon is not as effective on Domingo valves, which is why surgery is the preferred option[10]. The valvulotomy with balloon can be worth it if the Doppler maximum gradient is > 60 mm Hg in asymptomatic patients or if the Doppler maximum gradient is > 50 mm Hg in symptomatic patients. Surgery must be considered in patients that have undergone concurrent cardiac surgical procedures. The relevance of this reported case lies in the fact that it is about a patient with stenosis of a bioprosthetic pulmonary valve placed during her childhood. Said valves have an approximate life spam of 10 years, posterior to which it must be replaced due to the high risk of disfunction or valvular stenosis. However, the patient had already had that valve for over 30 years, which is why the failure was expected and a replacement with a mechanical valve had been indicated. Besides everything that was previously mentioned, the patient was pregnant, which increases the risk of complications. It is well established that pregnancy and delivery of a child lead to physiological changes that require the adjustment of the cardiovascular system. These changes are tolerated by pregnant women without heart disease but expose women with cardiovascular disease to great risks which is the reason why the prevention of cardiovascular complications must be the first objective of any cardiologist involved in the handling of pregnant patients with congenital of acquired heart disease. Slight or moderate PS are well tolerated during pregnancy with a good maternal-fetal prognosis[11]. Nevertheless, in patients with severe PS, pregnancy can lead to severe cardiac insufficiency or arrhythmias, which is why in this case and with the support of multiple departments of our hospital and despite the lack of evidence in the literature it was decided to perform in the General Hospital of Mexico "Dr. Eduardo Liceaga," the first valvuloplasty with balloon of a bioprosthetic pulmonary valve on a pregnant patient, which had a successful result.

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Conflicts of interest

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References

1. Cuypers JA, Witsenburg M, Van der Linde D, Roos-Hesselink JW. Pulmonary stenosis: update on diagnosis and therapeutic options. Heart. 2013;99:339-47.
2. Heaton J, Kyriakopoulos C. Pulmonic Stenosis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
3. Aguado FG, Domingo CA. Tratamiento percutáneo de la válvula pulmonar y las arterias pulmonares en cardiopatías congénitas. REC Interv Cardiol. 2021;3:119-28.
4. Ruckdeschel E, Kim YY. Pulmonary valve stenosis in the adult patient: pathophysiology, diagnosis and management. Heart. 2019;105:414-22.
5. Choi EY, Song J, Lee H, Lee CH, Huh J, Kang IS, et al. The effect of balloon valvuloplasty for bioprosthetic valve stenosis at pulmonary positions. Congenit Heart Dis. 2017;12:746-50.
6. Keane D, Bet Mishra M, Ross DN, Jackson G. Balloon dilatation of a bioprosthetic pulmonary valve. Int J Cardiol. 1993;38:323-5.
7. El Sayed MH, Darwazah AK, El Sayed HM. Double-balloon valvuloplasty of calcified bioprosthetic pulmonary valve twenty-three years after implantation. J Heart Valve Dis. 2013;22:265-9.
8. Rao PS. Percutaneous balloon pulmonary valvuloplasty: state of the art. Catheter Cardiovasc Interv. 2007;69:747-63.
9. Gillespie MJ, Rome JJ, Levi DS, Williams RJ, Rhodes JF, Cheatham JP, et al. Melody valve implant within failed bioprosthetic valves in the pulmonary position: a multicenter experience. Circ Cardiovasc Interv. 2012;5:862-70.
10. O'Connor BK, Beekman RH, Lindauer A, Rocchini A. Intermediateterm outcome after pulmonary balloon valvuloplasty: comparison with a matched surgical control group. J Am Coll Cardiol. 1992;20:169-73.
11. Siu S, Colman J. Congenital heart disease in pregnancy. Heart. 2001;85:710-5.

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CLINICAL CASES

Oropharyngeal dysphagia spectrum in Wallenberg syndrome: a case report

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Abstract

Swallowing disorders are common clinical data in patients with Wallenberg syndrome, although with a broad clinical spectrum previously described. The objective of the study was to describe the characteristics of the spectrum of oropharyngeal dysphagia presentation in patients with Wallenberg syndrome. We performed a single-center, retrospective study in January 2016 and November 2020 with a series of cases and literature search. Data were collected from eight patients with ischemic spinal injury treated in the Phoniatrics Department of the General Hospital of Mexico. Eight cases were included, aged 28 and 74 years. In the first Fiber-optic Endoscopic Evaluation of Swallowing (FEES), the diagnosis was severe oropharyngeal dysphagia in 7 of the 8 patients (87.5%), compared to the second evaluation where mild oropharyngeal dysphagia was present in four patients, and severe oropharyngeal dysphagia on the other half. Oropharyngeal dysphagia can be found in 51-94% of patients with Wallenberg syndrome. In the first evaluation, difficulty with bolus propulsion of the oral phase in FEES was present in 62.5% of the patients. Still, in the second evaluation, the oral stage was reported with no alterations. Thus, patients could persist with severe dysphagia even passing the month of diagnosis. Wallenberg syndrome is a well-known condition that presents in a very variable way. Dysphagia could be severe, even passing the month after establishing the disease. The evaluation of dysphagia will allow their early rehabilitation and reduce the risk of complications.

Keywords: *Oropharyngeal dysphagia. Lateral medullary syndrome. Wallenberg syndrome. FEES.*

Introduction

Swallowing is a sensorimotor act involving a diverse neural network, which requires coordination of cortical and brainstem regions for the safe and efficient transport of liquids and food from the mouth to the stomach[1-3]. Swallowing disorders are a medical disability that affects the digestive system and is associated with increased mortality and health-care costs, without the psychosocial consequences that this generates on patients, such as depression and isolation[4-8]. These functional disorders are usually due to alterations in the physiological processes of the oral and pharyngeal phase of swallowing, including the reflex of absent swallowing, reduced peristalsis and pharyngeal pressure, and coordination problems due to the reflex of late swallowing[8-12].

Acute, subacute, or chronic interruption of arterial blood flow in any spinal territory commonly developed medullary ischemia (anterior and posterior spinal artery

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syndrome) or stroke; and less prevalent transient ischemic accidents (TIAs), spinal claudication, and hypoxic-ischemic myelopathy from global hypoperfusion[13,14].

Approximately 25-50% of stroke patients experience dysphagia. In comparison, the incidence increases exponentially in patients with lateral spinal infarction with about 51-100%, as significant swallowing centers such as the ambiguous nucleus and solitary tract are found in the dorsolateral spinal bulb[14-16].

Wallenberg syndrome, the most common cause of lateral spinal infarction, is also known as posteroinferior cerebellar artery syndrome caused by damage to the lateral segment of the posterior marrow to the lower olive nucleus[17,18]. There is no exact described prevalence of this syndrome; in the United States, approximately 800,000 people have an acute stroke each year, 20% occur in the posterior circulation, leading to an estimated 60,000 new cases of Wallenberg syndrome each year[19]. Its primary etiology is given by atherothrombotic occlusion of the vertebral artery and the posteroinferior cerebellar artery. The main most prevalent risk factor is hypertension followed by smoking and diabetes[20,21]. Dysphagia has been reported in 51-94% of these patients; in most cases, it is initially severe but often improves rapidly. However, some patients may not recover in months or years[21]. Patients with the complete syndrome are rare, have Horner syndrome, cross hemisensory alteration, and ipsilateral cerebellar signs such as vertigo, central nystagmus, dysarthria, and dysphagia[22,23].

Although Wallenberg syndrome has a broad clinical spectrum, swallowing disorders are a common finding in these patients; unfortunately, swallowing disorders related to Wallenberg syndrome have been described only as case reports or in limited patients. This article describes the characteristics of the spectrum of oropharyngeal dysphagia presentation in patients with Wallenberg syndrome and our experience within a national reference center.

Methodology

We describe eight patients with ischemic spinal injury treated in the Phoniatrics Department of the General Hospital of Mexico “Dr. Eduardo Liceaga.” The series of cases were conducted from January 2016 to November 2020, including patients between 18 and 80 years, with magnetic resonance imaging of the skull showing lateral spinal ischemic injury plus swallowing evaluation with the Fiber-optic Endoscopic Evaluation of Swallowing (FEES) twice, the first during hospitalization and the second after discharge. The swallowing was assessed in the oral and pharyngeal phases through four textures in the following order: pudding, nectar, liquid, and solid (cookie), mixed with blue dye to improve visualization. The FEES protocol consisted in administer 2.5 ml of pudding with an increase to 5 ml in case of no aspiration, followed by nectar and water at the same volumes mentioned; finally, 1/4 cookie was offered as solid. The protocol was modified for patient safety, stopping the test if at any time patients had intrusion to the airway. Aspiration was defined as the passage of food to the lower airways, below the vocal folds. Penetration was defined as the entry of food into the larynx above the vocal folds; and pharyngeal residue as the residual material presents in the pharynx after completing the pharyngeal phase of swallowing[11,22,23]. The severity of dysphagia was classified as mild, moderate, and severe, based on O’Neil’s severity scale[24,25].

Results

We included eight patients, four women and four men, randomly caught, aged 28-74 years (average 40 years). Six of the patients (75%) suffered from high blood pressure, one patient had alcoholism (12.5%), and three had a smoking habit (37.5%).

With respect to the magnetic resonance imaging, the T2-weighted sequence shows four patients with lesion with low signal intensity in the right lateral medullary area (Fig. 1A), three patients with the left lateral lesion (Fig. 1B), and one last patient had two hypointense areas, one right upper and anterior medulla and the other in the left lateral and posterior medulla (Fig. 1C).

Concerning the characteristics of the oral phase FEES study in the first evaluation, we found five patients had difficulty bolus propulsion, six posterior spill, and two patients had delayed reflex swallowing, finding more than 1 alteration in one patient. However, in the second evaluation, the oral phase was described as normal in all the patients.

The pharyngeal phase in the FEES study demonstrated in the first evaluation was tolerated by the eight patients who could handle the survey in the passage of pudding, seven nectar consistency, three patients achieved liquid texture, and none could be evaluated for solid. In the second evaluation, all patients were evaluated with nectar and pudding; six patients achieved liquid consistency and one to solid texture. Aspiration was found in seven of eight patients at the first evaluation (Fig. 2), this number was reduced to two of eight patients at the second evaluation.

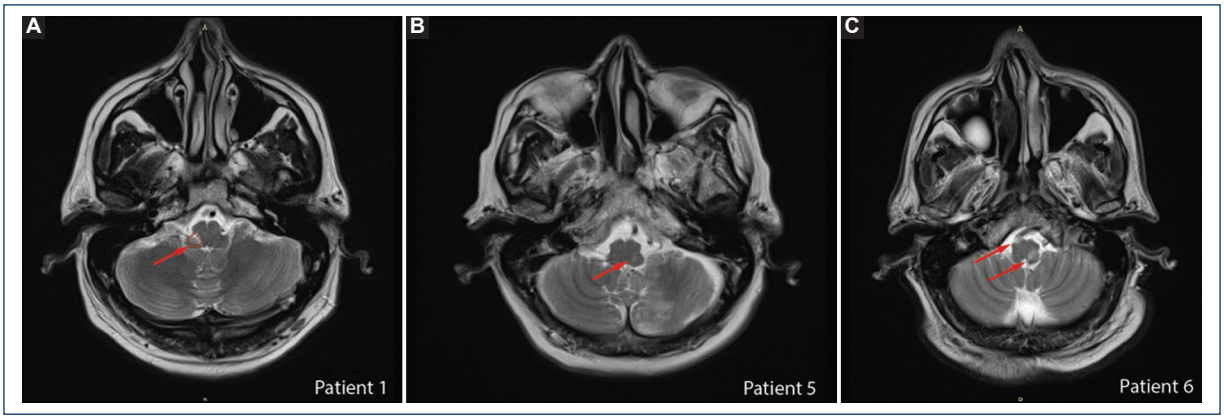

Figure 1. T2-weighted magnetic resonance imaging (MRI). **A:** demonstrating a hyperintense lesion in the right lateral and posterior medulla. **B:** demonstrating a hyperintense lesion in the left lateral and posterior medulla. **C:** demonstrating two lesions, one hyperintense lesion right upper and anterior medulla and other in the left lateral and posterior medulla.

Phoniatric diagnosis in the first evaluation was severe oropharyngeal dysphagia in 7 of the 8 patients (87.5%). The other patient had mild dysphagia; one patient had left vocal fold paralysis, other patients with severe dysphagia had bilateral palsy, and one patient had flaccid dysarthria. Phoniatric diagnosis in the second evaluation was four patients with mild oropharyngeal dysphagia and four patients with severe oropharyngeal dysphagia; none of the patients had vocal fold paralysis. The individual characteristics of the patients and clinical evolution are mentioned in Table 1.

Discussion

The typical signs and symptoms of Wallenberg syndrome are vertigo or dizziness, ataxia, nystagmus, Horner sign ipsilateral weakness of the palate and vocal folds, decrease in the gag reflex, and oropharyngeal dysphagia[20,22,26,27], the last one is the least studied, nevertheless is a common symptom which can be found in 51-94% of patients[14,28-30]. All the patients studied in our center had swallowing disorders with a wide clinical spectrum as demonstrated.

Hypertension was comorbidity found in 75% of our patients; it is a common risk factor as seen in a cohort of acute ischemic stroke patients studied by Flowers et al. included 160 patients with a mean age of 66.7 years, of which 111 (69.4%) had hypertension[31-35].

There are many studies regarding stroke related to dysphagia, but our study is the only one in which dysphagia is evaluated specifically at the time of diagnosis and after a month in patients with Wallenberg syndrome. Regarding the oral phase in the first evaluation, the trouble with bolus propulsion was observed in 5 patients (62.5%), posterior spill in 6 patients (75%), and 2 patients had delay reflex swallow (25%); but in the second evaluation, the oral phase improved to normal in all patients. With these findings, we could say that the oral phase has a fast recovery; there is poor information about the description or evolution of the oral phase in the literature to compare. Despite an apparent good recovery in the oral phase, combining these alterations with the observed in the pharyngeal phase at FEES means for the patient, especially during the 1st weeks of the disease, that at the moment of swallowing will be an action even more difficult. Furthermore, if alterations at pharyngeal phase are persistent, the degree of dysphagia will still be severe, passing the month after disease installation.

The literature says that the severity of dysphagia will depend on the extent of involvement of the swallowing-related structures in the infarct lesion because all the central control of the swallowing is located in the lateral medulla[32,35-39]. In our study, most of the patients do not follow the rule that says severity will depend on the location or extent, because even patients with right or left lateral lesions present the same evolution, and some patients with one lesion present better evolution than the patient with 6 with two different lesions.

Nearly, all the case reports of dysphagia related to Wallenberg syndrome mentioned that the evolution of the dysphagia will be toward improvement almost back to normal[14,17,21,23]. In our case, almost all the patients remained in severe dysphagia, and only three patients showed improvement.

Table 1. Clinical evolution of patients included in the study

Patient	Age	Gender	Days of evolution	Oral phase				Pharyngeal phase				
				difficulty bolus propulsion	Anterior spill	Posterior spill	Difficulty for bolus propulsion	Pudding	Nectar	Liquid	Solid	Delay reflex swallow
1	29	F	10	Y	Y	Y	N	Normal	Aspiration (2.5 ml)	Not tested	Not tested	N
2	28	F	30	Y	Y	Y	N	Normal	Penetration (2.5 ml)	Aspiration (2.5 ml)	Not tested	Y
3	74	F	30	N	N	N	N	Postswallowing residue	Posdeglutory residue	Aspiration (2.5 ml)	Not tested	N
4	44	M	365	Y	N	Y	Y	Normal	Aspiration (5 ml)	Not tested	Not tested	N
5	47	M	15	N	N	Y	Y	Penetration (2.5 ml)	Penetration (2.5 ml)	Aspiration (2.5 ml)	Not tested	N
6	62	M	60	N	N	Y	N	Penetration (2.5 ml)	Aspiration (2.5 ml)	Not tested	Not tested	N
7	36	M	60	Y	N	N	N	Penetration (2.5 ml)	Aspiration (2.5 ml)	Not tested	Not tested	N
8	56	F	7	Y	Y	Y	Y	Aspiration (2.5 ml)	Not tested	Not tested	Not tested	N

	Dx	2nd evaluation (days after)	Oral phase	Pharyngeal phase				Dx
				Pudding	Nectar	Liquid	Solid	
1	Severe dysphagia + left vocal fold paralysis	30	Normal	Penetration (2.5 ml)	Aspiration (2.5 ml)	Not tested	Normal	Severe dysphagia
2	Severe dysphagia + bilateral vocal fold paralysis	15	Normal	Normal	Normal	Penetration (2.5 ml)	Not tested	Mild dysphagia
3	Mild dysphagia	25	Normal	Normal	Normal	Penetration (2.5 ml)	Not tested	Mild dysphagia

(Continues)

Table 1. Clinical evolution of patients included in the study (*continued*)

Patient	Age	Gender	Days of evolution	Oral phase		Pharyngeal phase				
4	Severe dysphagia	30	Normal	Normal	Penetration (2.5 ml)	Penetration (2.5 ml)	Not tested	Severe dysphagia		
5	Severe dysphagia + Flacid dysarthria	27	Normal	Penetration (5 ml)	Penetration (5 ml)	Penetration (5 ml)	Not tested	Severe dysphagia		
6	Severe dysphagia	30	Normal	Normal	Normal	Aspiration (5 ml)	Not tested	Mild dysphagia		
7	Severe dysphagia	16	Normal	Penetration (5 ml)	Penetration (5 ml)	Not tested	Not tested	Severe dysphagia		
8	Severe dysphagia	29	Normal	Normal	Normal	Penetration (5 ml)	Not tested	Mild dysphagia		

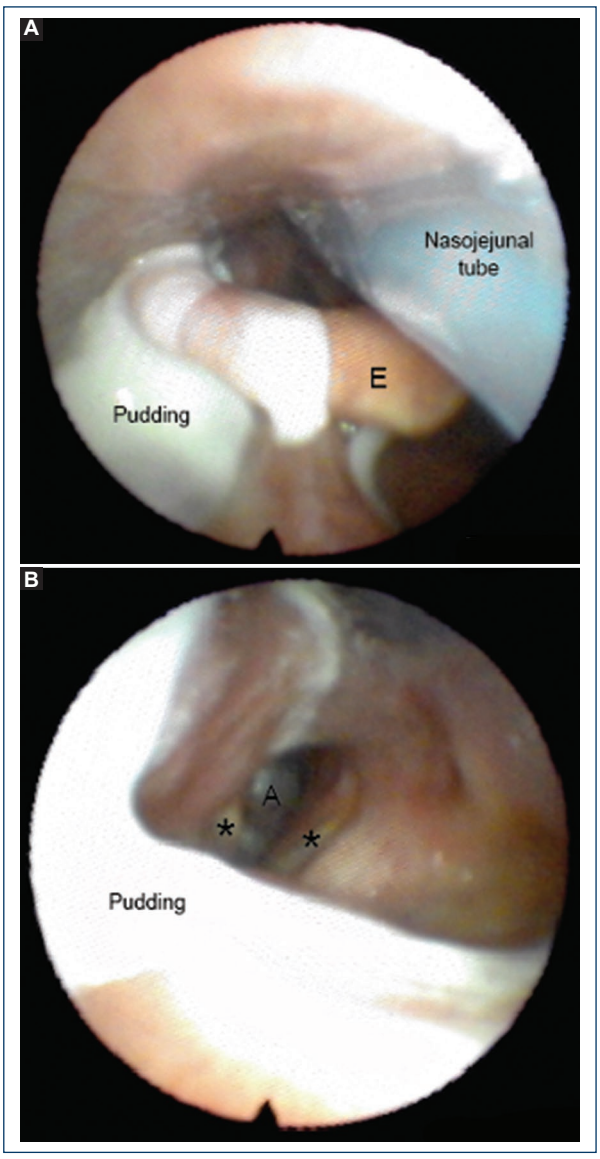

Figure 2. A-B: fiber-optic Endoscopic Evaluation of Swallowing (FEES): penetration and aspiration of bolus. E: epiglottis; A: aspiration; *: vocal folds.

The nucleus ambiguous controls the muscles of the palate, pharynx, and larynx so a lesion also results in vocal fold paralysis[28,33,39]. This, in addition to explaining the variation in the severity of dysphagia in our patients, could explain the two patients with vocal fold palsy.

Conclusions

The evolution of dysphagia related to Wallenberg syndrome could be more severe than expected, especially passing the 1st month after establishing the disease. Therefore, evaluation of dysphagia is essential, since a

prompt diagnosis will allow their early rehabilitation reducing the risk of complications, such as aspiration pneumonia, malnutrition, and increased mortality[4,6,40,41]. Furthermore, patients follow-up should be more strict, given the apparent probability of maintaining severe dysphagia. The presence of other clinical findings like vocal fold palsies should be investigated, to offer an oriented therapy and rehabilitation. Because of being a rare syndrome, further studies describing the evolution of related dysphagia are needed to establish a long-term prognosis.

Patients consent

Informed consent was obtained from the patients reported in this article.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Declaration of Helsinki.

Data confidentiality. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained the approval of the ethics committee for the analysis and publication of routinely obtained clinical data. The informed consent of the patients was not required as it was a retrospective observational study.

References

1. Shaw SM, Martino R. The normal swallow: muscular and neurophysiological control. Otolaryngol Clin North Am. 2013;46:937-56.
2. Matsuo K, Palmer JB. Anatomy and physiology of feeding and swallowing: normal and abnormal. Phys Med Rehabil Clin N Am. 2008;19:691-707.
3. Steele CM, Miller AJ. Sensory input pathways and mechanisms in swallowing: a review. Dysphagia. 2010;25:323-33.
4. Altman KW, Yu GP, Schaefer SD. Consequence of dysphagia in the hospitalized patient. Dysphagia. 2011;26:200-1.
5. Roy N, Stemple J, Merrill RM, Thomas L. Dysphagia in the elderly: preliminary evidence of prevalence, risk factors, and socioemotional effects. Ann Otol Rhinol Laryngol. 2007;116:858-65.
6. Cabre M, Serra-Prat M, Palomera E, Almirall J, Pallares R, Clavé P. Prevalence and prognostic implications of dysphagia in elderly patients with pneumonia. Age Ageing. 2009;39:39-45.
7. Ekberg O, Hamdy S, Woisard V, Wuttge-Hannig A, Ortega P. Social and psychological burden of dysphagia: its impact on diagnosis and treatment. Dysphagia. 2002;17:139-46.
8. Rommel N, Hamdy S. Oropharyngeal dysphagia: manifestations and diagnosis. Nat Rev Gastroenterol Hepatol. 2016;13:49-59.
9. Hosseini P, Tadavarthi Y, Martin-Harris B, Pearson WG. Functional modules of pharyngeal swallowing mechanics. Laryngoscope Investig Otolaryngol. 2019;4:341-6.
10. Sasegbon A, Hamdy S. The anatomy and physiology of normal and abnormal swallowing in oropharyngeal dysphagia. Neurogastroenterol Motil. 2017;29(11):1–15
11. Beharry A, Michel P, Faouzi M, Kuntzer T, Schweizer V, Diserens K. Predictive factors of swallowing disorders and bronchopneumonia in acute ischemic stroke. J Stroke Cerebrovasc Dis. 2019;28:2148-54.
12. Gasca-González OO, Pérez-Cruz JC, Baldoncini M, Macías-Duvignau MA, Delgado-Reyes L. Neuroanatomical basis of Wallenberg syndrome. Cir Cir. 2020;88:376-82.
13. Labeit B, Mueller H, Muhle P, Claus I, Warnecke T, Dziewas R, et al. Predicting dysphagia with national institute of health stroke scale: distinction between infra-and supratentorial region is essential. Cerebrovasc Dis. 2018;46:150-8.
14. Chun MH, Kim D, Chang MC. Comparison of dysphagia outcomes between rostral and caudal lateral medullary infarct patients. Int J Neurosci. 2017;127:965-70.
15. Finestone HM, Teasell RW, Heitzner J. Case study of dysphagia and aspiration following a brain stem stroke. Top Stroke Rehabil. 1999;6:41-5.
16. Logemann JA, Kahrilas PJ. Relearning to swallow after stroke-application of maneuvers and indirect biofeedback: a case study. Neurology. 1990;40:1136-8.
17. Jang SH, Kim MS. Dysphagia in lateral medullary syndrome: a narrative review. Dysphagia. 2021;36:329-38.
18. Kunieda K, Sugi T, Ohno T, Nomoto A, Shigematsu T, Kanazawa H, et al. Incoordination during the pharyngeal phase in severe dysphagia due to lateral medullary syndrome. Clin Case Rep. 2021;9:1728-31.
19. Saleem F, Das MJ. Lateral Medullary Syndrome. StatPearls. Treasure Island (FL): StatPearls Publishing; 2021.
20. Mikushi S, Kagaya H, Baba M, Tohara H, Saitoh E. Laterality of bolus passage through the pharynx in patients with unilateral medullary infarction. J Stroke Cerebrovasc Dis. 2014;23:310-4.
21. Kang HG, Kim BJ, Lee SH, Kang DW, Kwon SU, Kim JS. Lateral medullary infarction with or without extra-lateral medullary lesions: what is the difference? Cerebrovasc Dis. 2018;45:132-40.
22. Aydogdu I, Ertekin C, Tarlaci S, Turman B, Kiylioglu N, Secil Y. Dysphagia in lateral medullary infarction (Wallenberg's syndrome): an acute disconnection syndrome in premotor neurons related to swallowing activity? Stroke. 2001;32:2081-7.
23. Day GS, Swartz RH, Chenkin J, Shamji AI, Frost DW. Lateral medullary syndrome: a diagnostic approach illustrated through case presentation and literature review. CJEM. 2014;16:164-70.
24. Alagiakrishnan K, Bhanji RA, Kurian M. Evaluation and management of oropharyngeal dysphagia in different types of dementia: a systematic review. Arch Gerontol Geriatr. 2013;56:1-9.
25. O'Neil KH, Purdy M, Falk J, Gallo L. The dysphagia outcome and severity scale. Dysphagia. 1999;14:139-45.
26. Khedr EM, Abo-Elfetoh N. Therapeutic role of rTMS on recovery of dysphagia in patients with lateral medullary syndrome and brainstem infarction. J Neurol Neurosurg Psychiatry. 2010;81:495-9.
27. Vigderman AM, Chavin JM, Kososky C, Tahmoush AJ. Aphagia due to pharyngeal constrictor paresis from acute lateral medullary infarction. J Neurol Sci. 1998;155:208-10.
28. Kim H, Chung CS, Lee KH, Robbins J. Aspiration subsequent to a pure medullary infarction. Arch Neurol. 2000;57:478-83.
29. Kim JS, Lee JH, Suh DC. Spectrum of lateral medullary syndrome. Correlation between clinical findings and magnetic resonance imaging in 33 subjects. Stroke. 1994;25:1405-11.

30. Grant G. Infarction localization in a case of Wallenberg's syndrome. A neuroanatomical investigation with comments on structures responsible for nystagmus, impairment of taste and deglutition. J Hirnforsch. 1966;5:419-30.
31. Flowers HL, Alharbi MA, Mikulis D, Silver FL, Rochon E, Streiner D, et al. MRI-based neuroanatomical predictors of dysphagia, dysarthria, and aphasia in patients with first acute ischemic strokea. Cerebrovasc Dis Extra. 2017;7:21-34.
32. Duane EH. Neuroanatomy: an atlas of structures, sections, and systems. Philadelphia: Lippincott Williams & Wilkins; 2004.
33. Nilsson H, Ekberg O, Sjöberg S, Olsson R. Pharyngeal constrictor paresis: an indicator of neurologic disease? Dysphagia. 1993;8:239-43.
34. Verin E, Leroi AM, Marie JP. Restoration of normal swallowing function in Wallenberg syndrome by repetitive transcranial magnetic stimulation and surgery. Ann Phys Rehabil Med. 2016;59:343-5.
35. Crary MA. A direct intervention program for chronic neurogenic dysphagia secondary to brainstem stroke. Dysphagia. 1995 Winter;10(1):6-18.
36. Sacco RL, Freddo L, Bello JA, Odel JG, Onesti ST, Mihr JP. Wallenberg's lateral medullary syndrome. Clinical-magnetic resonance imaging correlations. Arch Neurol. 1993;6:609-14.
37. Meng NH, Wang TG, Lien IN. Dysphagia in patients with brainstem stroke: incidence and outcome. Am J Phys Med Rehabil. 2000;2:170-5.
38. Kim H, Lee HJ, Park JW. Clinical course and outcome in patients with severe dysphagia after lateral medullary syndrome. Ther Adv Neurol Disord. 2018;11:1756286418759864.
39. Gupta H, Banerjee A. Recovery of dysphagia in lateral medullary stroke. Case Rep Neurol Med. 2014;2014:404871.
40. Nair SS, Surendaran AJ, Menon JR, Sreedharan SE, Sylaja PN. Persistent post-stroke dysphagia treated with cricopharyngeal myotomy. Ann Indian Acad Neurol. 2016;2:249-51.
41. Foley NC, Martin RE, Salter KL, Teasell RW. A review of the relationship between dysphagia and malnutrition following stroke. J Rehabil Med. 2009;41:707-13.

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CLINICAL CASES

Schwannoma of the dorsal nerve of the penis: case report and differential diagnoses

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Abstract

Schwannomas are tumors that appear in the sheath that surrounds the nerves; they are formed of Schwann cells which form the myelin sheath in peripheral nerves. In this document, we report a case of Schwannoma of the dorsal nerve of the penis in a man 40-year-old male with no history of neurofibromatosis. Despite the abundant innervation of the penis, it is rare to find them in this location with < 50 cases reported in the literature. Its diagnosis is integrated based on physical examination and supported by imaging. The definitive diagnosis is obtained with histopathology with immunohistochemistry.

Keywords: *Schwannoma. Penis. Clinical case.*

Introduction

Schwannomas are benign tumors of the Schwann cells which produce the myelin sheath that covers the peripheral nerves which can be found in patients with neurofibromatosis or without it[1-2].

Despite the great innervation of the penis, the presence of these tumors constitutes an atypical manifestation with < 200 cases reported in the literature since its first description in 1968[1-4].

Case presentation

This is a 40-year-old male patient who presented to the urology specialist with the following characteristics. Patient denies important family history, denies smoking, and reports occasional alcohol consumption. The patient denies chronic-degenerative diseases, as well as previous hospitalizations. As the only surgical history, he refers adenotonsillectomy.

Within sexual life, the patient refers being married and reports having four additional partners, denies history of sexually transmitted diseases, as a contraceptive method he uses condom occasionally. Patient denies anal sex.

He began his current condition 7 years before the consultation with multiple new lesions on the genitals, which caused him pain during sexual intercourse.

On physical examination, five nodular-looking lesions with sizes ranging from 2 mm to more than a cm in diameter are observed in the dorsal portion of the penis, which is why sebaceous cysts are suspected (Fig. 1). Options are discussed with the patient; a preoperative US Doppler of the penis was requested, and

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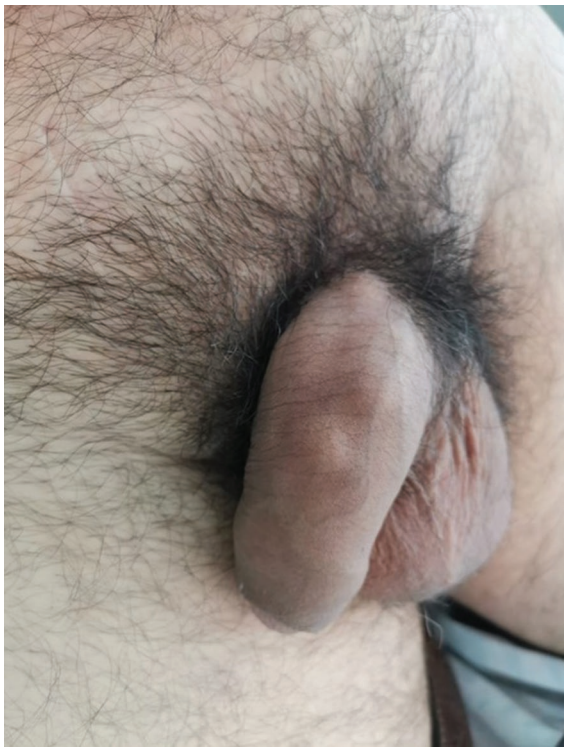

Figure 1. Photography of the penis of the patient.

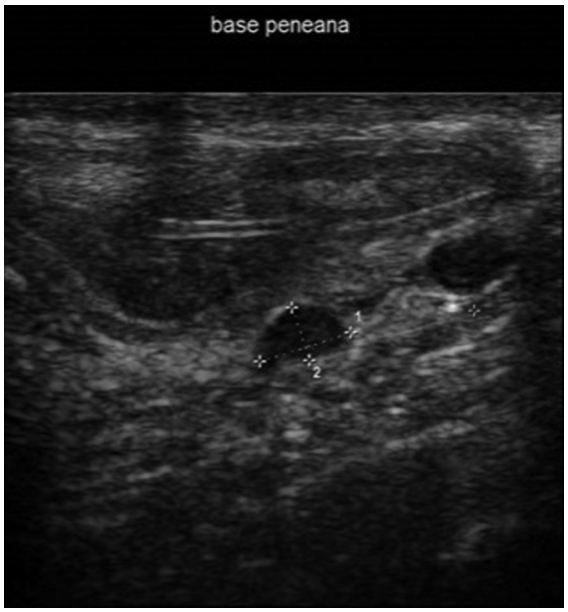

Figure 2. Ultrasonography of the penis of the patient.

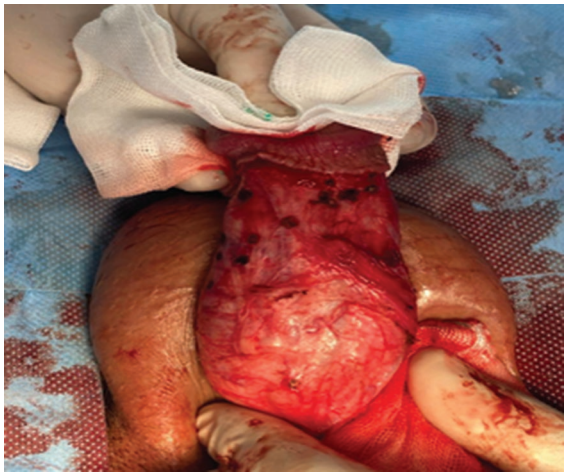

Figure 3. Photography during the surgery of the patient.

circumcision was scheduled with resection of the penile tumors with vasectomy.

The ultrasound reported the presence of hypoechogenic nodular images with a trajectory toward the lateral region of the penis with displacement of the vascular structures (Fig. 2). Rest of the penis within normal characteristics.

The patient underwent surgical treatment, where seven irregular nodular tumors of multiple sizes with a smooth, opaque surface, and a grayish-white appearance were removed, which were well defined (Fig. 3). During surgery, no invasion of the corpus cavernosum or corpus spongiosum was identified. Circumcision and vasectomy were completed, and the procedure was finished.

Histopathological report reveals benign well-defined mesenchymal neoplasms, with a capsule composed of spindle cells and poorly defined cytoplasmic boundaries, the cells form palisades and Verocay 1 and type 2 structures, elongated nuclei with granular chromatin without evident nucleoli, pleomorphism or atypical mitoses (Fig. 4). With the previous information schwannoma is suspected, so immunohistochemical staining is performed with PS 100 antibody, smooth muscle actin and CD 34, only the first one resulting positive, confirming the suspicion of schwannoma and ruling out the possibility of leiomyoma or benign fibrous histocytoma (Table 1 and Fig. 5).

The diagnosis of completely excised Schwannomas was integrated. The patient was informed about the importance of going to a neurologist to rule out neurofibromatosis.

The patient attends a follow-up consultation 7 days after and one month after surgery. The patient reported no sensory abnormalities or alterations in sexual

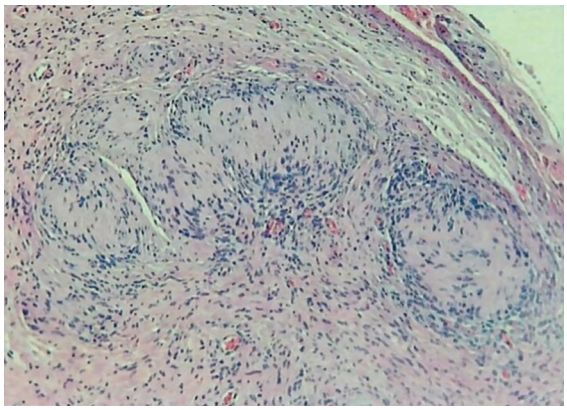

Figure 4. Histopathological image of the tumor.

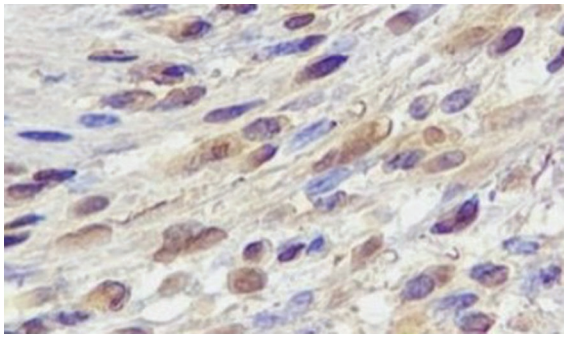

Figure 5. Tumor immunohistochemistry.

Table 1. Tumor immunohistochemistry

Antibody	Interpretation
PS100	Positive in the nuclei and the cytoplasm of all tumoral cells +++/´+++
Smooth muscle actin	Negative
CD 34	Negative

function, so he was discharged from the urology service. He decides not to see a neurologist.

Discussion

Schwannomas are benign tumors of the Schwann cells which produce the myelin sheath that covers the peripheral nerves, which can be found in patients with neurofibromatosis or without it[1-2]. These tumors are frequent in extremities, face or head. Despite the great innervation of the penis, the presence of these tumors constitutes an atypical manifestation with < 200 cases reported in the literature since its first description in 1968[1-4]. The average age of appearance is usually 39 years[1].

They are encapsulated tumors of which different histological subtypes have been described based on the cells that compose them, the main ones being cystic, epithelioid, melanocytic, with psammoma bodies, and plexiform[3].

These tumors have a very slow growth, so at diagnosis they can have several years of evolution[5], within the differential diagnoses are the cysts of the middle raphe such as apocrine cystadenomas or mucous cysts which are remnants of the periurethral glands de Littre, other diagnoses to consider in the differential are warts, intentionally inserted foreign bodies, pearly penile papules, and penile carcinoma[6,7]. Pearly penile papules are lesions that correspond to normal glands which appear on the crown of the glans during adolescence. Another diagnosis to consider is the parafrenular glands which, as their name implies, generally appear three or four on each side of the frenulum[6,7]. Sebaceous cysts also tend to enter the differential which are usually discarded due to their rapid growth, these masses also usually appear in the scrotum.

Patients with Schwannoma of the penis usually seek help for erectile dysfunction or pain during sexual intercourse, other manifestations are pain on ejaculation or may debut as Peyronie's disease. Pain is usually reported when the tumor grows between Buck's fascia and the tunica albuginea[5]. These tumors are classified according to Antolini in Antolini A and Antolini B, being frequently mixed. Atolini A areas are composed of compact palisade cells with poorly defined cytoplasmic boundaries. Atolini B regions are made up of randomly distributed spindle cells[4-8]. In immunohistochemistry, these tumors are usually intensely positive for the S-100 protein, unlike median raphe cysts, which are usually positive for avidin-biotin peroxidase, epithelial membrane antigen (EMA) Human milk fat globule antigen 1 (HMFG1), proteases CK7, and CK13[5]. Multiple imaging studies may be useful in the diagnosis, these neoplasms on magnetic resonance imaging are usually isointense on T1 sequences and hyperintense on T2 sequences with fat saturation, they usually have homogeneous gadolinium enhancement. On ultrasound, these tumors can be hyperechoic[1-4].

The only curative treatment for these neoplasms is surgical resection, which is usually sufficient on its own in most cases; in extremely rare cases of malignant Schwannoma, penectomy plus adjuvant radiotherapy may be indicated[3].

Conclusion

Schwannomas of the penis are a rare neoplasm with very few cases in the literature; the diagnosis is based on physical examination and imaging studies, with the histopathological study confirming it. In almost all cases, these tumors are benign, with surgical treatment being the treatment of choice, with no cases of recurrence reported to date.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments have been performed on humans or animals for this research.

Data confidentiality. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

References

1. Han H, Lei HE, Tian L, Zhang XD. Isolated penis schwannoma: a rare case report. Urology case reports. Urol Case Rep. 2018;21:12-3. Available from: https://search.ebscohost.com/login.aspx?direct=true&AuthType=ip&db=cmedm&AN=30128295&lang=es&site=eds-live&scope=site [Last accessed on 2022 Apr 27].
2. Kumar U, Jha NK. Schwannoma of the penis, presenting as a scrotal mass, rare entity with an uncommon presentation. Urol Ann. 2017;9:301-3. Available from: https://ebsco.udemproxy.elogim.com/login.aspx?direct=true&AuthType=ip&db=edsgao&AN=edsgcl.498890973&lang=es&site=eds-live&scope=site [Last accessed on 2022 Apr 27].
3. Gkekas C, Kalyvas V, Symeonidis EN, Malioris A, Papathanasiou M, Kalinderis N, et al. Plexiform schwannoma of the penis: a rare subtype of genital schwannoma. Case Rep Urol. 2019;2019:1752314. Available from: https://ebsco.udemproxy.elogim.com/login.aspx?direct=true&AuthType=ip&db=edsgao&AN=edsgcl.617387654&lang=es&site=eds-live&scope=site [Last accessed on 2022 Apr 27].
4. Algaba F, Chivite A, Rodríguez-Villalba R, Sarquella J, Martínez-Montelongo R, Ruiz-Castañé E. Schwannoma of the penis: a report of 2 cases. J Androl. 2003;24:651-2. Available from: https://ebsco.udemproxy.elogim.com/login.aspx?direct=true&AuthType=ip&db=cmedm&AN=12954653&lang=es&site=eds-live&scope=site [Last accessed on 2022 Apr 27].
5. Mohammadi A, Rosa M, Rhatigan R. Verocay body prominent schwannoma of penis: an unusual localization for this lesion. J Cutan Pathol. 2008;35:1160-2.
6. O'Mahony C. 8. Genital lumps and bumps: what is normal? Trends Urol Gynaecol Sex Health. 2007;12:25-7.
7. Ghaly AF, Orange GV. Not every penile lump is a wart! Schwannoma of the penis. Int J STD AIDS. 2000;11:199.
8. Bilommi R. Malignant peripheral nerve sheath tumor (Schwannoma) of the dorsal penis: A case report and review of the literature. Pediat Urol Case Rep. 2019;6:95-9.