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BREAKING PARADIGMS
NEW BREAST CANCER REHABILITATION METHODS FROM OCCUPATIONAL THERAPY
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OCCUPATION AND HEALTH

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Understanding and making visible the actions, activities or tasks that have a purpose or meaning in people's lives is one of the objectives of occupational therapy. This discipline also seeks to demonstrate which occupations actually cause a repairing effect, which increase motivation and which strengthen the immune system. The existing relationship between occupation and well-being is one of the aspects that help understanding human occupation. Case studies that allow expanding and consolidating the therapeutic evidence are also intended.

In 1994, Christiansen (1) talked about understanding the concept of occupation and differentiating it from the concept of activity. So, he defined occupation "as the group of activities that are identified, organized and valued by a group of people and a culture". (1, p5)

To make known the existence and effectiveness of the results achieved through occupational therapy is a pressing need; in addition, the person who suffers a health condition and his family should know about the options that complement and lead to improve and increase functionality, because we are faced with chronic health conditions, permanent pain or states that have an impact on a satisfactory evolution.

Therefore, having states of well-being and moments of tranquility or being able to focus attention on something other than pain is what makes a difference between one patient and another. Each person is unique and has a history, beliefs, needs and individual and specific tastes that create a unique life. Only in the presence of an adverse event or situation that alters health, people look at the past and think about the future, although they are living in the present, here and now. In those moments, people really cherish what they have, what they do and what they are.

As an occupational therapist with experience in the clinical area, it is satisfying to find published cases that allow us to understand and reveal what a profession can do for the physical, mental and emotional health of a human being. There are studies on aging that show that occupational therapy not only improves the quality of life of older adults, but also improves health economy by reducing costs, because people get sick less when they are engaged in something they like. (2) On the other hand, it is not necessary to establish causal relationships between occupation, health and well-being; however, there are strong relationships between these concepts, so it can be said that healthy people engage in several occupations. (3)

Therefore, the challenge for health professionals in the 21st century is to be able to conduct studies based on health economics and effectiveness in terms of expected results, studies in which occupational therapy can demonstrate that therapeutic activities work in all dimensions of a person, ranging from the physical, emotional and mental aspects, through the family dimension to achieve a social impact. Therefore, the perception of a person's well-being can have greater and better times.

As a professional duty and from an ethical point of view, I consider that it is necessary to be able to commit to investigations on how occupations and activities contribute to people's health, as well as to show the main and most effective therapeutic alternatives that aim to satisfy the essential needs of human beings suffering from health conditions, doing a reflection in order to achieve a better quality of life. Thus, each case we have is an investigation: the methodology chosen, its rigor, the formality in data recording and the veracity of the instruments chosen support the results or indicators of change in the people who receive a treatment.

Finally, I call on more occupational therapists to write down their daily experiences

and share the importance of occupation in overall health and well-being.

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BREAKING PARADIGMS, NEW BREAST CANCER REHABILITATION METHODS FROM OCCUPATIONAL THERAPY: CASE REPORT

Keywords: Occupational therapy; Breast cancer lymphedema; Breast neoplasms; Comprehensive health care.
Palabras clave: Terapia ocupacional, Linfedema del cáncer de mama; Neoplasias de la mama; Atención integral de salud.

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ABSTRACT

Introduction: Breast cancer is one of the most frequent diseases in Colombia and worldwide. Thousands of women, who undergo treatment, survive and require timely and comprehensive occupational therapy intervention. This paper presents a rehabilitation case study that followed the biopsychosocial and quality of life in persons model.

Case presentation: Intervention on a 64-year-old woman referred to the occupational therapy service with a diagnosis of infiltrating ductal carcinoma of the left breast with neoadjuvant radiotherapy, after modified radical mastectomy and stage III lymphedema. She presented with restricted participation and occupational performance, specifically in activities of daily living, with relevant psychosocial and socio-emotional consequences.

An intervention focused on the individual, following a biopsychosocial approach, was proposed in order to apply strategies on restorative, empowerment and maintenance activities of occupational skills involved in activities of daily living. Emphasis was placed on socio-emotional, occupational biomechanics and education aspects with special care to involve the interests of women.

Conclusions: Rehabilitation for breast cancer patients not only involves biomedical care but also approaches psychosocial aspects that sometimes have to be solved in advance to get results that are later evident in the health of the person. In this case, a breast prosthesis was elaborated by and for the person, using all kinds of strategies that responded to biomedical axes and well-being and health.

RESUMEN

Introducción. El cáncer de mama es una enfermedad recurrente en el mundo y en Colombia. Miles de mujeres que la padecen se someten a tratamiento, sobreviven y necesitan una oportuna, y sobre todo holística, intervención desde la terapia ocupacional. Se presenta un estudio de caso de rehabilitación en concordancia al modelo biopsicosocial y centrado en la persona.

Presentación del caso. Mujer de 64 años remitida al servicio de terapia ocupacional con diagnóstico de cáncer ductal infiltrante de mama izquierda con neoadyuvancia por radioterapia, posterior a mastectomía radical modificada y linfedema etapa III, quien presenta restricciones en la participación y desempeño ocupacional, en específico en actividades de la vida diaria con alteraciones psicosociales y socioemocionales relevantes.

Se planteó una intervención centrada en la persona, con enfoque biopsicosocial, en donde se aplicaron diferentes estrategias en actividades de tipo restaurativo, potenciación y mantenimiento de destrezas ocupacionales implicadas en actividades de la vida diaria. Se hizo énfasis en las áreas socioemocional, de biomecánica ocupacional y de educación con especial cuidado de involucrar los intereses de la mujer.

Conclusiones. La rehabilitación del cáncer de mama no solo implica atención biomédica, sino también abordaje de aspectos psicosociales que en ocasiones tienen que ser resueltos con antelación para conseguir resultados que se evidencien en la salud. En este caso la elaboración de una prótesis de

mama por y para la persona vinculó toda clase de estrategias que respondían a ejes biomédicos y comprendían en su totalidad el bienestar y la salud.

INTRODUCTION

Breast cancer is a high-impact disease worldwide that affects women around the world in a 1:2 ratio. In Colombia, the most recent data show that about 7 000 new cases are diagnosed and that around 4 500 women survive per year. (1,2) Currently, the country has guidelines and management protocols for this disease, which include rehabilitation through relevant interventions such as occupational therapy in order to increase the impact on the persons and their health. (1,3)

In general, some of the health and occupation alterations caused by cancer, especially breast cancer, are related to physical, emotional and cognitive impairments. (4) Regarding daily life, women who suffer and survive this disease present alterations in the activities of daily living, work, education, leisure, etc., resulting in restrictions that involve everything from body structures and functions to emotionality. (5-10)

Occupational therapy positively impacts the rehabilitation process of a person with cancer (5,6,8,10-14), covering important aspects including initial diagnosis, survival phase or final stage of life (4), even in subjects who relapse in intensive care units. (15) The activities performed by an occupational therapist in breast cancer rehabilitation involve those related to prevention of alterations and occupational restrictions and the improvement and enhancement of skills (4,6-8,13,14,16) through activities and strategies such as motor rehabilitation, enhancement of the execution of activities of daily living, prevention of cognitive dysfunctions, teaching techniques, using splints, the psychosocial approach, among others. (4-8,11,13,14,17)

The importance of the following case lies in the comprehensive epistemological stance from occupational therapy. Said stance arises from knowledge based on the dynamic interaction of the personal areas (public, private, "the me") and the medical, social and environmental areas, grounded on reflection by the subjects involved through their participation and change process. (18)

CASE PRESENTATION

64-year-old woman, living in Bogotá D.C., referred to the occupational therapy service 9 months after modified radical mastectomy surgery and neoadjuvant therapy with radiotherapy by the Physical Medicine and Rehabilitation Service of the Instituto Nacional de Cancerología Empresa Social del Estado (National Institute of Cancerology Social Enterprise of the State - INC) with diagnosis of infiltrating ductal carcinoma of the left breast. During consultation, restrictions in participation and occupational performance were observed, which in part were caused by the diagnosis and subsequent complete breast tissue removal surgery (including the nipple, the areola and the secondary and sentinel lymph nodes). The surgery took place in January 2016, with subsequent development of lymphedema in the upper left limb.

Assessment

A comprehensive assessment process was initiated by occupational therapy through occupational history, observation of movements, execution of activities and application of tests by areas. During the process, the woman manifested difficulties to develop activities of daily living and socio-emotional distress related to the surgery and treatment. Regarding her general background, she stated being the head of the family, living with five children and close

relatives, being a housewife and having only elementary school education. She also said that she was self-employed in the sale of food, and that her hobbies included weaving, dancing and local music activities. She manifested that her family or close network accompanied her occasionally in rehabilitation.

In relation to executive skills, she responded positively to sensory, auditory, visual and vestibular stimuli, but with difficulties in affected areas such as the upper limbs, trunk and chest. The proprioceptive and tactile sensory systems were found to be affected at a deep, superficial and thermal hypoesthesia level. In a later study, she was diagnosed with severe carpal tunnel syndrome caused by bilateral median nerve entrapment.

Regarding motor skills, limitations in the upper left limb were observed such as mobility, strength and functional, integral and grip motor skills (Table 1), related, among others, to lymphedema.

Table 1. Specifications of the biomechanical assessment.

Aspect	Upper left limb	Upper right limb
Mobility Assessment by goniometry and compared with normal standards	▪ Limited flexo/extension reaching 120° in flexion and 20° in extension ▪ Complete abduction and limited adduction reaching 10° ▪ Internal and external rotations slightly altered, sometimes achieving full rotation ▪ Supination and pronation with minimum restriction at 85°, especially in supination ▪ The elbow and its movements show flexion limitations reaching 110°	Complete on all the evaluated planes
Strength Evaluated by Hand Grip Strength test	▪ Decreased in maintenance control and object pressure ▪ Below average (<22)	No limitations in maintenance control and object pressure were observed Above average (=30)
Functional skills	Difficulties were observed in the performance of functional skills (start-development-completion) with emphasis on those that require mobilization above the shoulder girdle such as hand, head and mouth	Complete in all evaluated skills
Motor skills	Difficulties were observed in motor skill patterns (start-development-completion) with special emphasis on vertical and diagonal movements such as reaching, grasping and throwing	Complete in all evaluated patterns
Grasp patterns	Difficulties were observed in palmar grasp, cylindrical grasp and full grip. Global limitation was evident at the level of fine clamps and tripods	Complete in all evaluated patterns

Source: Own elaboration.

The motor evaluation, by measuring the limb circumference and in accordance with the guidelines of the Consensus Document of the International Society of Lymphology, (19) showed a stage 3 lymphedema in the upper left limb, characterized by visible edema, enlargement of the affected area, hardening, difference between limbs of around 3-5 cm and thickening of the skin.

Regarding the cognitive-perceptual level, processing skills, time-place-person orientation, basic cognitive functions, basic learning devices and executive functions were functional and appropriate. The social-emotional aspect showed affectations referred and related directly to the loss of body image and self-awareness due to the removal of the mammary gland and the lymphedema. The person said that this was her main concern and the main reason for the alterations and difficulties in her activities of daily living and her health.

Regarding occupation, alterations were found in all the activities of daily living as the person mentioned that they were "difficult", slow and sometimes painful to perform. Sections of the Occupational Therapy Practice Framework were used for this item. (20) In relation to food, the person manifested difficulties for using cutlery, eating normally, preparing meals, reaching tools and implements located in elevated areas of the kitchen, general cleaning of food sites, among others, always in relation to bimanual activities.

Concerning with personal hygiene, she showed difficulties in activities such as showering, combing and putting on makeup as she needed to use the affected limb. When getting dressed, more relevant difficulties were mentioned due to the need to use the affected limb globally; in this regard, the person manifests pain when putting on underwear, blouses or coats, pants or skirts and shoes, and the need to make more efforts and put to test the resistance of her body. Additionally, she expressed discomfort and night pain due to the lymphedema, and that she did not know how to position it to be able to rest.

When asking her about her thoughts on the disease and her way of coping with it, in relation to her daily life, she mentioned two main ideas: one related to the her body image and her routine to shape her breast using pads and cottons in order to wear bras (body ←→ getting dressed) and another related to her emotional and physical distress, which she must set aside to carry out her daily activities, specifically, mobility restrictions when doing housework (psychosocial ←→ participation). Regarding her family role and networks, she says that her relationships with others and her body image have been altered, especially her participation at home. Finally, with respect to family accompaniment, her children and the people close to her occasionally accompany her during the intervention process; however, it is clear that the process is mostly individual.

Occupational concept

Female person diagnosed with infiltrating ductal carcinoma, treated with neoadjuvant radiotherapy after modified radical mastectomy and current lymphedema in upper left limb who attends occupational therapy sessions. An evaluation was applied, showing participation and occupational performance restrictions in specific activities of daily living, work, leisure, etc. In addition, psychosocial and socio-emotional repercussions were evident. Her potential strengths include the will to adapt, clear preferences and interests used to develop activities, discipline and quick learning of actions and recommendations.

Intervention

The person underwent occupational therapy intervention in the Rehabilitation Unit of the INC in April-May 2017, with a total of 10 sessions of 30 minutes each for 4 weeks. The sessions were distributed as follows: first week, two sessions; second week, two sessions; third week, three sessions; and fourth week, three sessions. The purpose of the intervention addressed the reason for referral, her priorities and the greatest amount of information about her condition and how to develop different activities of daily living. To this end, the activities focused on addressing self-perception, self-care, participation and performance in activities of daily living through socio-emotional and biomechanical intervention using the educational approach.

Intervention activities

To fulfill the proposed objectives, and taking the person as the center of the intervention, mainstreaming care through a project executed by and for the person was decided, including tasks and specifications that met the occupational therapy objectives.

The sessions were structured in: A) introductory activity, B) education activity and C) central activity. Table 2 lists the activities and strategies used.

Table 2. Introductory, educational and central activity strategies.

Activity	Strategies	Sub-strategy	
Introductory	Alignment and postural correction		
	Proprioceptive loading	Alternation and tolerance	
	Passive mobility range	Maximum limit	
	Active mobility range	As tolerated	
	Lymphatic drainage exercises		
	Functional exercises	Motor/functional skills	
	Joint protection		
	Energy efficiency		
	Extension of joint range in upper limbs	ADL Feeding	Motor skills Planes of motion
		ADL Getting dressed	Alternation in getting dressed Sequences for getting dressed Technical help
		ADL Hygiene	Alternation Activity adaptation
		Game	Handling of vertical and diagonal planes
Education	Knowledge on the condition	Training	

Continues.

Activity	Strategies	Sub-strategy
Education	Getting dressed: clothes, sequence, order	Training
	Joint protection	
	Energy efficiency	
	Modification and adaptation of activities	Workshop
	Decrease and control of lymph-edema in activities of daily living	
	Activities at home plus home plan	Plan delivery at home
	Pumping and heat prevention	
	Technical aids of low and medium complexity	Connection with central activity
	Stress and relaxation management techniques	Workshop and indications
	Handling weights, pressures and movements	
	Location and positioning	
Central	Body mirror therapy	Transversal central project
	Expressing feelings related to the consequences and daily living	
	Working with family and community networks	

Source: Own elaboration.

In particular, the central strategy combines performance skills (motor and socio-emotional), occupation areas and occupational history, building the ideal link between likes and interests and the latent needs of the person.

The occupational project included a series of requirements that allowed the person to relate to motor, sensory, socio-emotional and relational demands. The occupational therapists also used the therapeutic relationship as an opportunity to engage in and allow for a social-emotional intervention. For this, the central activity was based on using skills that would help the person to make a breast prosthesis.

Creating a breast prosthesis is as an alternative strategy to breast reconstruction and surgery for vulnerable women with low incomes or those who do not have the possibility of benefitting from this surgery. The activity begins with the identification of the need and the voluntary involvement of the person for its elaboration. It is important to start socializing the final result, as shown in Figure 1, and invite the person to build her own prosthesis following a rehabilitation plan whose focus is occupational therapy.

Figure 1. Final result and person
Source: Document obtained during the study

Results

Favorable results in the performance of the skills and effective responses —remarkably faster with respect to sensory stimuli, especially at the tactile level—, were achieved during the intervention and after the scheduled sessions, which also correlates with management and self-care of the lymphedema by the person. At a biomechanical level, a goniometric evaluation was carried out, showing mobility and plane degrees close to the normal ranges: flexion reached 170°; extension, 38°; adduction, 35°; and elbow flexion, 135°. Regarding strength, both members stabilized at an average rating of 29.

Regarding functional and motor skills, greater progress was observed in the actions that involve activities of daily living, games and education. It was evident that the person can now perform all functional and motor skills correctly, completely and slowly, with specific adaptations.

Regarding the cognitive-perceptual component, no time-space-person alterations were found; her responses and attention were adequate to environmental stimuli, managing to initiate, execute and finalize activities; in consequence, the final assessment was preserved, according to age and schooling.

At the psychosocial level, the woman responded to the requirements for social interaction and emotional regulation by combining rehabilitation tools and experiences considering her current situation. This was evident in her attitude and willingness to develop the activities and to attend to all sessions, handing in homework, and the improvement of her body schema, among others.

In this sense, the breast prosthesis activity included an approach based on functional skills, occupation areas and her personal background. Figure 2 shows the previous correlations with the requirements of the activity.

The different tasks and requirements needed accessible and comprehensive-real language with the person, which was complemented with introductory and education activities. For example, strategies such as postural feedback, passive and active motion in different ranges, and work planes and tasks ranging from gross to fine motor skills were used to strengthen a comprehensive therapeutic process that would allow designing, molding, sewing or filling her own prosthesis.

This project and the central occupational activity began with an explanatory task as shown in Figure 3. From that moment, the activity began, allowing the person to lead her own project, and developing and integrating

it with her routine. It is worth noting that the progress was >80% in each of the tasks in some sessions, yielding favorable responses to the requirements. In other occasions, sessions focused more on introductory activities, clearly related to biomechanics due to its high correlation with the performance of activities of daily living.

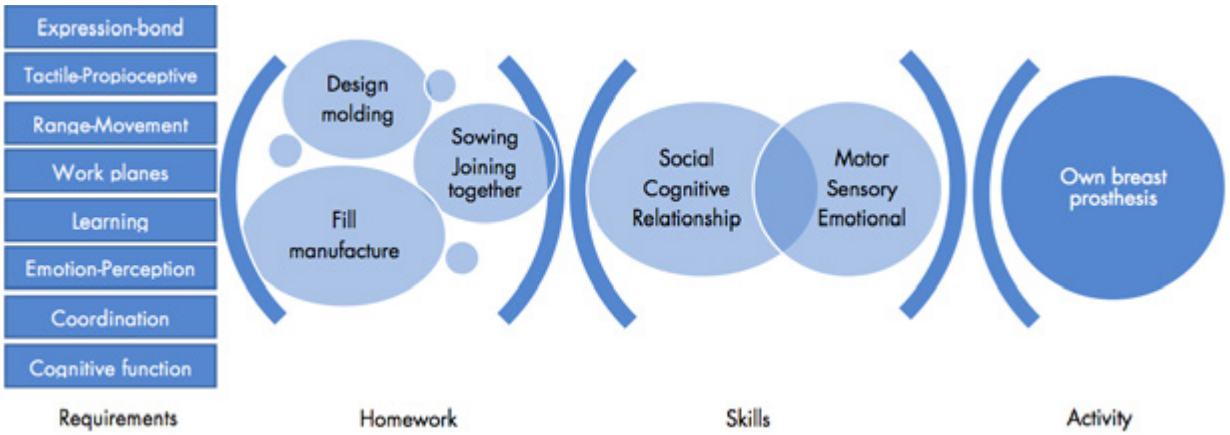

Figure 2. Intervention and activity correlations
Source: Own elaboration.

Figure 3. Explanatory task.
Source: Document obtained during the study.

Throughout the sessions, an increase in the amplitude of the range of motion expressed by the person in relation to her activities of daily living was observed in activities such as reaching objects located at the top of the cupboard and in the decrease of pain when putting cloths on her upper body or when bathing, which she was now able to do in shorter times. Another result achieved with education strategies was the considerable

reduction of the lymphedema, in collaboration with physiotherapy, stabilizing in stage 2.

Manual activity was relevant to integrate fine motor requirements, becoming a space for emotional expression, and integrating many of the rehabilitation strategies as shown in Figure 4. At the end of the sessions, the tasks were carried out in shorter times and the elements were distributed in a work plane as required by the person herself for better performance. As these tasks were related to her likes and interests, manipulation, coordination and efficiency were evident in each sensorimotor process performed.

Figure 4. Manual task.
Source: Document obtained during the study.

In terms of adherence and tolerance to treatment, the person adhered to the plan and the proposed sessions. It was necessary to perform constant feedback after completing each therapeutic activity and make sure that the results were evident at home. Likewise, she was able to adapt information about her diagnosis, risks and prevention at home, tasks and modified daily activities during the final sessions.

Adverse and unexpected events

During these activities, pain management was approached from two different perspectives: the first involved the use of physical means such as heat and cold therapy, massages, and the interdisciplinary intervention of doctors, nurses and physiotherapists; the second was related to prevention and education for activities not supervised by a health professional; the person received information about limiting movements, energy efficiency techniques, steps or analysis of tasks/simple and daily actions and handling of weights, tools, etc.

DISCUSSION

In Colombia, breast cancer figures continue to increase and its survival rate is approximately 64%. (2) This condition requires massive rehabilitation intervention efforts that focus on the person and not on the health system. (1,3,5,6,13) To this end, interdisciplinary teams, including physicians, physiotherapists, speech

therapists, psychologists and occupational therapists, have evolved and consolidated as an essential transforming link for rehabilitation, proposing new forms of intervention where biomedical parameters can interact with psychosocial parameters. (5,10,11,14,17) An example of this situation is the intervention proposed here, where care components were intertwined with all functional skills and areas of occupation.

This case report is an alternative to purely biomedical interventions and includes biopsychosocial perspectives, taking into account the different dimensions of the human being. It is worth pointing that this work does not use the word "patient" because of its connotation, and that it intends to show that the objectives of rehabilitation and treatment can focus on the person, bearing in mind expressions, actions and therapeutic relationships, without neglecting the diagnostic reality. (5,10,11,14)

Said diagnostic reality implies an alternative management of rehabilitation procedures; for this, an occupational assessment was used to know the perspectives of the person, understanding that the central activity was focused on socio-emotional management and that biomechanical, sensory and daily life concepts could mix with it. The activity consisted of movements in planes that favored not only the motor component, but her performance in activities of daily living such as taking down a container from the cupboard or putting on cloths, which are used to face the tasks of a normal day and have a real impact on health. (10)

Occupational therapy intervention, in this case, comprised the needs that arise after surviving breast cancer, surgeries and reality, considering a group of structures, functions, actions, procedures and experiences that involve this population. It is worth mentioning that the role of occupational therapists is involved with the process of consolidation thanks to the transmission of knowledge, techniques and strategies through experience.

CONCLUSIONS

It is clear that a comprehensive intervention, focused on the person and responding to a biopsychosocial model, can be a valid rehabilitation strategy that addresses and solves the needs of the person in constant relation with the medical or traditional intervention. In the case of occupational therapy, a meaningful activity in combination with motor, sensory, cognitive and socio-emotional requirements serves and is ratified as a means of differential and potential intervention by a rehabilitation team.

In this case, focused rehabilitation divided into steps to respond to the needs of the person and her health was established as a benefit additional to traditional health intervention, directly impacting her physical health, functionality and psychosocial well-being. To that extent, the activities and global interventions of occupational therapy in the biosocial or clinical field should be informed in case reports that allow replicating successful intervention models and that understand and dialogue with the person, their culture and their work.

Perspective of the patient

Throughout the sessions, and especially at the end of the proposed treatment plan, the person expressed her gratitude for the process, wore her prosthesis and took the designs she had made in order to continue with this activity at home, looking to the future. She also said that, thanks to the strategies, recommendations and training received during the treatment, she was able to carry out daily activities with modifications, and a change in

her attitude was noticeable. Occasionally, she visits the rehabilitation area, where she expresses and disseminates her experience with other people, bringing together other survivor women to join the program.

CONFLICT OF INTERESTS

None stated by the author

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GLIOSARCOMA IN A YOUNG PATIENT WITH NEUROFIBROMATOSIS TYPE 1. CASE REPORT

Keywords: Neurofibromatosis 1; Gliosarcoma; Glioblastoma; Neurofibroma.
Palabras clave: Neurofibromatosis 1; Gliosarcoma; Glioblastoma; Neurofibroma.

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ABSTRACT

Introduction: Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder that has variable phenotypic expressivity, with manifestations ranging from cutaneous lesions to functional compromise. It manifests clinically during childhood and adolescence. The NF-1 gene encodes a protein, neurofibromin gene, which acts as a tumor suppressor under normal conditions by regulating another protein that stimulates cell growth and proliferation. In case of alteration, different tumor processes may occur, such as the one seen in a small number of cases.

Case presentation: 20-year-old male patient with NF1, who presented café-au-lait spots and developed a glioblastoma, which happens infrequently.

Discussion: Immunohistochemistry methods that contribute greatly to prognosis are included to achieve the confirmed diagnosis since the median overall survival of glioblastoma patients is higher in patients with NF1 than in those without said pathological entity.

Conclusion: The early diagnosis of the lesions favors a timely management of NF1. These patients require a comprehensive and interdisciplinary management to achieve full rehabilitation.

RESUMEN

Introducción. La neurofibromatosis tipo 1 (NF1) es una condición autosómica dominante que presenta una expresividad fenotípica variable, con manifestaciones que van desde lesiones cutáneas hasta compromiso funcional. Se manifiesta clínicamente durante la infancia y la adolescencia; su gen codifica una proteína, la neurofibromina, que actúa como un supresor tumoral en condiciones normales regulando, a su vez, otra proteína que estimula el crecimiento y proliferación celular. En caso de alteración se podrían presentar diferentes procesos tumorales como el que se evidencia en un reducido número de casos.

Presentación de caso. Paciente masculino de 20 años con NF1, quien presentaba lesiones cutáneas como manchas color café con leche y desarrolló un glioblastoma, lo cual sucede de manera infrecuente.

Discusión. Para obtener el diagnóstico confirmado se incluyen métodos de inmunohistoquímica que contribuyen en gran medida al pronóstico puesto que la mediana de supervivencia global de los pacientes de glioblastoma es mayor en pacientes con NF1 que aquellos sin dicha entidad patológica.

Conclusión. El diagnóstico temprano de las lesiones favorece un manejo a tiempo de la NF1. Estos pacientes requieren un manejo integral e interdisciplinar para favorecer su rehabilitación total.

INTRODUCTION

Neurofibromatosis type 1 (NF1) has been indisputably linked to neurofibromatosis type 2 (NF2). Both are autosomal dominant, hereditary, neurocutaneous disorders that have high rates of de novo mutation and a high risk of tumor development. However, they are clinically and genetically distinct diseases and should be considered as different entities. On the one hand, NF1 is a common disease that affects chromosome 17, shows clinical evidence in the skin and peripheral nervous system, and

causes bone dysplasia. On the other, NF2 involves chromosome 22 and is considered a rare disorder with a relative scarcity of cutaneous manifestations and high-grade malignancy; it is also very rare (Table 1). (1)

Table 1. Oncogenic risk and genetic localization in neurofibromatosis.

Disorder	Greater risk	Location of genetic alteration
Neurofibromatosis type 1	Neurofibromas, optic gliomas, astrocytomas, neural crest cell-derived tumors, germinal	Chromosome 17
Neurofibromatosis type 2	Schwannomas and acoustic neurinomas, ependymomas and meningiomas	Chromosome 22

Source: Own elaboration based on (1).

NF1 is an autosomal dominant disorder that has a variable phenotypic expression, with manifestations ranging from moderate cutaneous lesions to severe orthopedic complications and functional alterations. (2) Its incidence is 1 per 3 000 live births and manifests clinically during childhood and adolescence. Half of the cases are sporadic, since no lesions are found in any of the parents; 90% of these mutations occur in paternal gametes. (3) The NF1 gene encodes a protein, neurofibromin, which acts as a tumor suppressor under normal conditions, regulating, in turn, another protein that stimulates cell growth and proliferation. In case of alteration, different tumor processes could be presented, such as the one observed in a small number of cases. (4,5)

According to the World Health Organization, gliosarcoma is identified as a grade IV neoplasm. It was first reported in 1895 by Strobe, but it was not widely accepted until 1955 when Gross and Feigen described three patients with this type of lesion. (6) It is a mixed primary tumor of the central nervous system, composed of astrocytic anaplastic and malignant mesenchymal elements. (7) Furthermore, its represents between 1.8% and 8% of glioblastoma multiforme (GBM) cases. (8) It mostly affects supratentorial regions and is located in the temporal and parietal lobes, followed by the frontal and occipital lobes. (9-11) Regarding distribution by age and sex, it is observed more frequently in men, and its incidence increases significantly between ages 40 and 70; it is rare in adolescents and pediatric patients. (12,13) Its prognosis is similar to that of GBM, with a higher incidence of extraxial metastases being reported. (14)

Regarding care, after establishing a possible diagnosis, surgery should be performed for characterization and as a therapeutic strategy for glioblastoma to relieve pressure and safely remove as much of the tumor as possible. Radiation therapy is almost always used, along with chemotherapy, after surgery or biopsy. The most commonly used chemotherapy drug in adults is temozolomide. Another area of interest for research has led to the development of techniques such as immunotherapy through vaccines or immunizations to treat this pathology. (15)

CASE PRESENTATION

A 20-year-old male patient, of mestizo, from Popayán, Cauca, and with medium socioeconomic level attended the emergency service on March 7, 2016 due to intense headache and loss of postural tone. The patient reported history of NF1 only.

The patient showed a clinical picture of a month of evolution consisting of left hemicraneal

headache, which did not yield to analgesics. He also presented impaired consciousness stupor, disorientation, preserved memory, dysarthria, loss of strength of the right half of the body, normal cranial nerves, decreased osteotendinous reflexes, and normal superficial and deep sensitivity. On admission, he presented two episodes of projectile emesis, while physical examination revealed *pectum exacavatum*, and multiple hyperpigmented skin lesions (café-au-lait spots) disseminated in the anterior region of the chest. Diagnostic studies were initiated and their academic importance was explained; the family understood and accepted said concept.

The patient was assessed by neurology, which requested a simple computed axial tomography (CT) of the brain, whose report suggested spontaneous intracerebral hemorrhage, described as a temporary lesion that displaces the midline and is accompanied by bleeding and perilesional edema (Figure 1). Various differential diagnoses were proposed, including brain tumor, glioblastoma, astrocytoma and middle cerebral artery aneurysm.

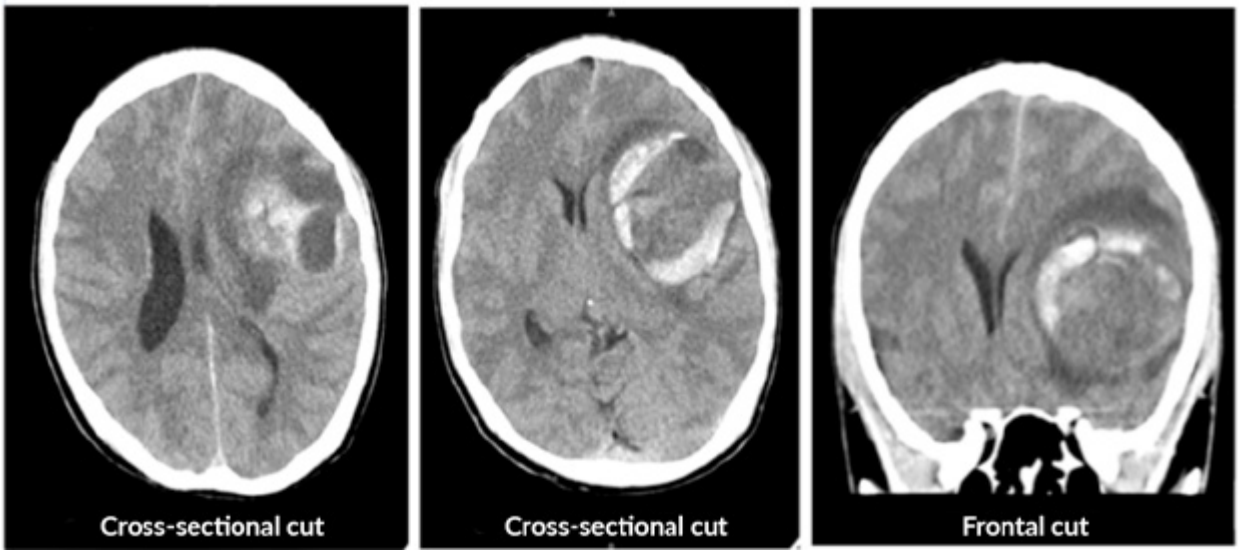

Figure 1. Simple computerized axial tomography of the brain prior to surgery.
Source: Document obtained during the study.

An emergency craniotomy for drainage was scheduled based on the results of the CT scan. Craniotomy showed a yellowish, hard tumor mass with necrosis and suggestive of astrocytoma. The patient did not require antibiotic management after the procedure and a new CT scan was requested, which showed satisfactory tumor resection with residual perilesional edema, without deviation from the midline (Figure 2). The histopathological study described resection compatible with glioblastoma (Figure 3).

Immunohistochemistry studies were performed to confirm diagnosis, describing diffuse positive mesenchymal component for vimentin CD99, very occasional for desmin and negative for smooth muscle actin. It was also necessary to find the positive component for GFAP, S100. Immunohistochemical staining for GFAP complemented reticulin staining by confirming the presence of two cell populations in gliosarcoma; it revealed epithelial spindle cell proliferations and intramural fusiform cells

within thick-walled vessels stained for GFAP, S-100 protein and/or vimentin. The lesion was negative for estrogen receptors and occasional positive cells for progesterone receptors and EMA (epithelial membrane antigen) were found. The proliferation index measured by Ki67 was 60%, which confirmed the diagnosis of grade IV gliosarcoma.

During his recovery, the patient was hemodynamically stable, with motor, disharmonic and facial asymmetry that evolved satisfactorily with the help of phonoaudiological therapy. The patient was capable of returning to his daily activities after two weeks without any problem and continued receiving treatment with radiotherapy and chemotherapy.

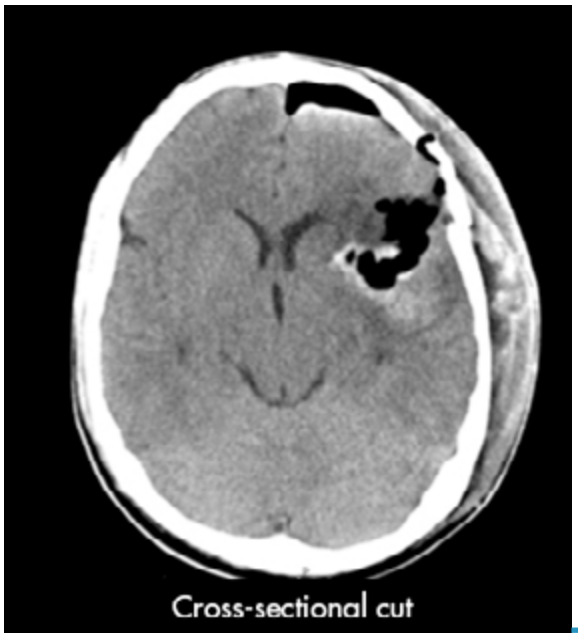

Figure 2. Simple computed tomography of the brain after surgery.
Source: Document obtained during the study.

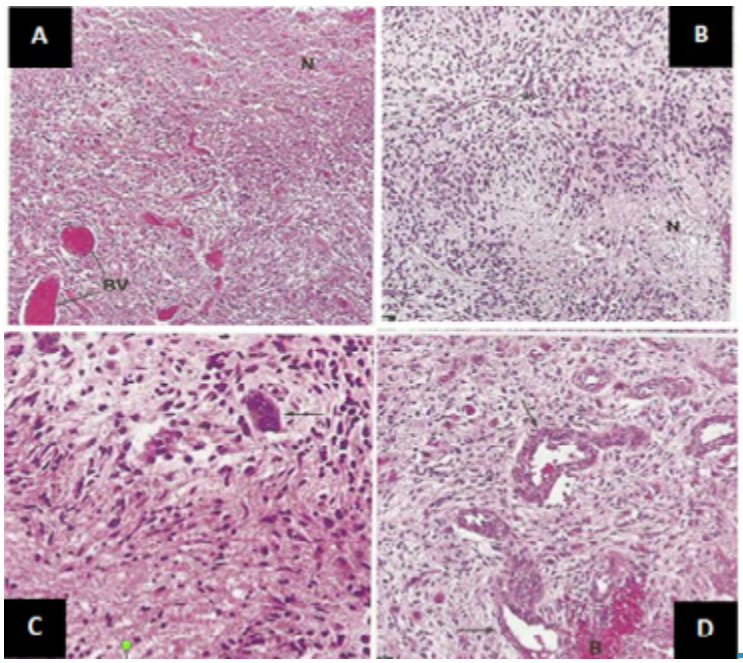

Figure 3. Histopathological findings. A) high cellularity, abundant blood vessels and wide necrotic areas; B) prominent cellularity around a vessel and pseudoempalized cellularity around a necrotic area; C) variation in size and shape of the nuclei, some are markedly enlarged; D) small and medium blood vessels with thick walls that tend to bleed and endothelial cell proliferation.
Source: Document obtained during the study.

DISCUSSION

Malignant gliomas represent 35-45% of all adult brain tumors and about 85% of them are glioblastomas; therefore, glioblastomas represent 29.7-38.2% of all brain tumors in adults. (12,16) In turn, gliosarcoma represents about 2% of all glioblastomas and 0.59-0.76% of all adult brain tumors (10); it is usually found in the supratentorial region with a slight preference for the temporal lobes (8), although it can affect the frontal, parietal or occipital lobes and corpus callosum less frequently. (17) Its clinical profile may include an intracranial hypertension syndrome such as headache, dizziness, vomiting, papilledema, seizures and motor deficit. CT usually shows a well-defined hyperdense lesion with marked perilesional edema, necrotic areas, and mass effect. (18)

Feigin and Gross (19) were the first to demonstrate that gliosarcoma originates from the neoplastic transformation of blood vessels in a pre-existing glioblastoma. Currently, immunohistochemistry and genetic studies support that theory, suggesting a monoclonal origin for histological elements. (20)

Immunohistochemical findings allow identifying the glial component of the glial fibrillary acidic protein (GFAP) and the S-100 protein. (14) Epithelial components include cytokeratins and immunoreactivity for p53 and, sometimes, actin if there is a muscular component. (21) GFAP immunostaining is more important to differentiate between gliosarcoma and glioblastoma, since it is found in the glial regions, although in very low amounts in sarcomatous regions. Vimentin is a marker of mesenchymal cells, with strong staining in sarcomatous areas. (22,23)

Several treatment options are used to combat this form of brain cancer and the selected procedure depends on the location and severity of the tumor. In general, the treatment includes surgery, radiotherapy and chemotherapy with nitrosoureas, misonidazole, dacarbazine, mithramycin, ametophtherin, thalidomide, temozolomide, irinotecan, vincristine, cisplatin or doxorubicin. (16) The tumor can be removed surgically if its location is favorable for performing an extraction surgery and, usually, this procedure is followed by chemotherapy. Some research suggests that drugs such as temozolomide and bevacizumab (avastin) can be used to treat this pathology. (24,25)

Some of the studies found show evidence of the interaction between patients with NF1 and gliosarcoma. Pathological characteristics (increased expression of p53) suggest that there is no overexpression of EGFR, as in primary glioblastomas, and that the increase of proliferation indexes could anticipate a bad prognosis in general. However, statistics report that the median overall survival of glioblastoma patients is 75% after 6 months and 19% after one year, and it is also better in patients with NF1. (4,26)

This study had some limitations since the samples for immunohistochemistry tests were processed in a different laboratory and the delivery of the results took some time.

CONCLUSIONS

The early diagnosis of glioblastoma favors its timely management as connecting it with neurofibromatosis favors the prognosis of these patients. Joint management with surgery and radio and chemotherapy is required, since this favors the survival of the treated patients. Maintaining constant follow-up of patients helps detecting recurrences and facilitates subsequent resection and joint management. These patients need comprehensive and interdisciplinary management to achieve full rehabilitation.

CONFLICT OF INTERESTS

None stated by the authors.

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MULTIPLE MYELOMA AND LIGHT-CHAIN AMYLOIDOSIS: A RARE PRESENTATION

Keywords: Amyloidosis; Multiple Myeloma; Myositis; Respiratory Insufficiency.
Palabras clave: Amiloidosis; Mieloma múltiple; Miositis; Insuficiencia respiratoria.

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RESUMEN

Introducción. La amiloidosis sistémica primaria hace parte del espectro de neoplasias de células plasmáticas, donde las cadenas livianas de inmunoglobulina se depositan en múltiples órganos. El compromiso miopático con falla respiratoria y mieloma múltiple asociado es poco frecuente.

Caso clínico. Se presenta el caso de un paciente con amiloidosis sistémica de cadenas livianas (AL) quien ingresó por miopatía con falla respiratoria e íleo adinámico, por lo que se llevó a la unidad de cuidados intensivos. Por histología se confirmó infiltración en piel y tracto digestivo y concomitantemente se presentó mieloma múltiple con lesiones óseas líticas y riñón de mieloma. El paciente tuvo buena respuesta al esquema CyBorD (ciclofosfamida, bortezomib, dexametasona), recuperó su función renal y tuvo disminución de las lesiones en piel. Sin embargo, el compromiso gastrointestinal y miopático fue difícil de manejar y se requirió soporte ventilatorio y nutrición parenteral.

Discusión. El clínico puede pasar por alto esta patología, por lo que es probable llegar a fases avanzadas de la enfermedad. En la actualidad, con nuevos agentes de quimioterapia y trasplante autólogo, se puede aumentar la sobrevida de estos pacientes.

Conclusión. La amiloidosis AL tiene un amplio espectro de manifestaciones y debe considerarse en los diagnósticos diferenciales a fin de hacer un diagnóstico precoz y hacerla una condición tratable.

ABSTRACT

Introduction: Primary systemic amyloidosis is part of the spectrum of plasma cell neoplasms, in which immunoglobulin light chains are deposited in multiple organs. However, myopathic involvement along with respiratory failure and associated multiple myeloma is a rare condition.

Clinical case: This paper presents the case of a patient with systemic light chain amyloidosis (AL) who was admitted due to myopathy with respiratory failure and adynamic ileus that required intensive care. Infiltration in skin and digestive tract was confirmed by histology. The patient presented with concomitant multiple myeloma with lytic bone lesions and myeloma kidney. The patient responded well to the CyBorD scheme (cyclophosphamide, bortezomib, dexamethasone), renal function was recovered and skin lesions decreased. However, gastrointestinal and myopathic involvement was difficult to manage, requiring ventilatory support and parenteral nutrition.

Discussion: Clinicians may oversee this pathology, leading to advanced stages of the disease. Currently, new chemotherapy agents and autologous transplantation may increase the survival of these patients.

Conclusion: AL amyloidosis has a wide spectrum of manifestations and should be considered in differentials to reach an early diagnosis and make it treatable.

INTRODUCTION

Amyloidosis comprises a heterogeneous group of diseases characterized by protein deposition (27 different types) that adopt a crossed β structure to form amyloid fibrils in the extracellular space. Primary systemic amyloidosis (amyloid light-chain, or AL) is one of them and is part of the spectrum of plasma cell neoplasms, in which an aberrant clone (<20% of plasma cells in the bone marrow) exaggeratedly produces immunoglobulin light chains (more frequently lambda), forming amyloid. (1) In the USA, the estimated annual incidence is 3 000 cases (2), the age at onset varies between the fourth and seventh decade of life, and is predominant in men. (3) Some patients may develop localized amyloidosis in the genitourinary or respiratory tract, in the lymph nodes or in the conjunctiva. (4,5)

Its pathophysiology is still not completely clear: the damage is the result of mechanical interference and amyloid accumulation in the extracellular matrix of the vessels with apoptosis and ischemic damage. (6,3) The first tissues to be affected are blood vessels, which generates early endothelial microcirculatory dysfunction. (6) AL amyloidosis is associated in 10-15% of multiple myeloma cases and may be preceded by it or developed concomitantly (7); a similar proportion of patients with multiple myeloma will develop asymptomatic amyloid deposition. (3,8) In general, this pathology can affect any organ, except the brain (4), and the most common presentations are nephrotic syndrome, cardiomyopathy, peripheral sensory-motor neuropathy and hepatomegaly. (6,9) The following is the case of a patient with systemic AL amyloidosis and concomitant multiple myeloma who presented with respiratory failure and adynamic ileus.

CASE PRESENTATION

Male, mestizo patient, aged 47 years, from Bogotá D.C., meat vendor, who consulted for dyspnea and muscle weakness. Functional classification had decreased progressively for 18 months and worsened in the last 3 months, reaching the IV/IV classification on the NYHA scale, which is associated with orthopnea and lower limb edema. The patient presented with shoulder myalgia and gradual reduction of proximal muscle strength 11 months before consultation, with no paroxysmal nocturnal dyspnea. On examination, moderate to severe pulmonary hypertension and restriction in spirometry were found with mild oxygenation and hypercapnia disorder associated with obstructive sleep apnea-hypopnea syndrome (apnea/hypopnea index: 8.7). Chronic thromboembolic pulmonary hypertension (CTEPH) was ruled out with ventilation/perfusion scan. Only class 1 obesity was reported as a pre-existing medical condition. The systems review revealed purplish eyelids and a mass in the perineal region —which increased with valsalva maneuvers—, abdominal distension, dysphagia to solids, constipation, erectile dysfunction and paresthesia of the hands.

On physical examination, the patient had a reading of 73% of arterial oxygen desaturation and positive purplish upper eyelids (raccoon eye) (Figure 1), class 2 jugular venous pressure, grade 2 systolic murmur in the tricuspid area, abdominal distension and decreased bowel sounds. A non-pruritic, non-painful tumor that bled easily was observed in the perineal skin (Figure 2). Grade II edema in lower limbs, decreased proximal muscle strength and single-breath counting of 12 (normal range ≥20) were also reported without muscle fatigability. Muscle

hypertrophy of the bilateral supraspinus, bilateral deltoids and forearm muscles with pseudohypertrophy of paraspinal muscles were also evidenced.

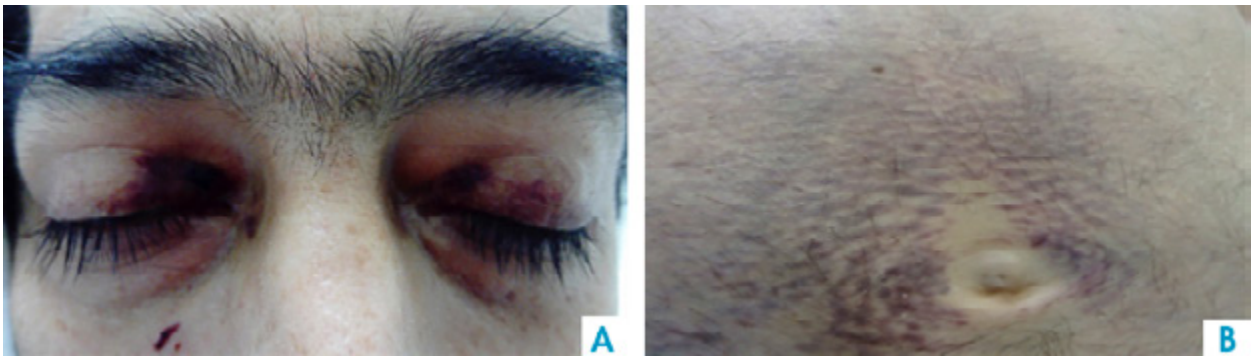

Figure 1. A. Periorbital ecchymosis. B. Perimumbilical purpuric macules.
Source: Own elaboration based on the data obtained in the study

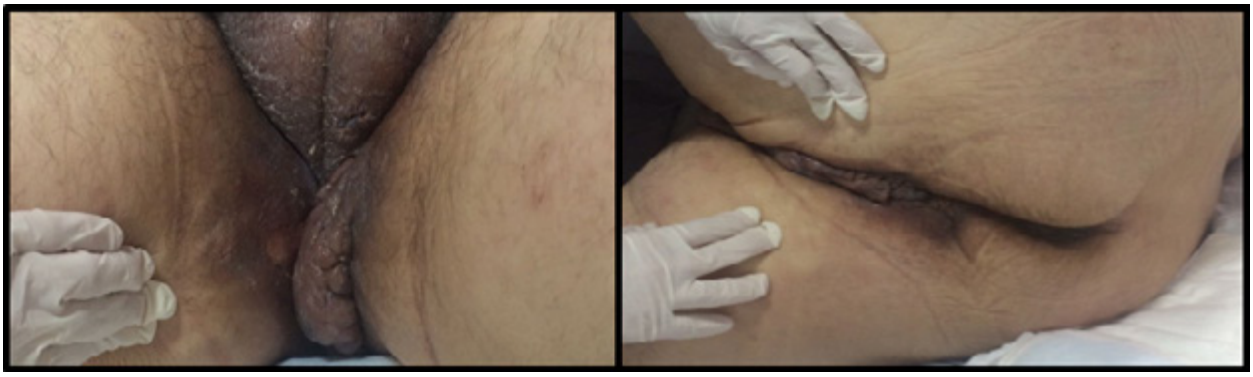

Figure 2. Hyperpigmentation and perineal tumor, and scrotal infiltration.
Source: Own elaboration based on the data obtained in the study.

On admission, myopathy studies were initiated (Table 1) and muscle enzymes, electromyography and muscle biopsy were requested, which excluded inflammatory myopathy. The autoimmune profile and HIV were negative. Adult Pompe disease was considered, but acid maltase was normal and syringomyelia was ruled out using contrast-enhanced cervical and brain MRI (Figure 3). Considering the lytic lesions observed in chest tomography, neoplasms (myopathy as a paraneoplastic phenomenon) were looked for as there was no compromise of the pulmonary parenchyma, only bibasal subsegmental atelectasis. No masses or organomegaly were observed in abdomen images (Figure 4).

Table 1. Summary of the main paraclinical tests of the case.

Name of the test and reference values		Results
Complete blood count	Leukocytes 4.8-10³ uL	8.850/uL
	Hemoglobin 14-18 g/dL	11.9 g/dL

Continues.

Name of the test and reference values		Results
Complete blood count	Hematocrit 45-54 %	27.6 %
	Platelets 150-450³ uL	268000/uL
Renal function	Creatinine 0.6-1.24 mg/dl	On admission: 0.8 mg/dL After 12 days: 3.84 mg/dL
	BUN 6-20 mg/dL	On admission: 11mg/dL After 12 days: 40 mg/dL
Transaminases	SGOT 15-41 u/L	29.3 u/L
	GPT 17-63 u/L	12.1 u/L
Bilirubin	Total 0.3-1.2 mg/dL	0.76 mg/dL
	Direct 0.1-0.5 mg/dL	0.3 mg/dL
Lactic dehydrogenase	105-300 u/L	265 u/L
Electrolytes	Potassium 3.5-5.1 meq/L	4.04 meq/L
	Calcium 1.16-1.32 mmol/L	1.26 mmol/L
	Sodium 135-145meq/L	142 meq/L
Total proteins	6.1-7.9 g/dL	5.5 g/dL
Albumin	3.5-4.8 g/dL	3.8 g/dL
ESR	0-15 mm/hour	38 mm/hour
CPK	39.0-308.0 UI/L	248 UI/L
Alkaline phosphatase	40.0-129.0 UI/L	88 UI/L
Hormonal tests	TSH 0.4-10 uui/mL	9.83 uui/mL
	Free T4 1.0-1.7 ng/dL	1.05 ng/ dL
	Prolactin 4-15.2 ng/mL	41.58 ng/mL
	Testosterone 4-30 pg/mL	1.4 pg/mL
	Cortisol am 10-20 ug/dL	10.5 ug/dL
	PTH 15 - 65 pg/mL	50.8 pg/mL
24-hour urine protein		3510 mg/24h
Protein electrophoresis and immunofixation		Hypogammaglobulinemia and lambda monoclonal peak
Lambda free light chains	5.71-26.30 mg/L	1146.12mg/L
Kappa free light chains	3.30-19.40 mg/L	15.70 mg/L
Beta-2 microglobulin	0.80-2.20 mg/L	19.46 mg/L
proBNP	10-53 pg/mL	1580pg/mL
Troponin T	0.000 - 0.013 ng/mL	0.177 ng/mL
Electromyography and nerve conduction velocity		Generalized myopathy, bilateral carpal tunnel syndrome
Bone survey		Lytic lesions in right humeral head, skull, T8, L3, sternum and 6th left costal arch

Continues.

Name of the test and reference values	Results
Transthoracic echocardiogram	Severe moderate concentric hypertrophy VI, mild systolic dysfunction with changes in myocardial texture, moderately dilated RV with free wall hypertrophy (10mm) and moderate PHT, SPAP 59 mmhg, TAPSE 22mmHg and septum of 18mm
Esophageal motility test	Mild pharyngeal hypomotility and mild motor dysphagia

RV: right ventricle; LV: left ventricle; TAPSE: tricuspid annular plane systolic excursion; SPAP: systolic pulmonary arterial pressure; PH: pulmonary hypertension.

Source: Own elaboration.

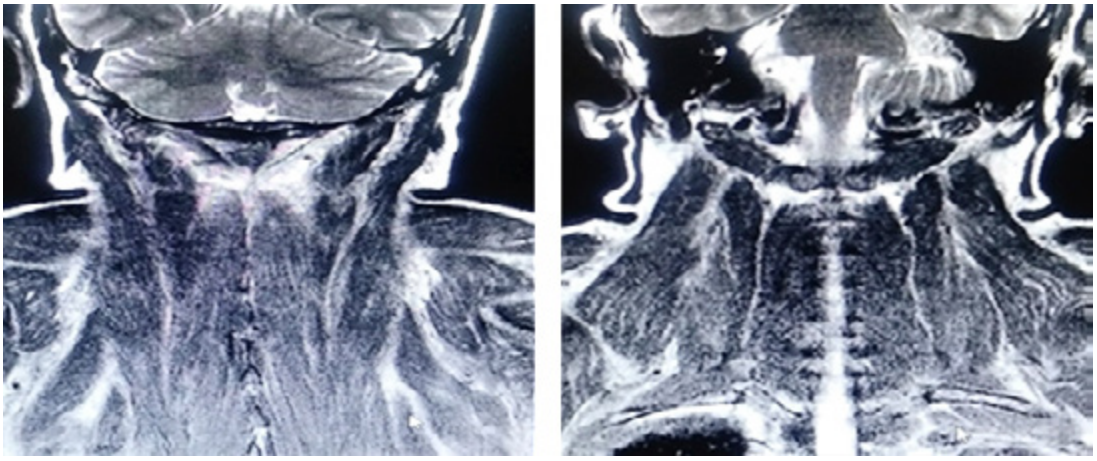

Figure 3. Contrast-enhanced MRI of the head and neck, coronal plane, with paraspinal muscular edema.

Source: Own elaboration based on the data obtained in the study.

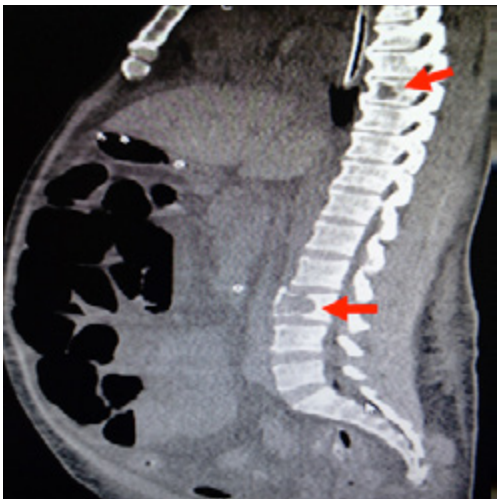

Figure 4. Sagittal CT scan of contralateral abdomen: distended loops and lytic lesions in T8 and L3 (arrows).

Source: Own elaboration based on the data obtained in the study

One week after admission, the patient presented acute kidney injury classified as stage 3 KDIGO (discarding prerenal origin, pharmacological toxicity and obstruction) and hypoxemic and hypercapnic respiratory failure, so he was transferred to the intensive care unit (ICU) for invasive mechanical ventilation and initiation of dialysis. Considering the presence of lytic bone lesions and hyperazoemia with nephrotic-range proteinuria by Bence Jones protein filtration, bone marrow aspiration and biopsy were performed, finding 80% of plasma cells (Figure 5). Lambda light chain multiple myeloma ISS III was diagnosed (Table 1). However, a colonoscopy was performed as the patient presented with myopathy, skin lesions, bilateral carpal tunnel, infiltrative cardiomyopathy, hypogonadism, erectile dysfunction and adynamic ileus that were not explained by the myeloma (Figure 6), finding extremely friable mucosa; perineal lesion and renal biopsy were taken to establish the presence of associated systemic amyloidosis.

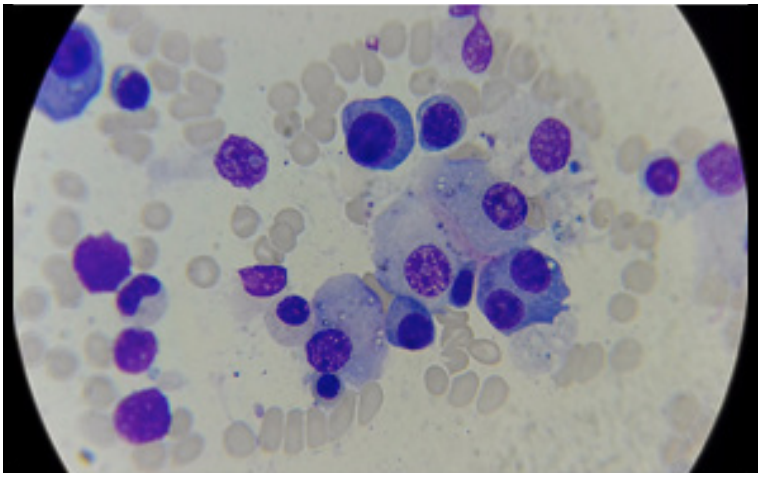

Figure 5. Bone marrow aspirate, 40x lens with plasmocytes, some atypical binucleated cells, eccentric nucleus, broad and basophilic cytoplasm.

Source: Own elaboration based on the data obtained in the study.

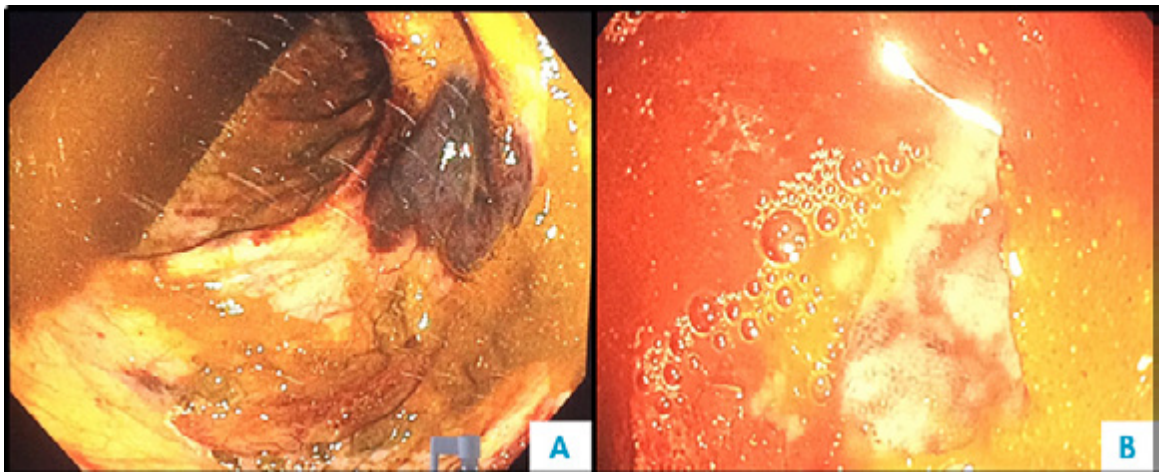

Figure 6. Colonoscopy. A) Submucosal hematoma and multiple mucosal ecchymoses; B) congestive mucosa and ulcer covered by fibrin.

Source: Own elaboration based on the data obtained in the study.

AL amyloidosis was confirmed by perianal lesion and colonic mucosa biopsy (Figures 7, 8, 9 and 10), where a deposit of eosinophilic amorphous material was found in the submucosa and vessel wall with the typical apple-green birefringence of Congo Red stained preparations under polarized light and confirmed with immunohistochemistry. Renal biopsy showed tubulopathy due to lambda free chain deposits, along with amyloid deposits in arterioles.

Chemotherapy following the CyBorD scheme was initiated due to the diagnosis of multiple myeloma with associated AL amyloidosis and the important systemic involvement in the patient. 20 days after the first cycle of chemotherapy, the subject was taken off dialysis. During the second cycle, bortezomib was discontinued and the dose of steroids was decreased to avoid potentiating its side effects (myopathy and neuropathy). Until that moment, the patient still depended on the ventilator due to a tracheostomy and required support pressure due to muscle fatigability. Adynamic ileus did not respond to multiple prokinetics nor neostigmine; enteral nutrition was maintained for trophic stimulation and total parenteral nutrition. After 4 months in the ICU connected to the ventilator with nutritional support and after four cycles of chemotherapy, the patient died due to ventilator-associated pneumonia and bacteremia due to *Klebsiella pneumoniae*, producer of carbapenemases.

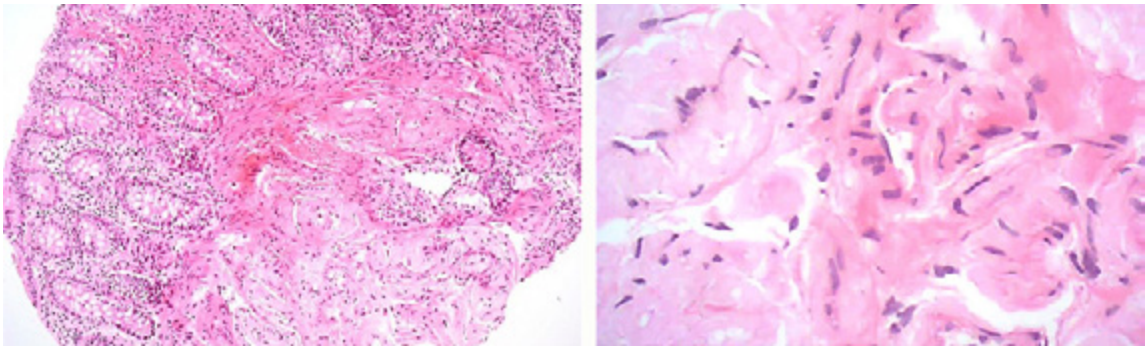

Figure 7. Colon, submucosa and vessel wall biopsy with amorphous eosinophilic material deposit, using hematoxylin and eosin stain. A) 4x lens; B) 40x lens.

Source: Own elaboration based on the data obtained in the study.

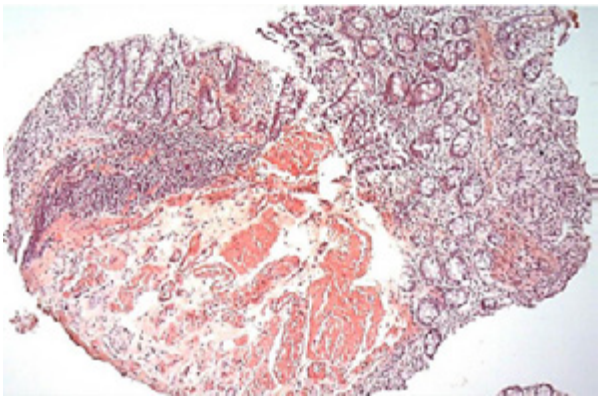

Figure 8. Colon biopsy, Congo red staining with salmon-colored deposits in the thickened wall of the vessels. 4x lens.

Source: Own elaboration based on the data obtained in the study.

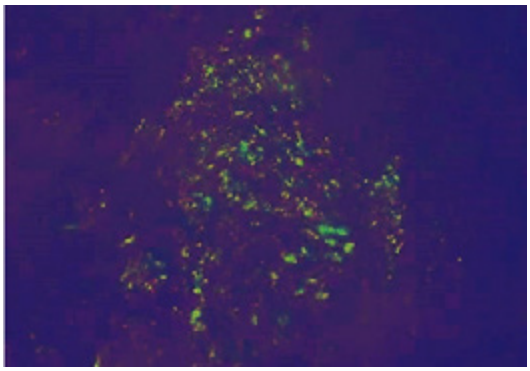

Figure 9. Colon biopsy, Congo Red staining. Apple-green birefringence on the wall of the glasses under polarized light with 40x lens.

Source: Own elaboration based on the data obtained in the study.

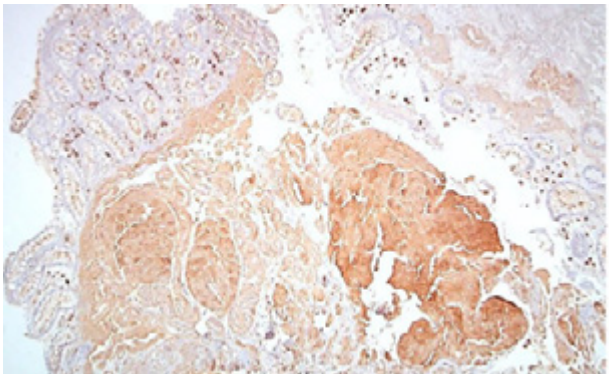

Figure 10. Colon biopsy, aspirated bone marrow. 40x lens with plasmocytes, some atypical binucleate cells, eccentric nucleus, broad and basophilic cytoplasm.

Source: Own elaboration based on the data obtained in the study.

DISCUSSION

The clinical case presented here is part of the 15% of AL amyloidosis cases associated with multiple myeloma. (7) Probably, amyloid deposits are present in patients with myeloma in a lesser proportion and such cases are not documented because there is no active search for these deposits. However, this case is relevant due to its clinical presentation, including severe involvement of multiple organs, onset with amyloidosis symptoms, development of myeloma with classic CRAB features on admission, and the diagnostic process represented by multiple differentials.

In a retrospective study conducted by the Mayo Clinic, of a total of 1596 patients, only 12 patients presented with myopathy, pseudohypertrophy, jaw claudication and creatine kinase concentration slightly increased to normal (6), so the specialists recommended measuring monoclonal protein during the evaluation of a patient with proximal non-inflammatory myopathy. (6) In a subsequent cohort of the same reference center, of 3 434 patients with AL amyloidosis treated between January 1995 and December 2015, 1.5% presented with muscle involvement, 22% myopathy only, 65% cardiac symptoms, 31% peripheral/autonomic neuropathy, 25% renal symptoms, 8% liver symptoms and 4% gastrointestinal symptoms. (10)

At the cardiac level, infiltration of the endocardium, atria and valves is found in amyloidosis, which generates contractile dysfunction due to restriction. (3,5) The most common early manifestation is dyspnea on exertion due to left ventricular diastolic dysfunction, which progresses to peripheral edemas and ascites. Atrial arrhythmia with thrombus formation (3), low blood pressure (due to decreased cardiac output and low peripheral tone), postural hypotension due to autonomic nerve disorder (3,5) and claudication of the jaw, legs and angina due to vascular involvement. For this, performing an electrocardiogram is recommended considering its low voltage, as well as an echocardiography with cardiomyocyte infiltration and magnetic resonance due to difficulty for draining the myocardium after gadolinium injection and a non-coronary pattern of increased gadolinium delay. Loop diuretics are the treatment of choice for this condition because angiotensin-converting

enzyme inhibitors, angiotensin receptor blockers and beta-blockers are poorly tolerated due to hypotension. (3)

Respiratory involvement, although rare, can occur with diaphragm or phrenic nerve infiltration; some cases have been reported. (11) In this case, significant muscle weakness with respiratory failure was observed, although a post-mortem diaphragm biopsy could not be performed. Pulmonary parenchymal, diffuse interstitial and tracheobronchial involvement, along with pulmonary hypertension type 1 by infiltration of the pulmonary vasculature, may also be observed. (11-13)

The patient had gastrointestinal involvement (3.2% frequency) (2); nevertheless, colonoscopy showed ulcerations and friability of the mucosa, classic findings of amyloidosis together with thickening of the intestinal wall, polypoid protuberances, erosions and fine granular appearance of the mucosa. (14) Common symptoms are abdominal pain, esophageal reflux, constipation and nausea. Others include diarrhea, weight loss and early satiety, which may be caused by autonomic neuropathy, bacterial overgrowth or cardiac cachexia. Replacement of intestinal smooth muscle causes dysmotility, pseudo-obstruction and even ischemia secondary to vascular infiltration or ganglion cells depletion. (2) The most involved sites are the duodenum, the rectum and the esophagus. (5,15) Hepatomegaly may be a consequence of congestion or infiltration (by kappa chains, hard and non-pulsatile liver). (3,5) Management is symptomatic with antiemetics, prokinetics and nutritional support (15), but in this case, no medication worked.

Cutaneous and mucosal involvement is diverse; this patient presented with periorbital ecchymosis or "raccoon eyes", which is pathognomonic when associated with macroglossia. Other manifestations described were petechiae, ecchymotic macules, plaques, papules and nodules that simulate amber, hemorrhagic, normochromic or non-pruritic vesicles, which can appear in eyelids, retroauricular area, lips, tongue, oral mucosa, neck, armpits, submammary, navel and inguinal and anogenital area; the latter can simulate condylomata. (4) The perivascular amyloid deposit produces vessel fragility and spontaneous wounds or wounds caused by minimal trauma, as in this patient.

Although AL amyloidosis presents with nephrotic syndrome caused by hyaline deposits in the mesangium, in the glomerular basement membrane, in small arteries and in the tubular basement membrane, the reported case presented with "myeloma kidney" (tubulopathy caused by light chain deposits). Amyloidosis should be suspected in patients with myeloma and nephrotic proteinuria due to albuminuria, infiltrative cardiomyopathy, autonomic neuropathy, hepatomegaly and symptoms of partial intestinal obstruction. (16) Hypoadrenalism or hypothyroidism is less common (8), but this patient presented with subclinical hypothyroidism with hypogonadism. Differential diagnosis is wide, so the amyloid type should be confirmed, as well as other hematological malignancies such as lymphomas, waldenstrom macroglobulinemia and POEMS syndrome, which should be ruled out. (17)

Diagnosis includes confirming paraproteinemia (around 90% of patients have it). Serum or urine electrophoresis sensitivity is approximately 50%, increasing to 80-90% with immunoelectrophoresis. (9) Histological confirmation by biopsy of the affected organ or subcutaneous fat has a sensitivity of 70-80%. (3) Hematoxylin and eosin show eosinophilic amorphous material, salmon red coloration in Congo red and apple green-birefringence in polarized light. Immunohistochemistry shows

up to 92% amyloid subtype depending on the availability of antibodies with some limitation for the determination of AL amyloid, which has been attributed to difficulties, on the one hand, in the detection of conformational differences of light chains and the characteristics of the antibody used (18) and, on the other, the limited availability in some centers of a very sensitive method such as immunofluorescence for luminescent derivatives of polythiophene conjugates and immunoelectromicroscopy with gold-labeled antibodies and fibrillar antiproteins. (19) Currently, the gold standard is proteomic analysis of amyloid deposits by mass spectrometry, after microdissection of Congo red–positive deposits. (3)

The prognosis of the disease depends on the number of affected organs, and there are prognostic biomarkers such as NT-proBNP and troponin T. The median survival is 6 months with cardiac involvement, but modern therapies based on bortezomib, dexamethasone and cyclophosphamide, followed by autologous stem cell transplantation, have shown longer survival rates with complete hematologic remission, unlike the first schemes with melphalan and prednisone (3,8), and are now the most commonly used schemes.

Likewise, there are reports of cases with localized involvement of the tracheobronchial vesicle that have been successfully managed by external beam radiotherapy. (20) The treatment of this systemic pathology is to suppress the plasmatic cell clone with chemotherapy and, in some cases, perform autologous bone marrow transplantation while supporting measures are taken to maintain the function of the organs involved as in the case of this patient. However, the progress of the disease, the prolonged stay in the ICU and the need for multiple devices favored his fatal outcome.

CONCLUSION

AL amyloidosis is a plasma cell dyscrasia that may be associated with multiple myeloma. Its onset spectrum is diverse, so a high index of suspicion should be considered so that it is not ignored, leading to an advanced stage that can be deadly. New chemotherapy schemes and timely diagnosis help improving survival.

CONFLICT OF INTERESTS

None stated by the authors.

FUNDING

None stated by the authors.

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HERLYN-WERNER-WÜNDERLICH SYNDROME: CASE REPORT

Keywords: Urogenital Abnormalities; Syndrome; Genitalia; Female; Uterus; Gynecologic Surgical Procedures; Pyometra.
Palabras clave: Anomalías Urogenitales; Síndrome; Genitales Femeninos; Útero; Procedimientos Quirúrgicos Ginecológicos; Piómetra.

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ABSTRACT

Introduction: The Herlyn-Werner-Wünderlich (HWW) syndrome is the association of three urogenital anatomic alterations of low incidence. Müllerian alterations are rare and are usually incidental findings; consequently, they are underdiagnosed and their genesis and correlation with having a higher probability of expression on the right side are unknown.

Case Report: This is the case of a 17-year-old patient who consulted for severe hypogastric abdominal pain linked to foul-smelling bleeding. On physical examination, a vaginal septum was found, while complementary images showed uterus didelphys and renal agenesis, leading to diagnose HWW syndrome. Furthermore, pyometra and hematocolpus were also documented and managed with antibiotic therapy. Given the adequate response to treatment, hospital discharge was authorized with follow-up by external consultation, since the definitive management could not be provided during hospital stay.

Discussion: One of the causes of recurrent abortions is the presence of this syndrome; however, when properly diagnosed, definitive treatment can be provided to reduce conceptional losses and urogenital hematopurulent collections.

Conclusions: HWW syndrome is a rare malformation that increases the risk of suffering from gynecological infectious diseases or blood collections. Surgical management of the vaginal septum is a definitive treatment that improves quality of life and reduces the risk of morbidities associated with the pathology.

RESUMEN

Introducción. El síndrome de Herlyn-Werner-Wünderlich (HWW) es una asociación de tres alteraciones anatómicas urogenitales de baja incidencia. Las alteraciones müllerianas son poco comunes y suelen ser hallazgos incidentales, por lo que se encuentran subdiagnosticadas y poco se conoce su génesis o su relación con tener más probabilidad de expresión en el lado derecho.

Reporte de caso. Se trata de una paciente de 17 años quien consultó por dolor abdominal hipogástrico de fuerte intensidad ligado a sangrado fétido. En el examen físico se encontró tabique vaginal y en las imágenes complementarias se evidenció útero didelfo y agenesia renal, diagnosticando así síndrome HWW. Igualmente, se documentó piómetra y hematocolpos que se manejaron con terapia de antibióticos; dada la adecuada respuesta al tratamiento, se dio egreso hospitalario con seguimiento por consulta externa, pues el manejo definitivo no se pudo proporcionar durante la estancia hospitalaria.

Discusión. Una causa de abortos a repetición es la presencia de síndrome HWW; sin embargo, al ser correctamente diagnosticado, se puede dar un tratamiento definitivo que disminuya las perdidas concepcionales y colecciones hematopurulentas urogenitales.

Conclusiones. El síndrome HWW es una malformación poco común que aumenta el riesgo de padecer cuadros infecciosos ginecológicos o colecciones hemáticas. El tratamiento definitivo consiste en el manejo quirúrgico del tabique vaginal que mejora la calidad de vida y disminuye el riesgo de morbilidades asociadas a la patología.

INTRODUCTION

The Herlyn-Werner-Wünderlich syndrome (HWW), also known as OHVIRA — obstructed hemivagina and ipsilateral renal agenesis— is the association of a series of urogenital anatomical alterations classified within the Müllerian pathologies. It is characterized by renal agenesis, uterus didelphys and complete or incomplete vaginal obstruction, predominantly on the right side. (1) These abnormalities often cause in patients dysmenorrhea, abnormal vaginal discharges, endometriosis, pyosalpinx, hematometra, hematocolpos, pyometra and pyocolpos.

Its etiopathology is not clear; however, when Müllerian ducts fuse, the uterus, cervix and vaginal dome are formed, so a deficit in their union explains the genital malformations. (2) Furthermore, the Wolf duct, which has a mesoderm origin, is poorly developed, affecting the embryogenesis of the kidney and the ipsilateral ureter, among other malformations of the urinary system. (3)

CASE PRESENTATION

A female 17-year-old patient, from the department of Casanare, Colombia, and of mixed race, visited the gynecological and obstetric emergency department for the first time due to strong acute abdominal pain in the hypogastric region and iliac fossae of one hour evolution (VAS 8/10), which did not irradiate, was not related to any activity or food consumption, and presented with slight foul-smelling vaginal bleeding. There was no evidence of emesis or diaphoresis nor was it related to febrile peaks.

The young woman did not report any pathological, family, surgical, allergic or pharmacological history or toxic habits. Menarche occurred at 12 years of age with irregular menstrual cycles, having the last menstrual period 3 months before the consultation; her first sexual intercourse occurred at age 16, stating that her sexual relations have been pleasant without pregnancies. The patient manifested using levonorgestrel subdermal implants for 5 months for birth control, which could be related to oligomenorrhoea symptoms.

Physical examination revealed normal heart and breathing rates, as well as temperature and blood pressure within normal ranges for physical body and age. The abdomen was not distended and no signs of peritoneal irritation were found; however, the patient felt pain on deep palpation in the right iliac fossa and hypogastrium. During the gynecological examination, the woman showed significant pain, making exploration difficult.

Considering the symptoms, pregnancy or infection of the urogenital tract were suspected; paraclinical results showed negative pregnancy test, blood count with leukocytosis without neutrophilia (leukocytes 15 300 and neutrophils 61.6%), without anemia (hemoglobin 14.2 gr/L, hematocrit 41%) and platelets 433 000/uL. Urinalysis did not suggest urinary tract infection. Transvaginal ultrasound and abdominal pelvic tomography were requested, revealing uterus didelphys (Figure 1) and renal agenesis (Figure 2).

Reassessment was performed after pain decreased with the administration of analgesics; speculation was performed, and hematopurulent discharge was observed after draining using a continuity solution of 1mm to 2 mm in length in the vaginal transverse septum, which documented hemato-pyometra.

Antibiotic treatment was initiated with clindamycin (600mg every 6 hours) and intravenous gentamicin (240mg every 24 hours) for 7 days. Although dysthermia was not documented during hospital stay, magnetic resonance imaging was performed, revealing uterus didelphys and hematocolpos (Figures 3 and 4).

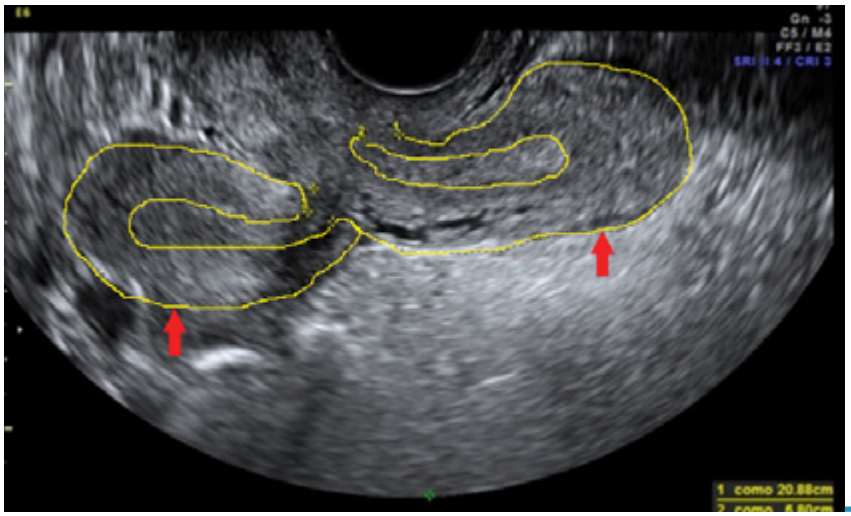

Figure 1. Transvaginal gynecology ultrasound showing the presence of uterus didelphys (demarcated in yellow).
Source: Document obtained during the study.

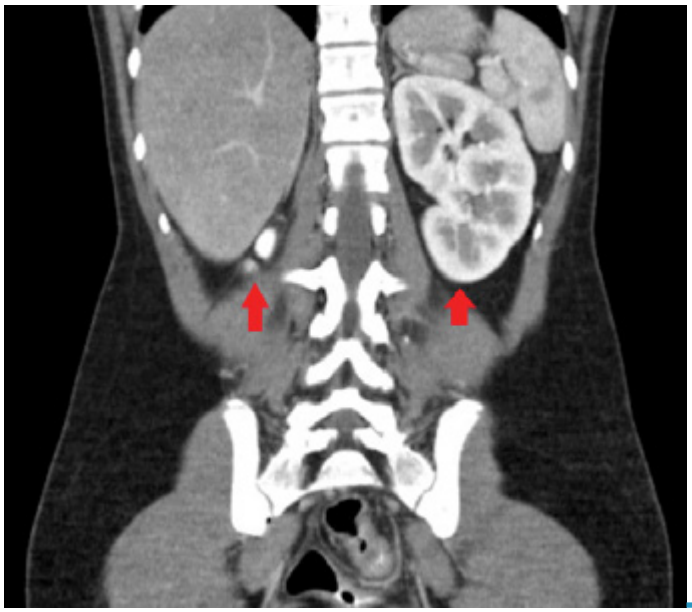

Figure 2. Coronal computed tomographic (CT) scan that shows the left kidney and right renal agenesis.
Source: Document obtained during the study.

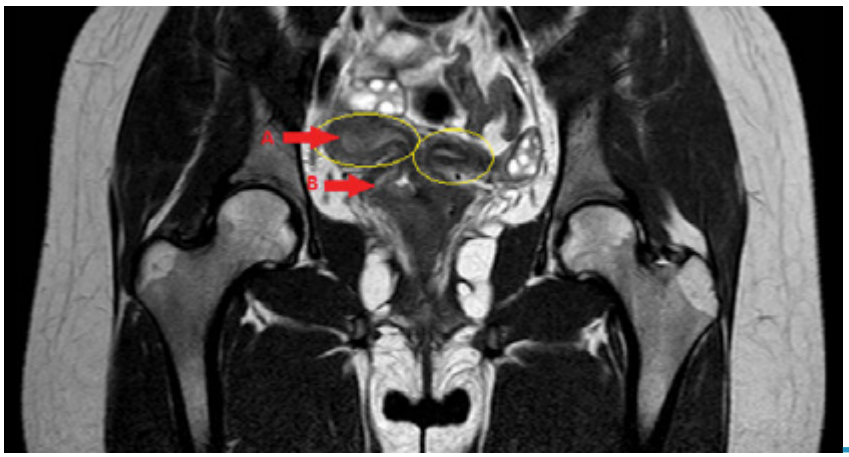

Figure 3. Magnetic resonance, coronal cut, that shows uterus didelphys, hemato-pyometra (A), hematocolpos (B) and their respective appendixes.
Source: Document obtained during the study.

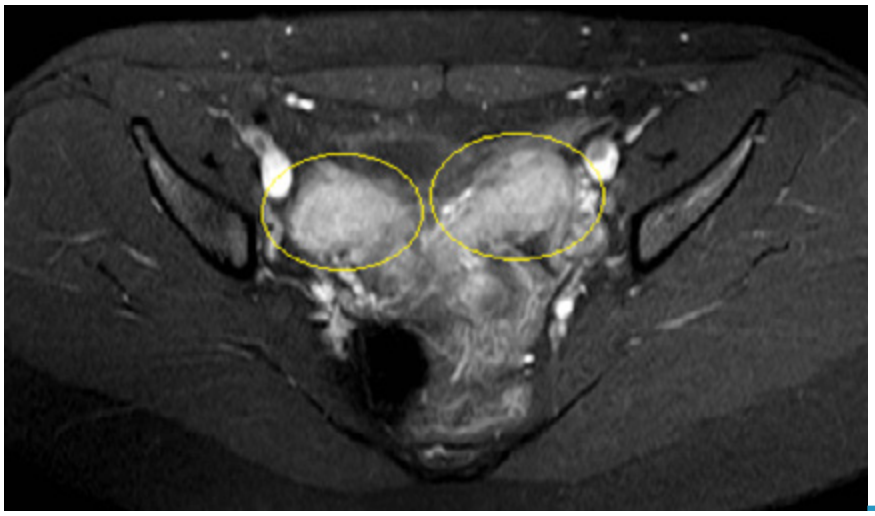

Figure 4. Cross-sectional magnetic resonance showing two uterine bodies.
Source: Document obtained during the study.

During hospital stay, the symptoms of the patient improved and pain resolved. Surgical management was proposed for marsupialization of the vaginal septum, but the patient and her relatives decided to dissent the procedure during hospitalization and expressed their desire to postpone it. Considering the resolution of the symptoms, hospital discharge was approved once the antibiotic management was completed without any further intervention.

Since the patient was referred to the hospital due to a company benefit plan that did not include outpatient consultation with the institution, it was not possible to perform institutional follow-up.

DISCUSSION

The reason why HWW syndrome presents with a higher prevalence of malformations on the right side as well as incomplete vaginal obstruction is unknown. These conditions, however, have an impact on the late diagnosis of complete vaginal obstruction, since the symptoms appear early in the latter category. (1)

The possibility of diagnosing this syndrome cannot be ignored when a physician receives a patient with foul-smelling vaginal discharge, whether it is small or rare, because partial perforations in the vaginal septum lead to this scenario.

Regarding anatomical variations, it is possible to classify HWW syndrome according the presence or not of septum or cervical fistulas in: type I, the vaginal septum is not perforated (Figure 5); type II, septal perforation is observed (Figure 6); and type III, the vaginal septum is unperforated with cervical fistula (Figure 7). (2) In the light of this anatomical classification, it is understood that the definitive treatment is surgical correction, in which the vaginal septum obstructing the hemi-uterus is resected, thus allowing communication with the vaginal lumen.

Figure 5. Herlyn-Werner-Wünderlich syndrome type I: unperforated vaginal septum that favors hematometra and hematocolpos.
Source: Own elaboration.

Figure 6. Herlyn-Werner-Wünderlich syndrome type II: perforated vaginal septum that communicates the flow with the lumen of the permeable hemivagina.
Source: Own elaboration.

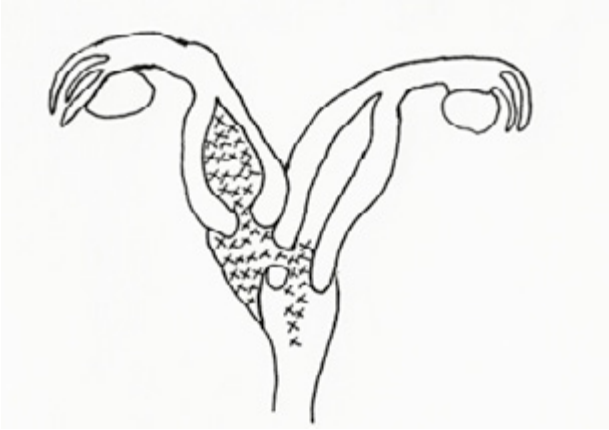

Figure 7. Herlyn-Werner-Wünderlich syndrome type II: vaginal septum without perforation that connects the cervix and allows cervix fistulization.
Source: Own elaboration.

Pregnancies are more likely to occur in the uterus opposite to vaginal septation, although post-marsupialization increases the possibility of pregnancy on the side ipsilateral to renal agenesis. (2) The possibility of miscarriage is not ruled out; however, only 15% of patients with HWW syndrome present conceptional losses.

Patients with this pathology benefit from marsupialization of the septum that makes up the blind or fistulized vagina, in such a way that the menstrual content of the obstructed hemi-uterus is easily expelled from the cavity, thus preventing the formation of blood or hematopurulent collections.

With respect to female urogenital malformations, only 3.53% present the diagnostic triad of the HWW syndrome. (4) Another study reveals that 2-3% of the population with fertility problems have HWW syndrome and that only 0.3% of the general population suffer from this pathology. (5) 1 in 2 000-28 000 women can develop this syndrome (6); the differences in frequency are explained by the iceberg theory, which would account for the disparate and unclear prevalence of the syndrome, since many patients are asymptomatic and others are underdiagnosed.

CONCLUSIONS

The HWW syndrome is a rare Müllerian malformation that can have a significant impact on the life of the patient who is suffering from this pathology, given that morphological changes make them more prone to consult for gynecological infectious diseases or blood collections (hematometra or hematocolpos). Definitive surgical management of vaginal septum improves the quality of life of patients and reduces the risk of morbidities associated with the pathology. Obstetric results are always linked to the implantation site of pregnancy.

Adequate articulation between the different networks of health service providers is required for better follow-up and adequate management of patients with HWW.

ETHICAL CONSIDERATIONS

It is hereby declared that the subject of this investigation, as well as her legal representative, participated voluntarily, following the principle of confidentiality, were aware of the

possible risks or discomforts, and had the right to refuse or withdraw from the study.

CONFLICTS OF INTEREST

None stated by the authors.

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CORONARY CAMERAL FISTULA: CASE REPORT

Keywords: Fistula; Coronary Disease; Heart Failure; Heart Defects, Congenital.
Palabras clave: Fístula; Enfermedad coronaria; Insuficiencia cardiaca; Cardiopatías congénitas.

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ABSTRACT.

Introduction: Coronary fistula is defined as a connection between a coronary artery and a cardiac chamber or any segment of the systemic or pulmonary circulation. Its incidence in angiographic series and general population is very low. In general, they are asymptomatic, and rarely show hemodynamic significance. They are typically found in the right cavities, and their location in the left cavities is less frequent.

Case description: 52-year-old male patient who presents with angina of effort, for which invasive stratification was performed. A coronary cameral fistula was found in the anterior descending artery to the left ventricle. Cardiac nuclear magnetic resonance was requested as a complementary study, in order to determine future therapeutic actions, but the patient failed to attend follow-up consultations.

Discussion: Coronary fistulas that cause coronary artery disease are rare and the drainage of a coronary fistula to the left ventricle is even more uncommon. The pathophysiological importance of a coronary fistula is related to the volume of blood flowing and the pressure gradient through communication. Most coronary fistulas are diagnosed incidentally in cardiac catheterization. Fistulas with clinical and symptomatic significance require short-term treatment.

Conclusions: In some cases, initial complementary tests in patients with clinical signs of myocardial ischemia, performed in a non-invasive manner, allow suspecting the presence of coronary fistulas. Coronary angiography continues to be the most accurate diagnostic test. Anatomical and physiological characteristics should be considered to determine if management is required and whether it will be done percutaneously or surgically.

Introducción. Una fístula coronaria se define como la comunicación entre una arteria coronaria y una cámara cardiaca o cualquier segmento de la circulación sistémica o pulmonar. Su incidencia en series angiográficas y población general es muy baja y, en general, cursan de modo asintomático, aunque en raras ocasiones presentan significancia hemodinámica. Su localización en cavidades izquierdas es menos frecuente.

Presentación del caso. Paciente masculino de 52 años quien presenta angina de esfuerzo, por lo que fue estratificado de modo invasivo encontrándose una fístula coronaria de la arteria descendente anterior al ventrículo izquierdo. Ante dichos hallazgos, le fue solicitada resonancia magnética nuclear cardiaca como estudio complementario para determinar conducta terapéutica a futuro; sin embargo, el paciente no asistió a controles, ni se le realizó dicho examen.

Discusión. Las fístulas coronarias que causan enfermedad arterial coronaria son raras y el drenaje de una fístula coronaria a ventrículo izquierdo es aún más infrecuente. La importancia fisiopatológica de una fístula coronaria está relacionada con el volumen de sangre que fluye y el gradiente de presión a través de la comunicación. La mayoría de fístulas coronarias son diagnosticadas incidentalmente en un cateterismo cardíaco; sin embargo, algunas de estas presentan significancia clínica, siendo sintomáticas y causando complicaciones, por lo que requieren tratamiento a corto plazo.

Conclusiones. En algunos casos, las pruebas complementarias iniciales en pacientes con clínica de isquemia miocárdica, realizadas de modo no invasivo, permiten sospechar la presencia de fístulas coronarias. La angiografía coronaria continúa siendo la prueba de mayor precisión diagnostica. Además, se deben

tener en cuenta las características anatómicas y fisiológicas para definir si requieren manejo y si este se hará por vía percutánea o quirúrgica.

INTRODUCTION

Coronary artery fistula is a rare condition defined as an abnormal communication between a coronary artery and a cardiac chamber (coronary-chamber fistula) or any segment of the systemic or pulmonary circulation (coronary arteriovenous fistula). The most frequent etiology is congenital malformation, which develops during the muscular and arterial organization embryonic stage, between days 31 and 39 of embryogenesis; the development of coronary arteries occurs during the advanced phase of heart morphogenesis. Since day 31, the spongy myocardium of the embryo becomes progressively massive, while subepicardial canicular networks, precursors of the coronary artery system, are formed. On day 35, the coronary buds of the aorta develop, and join the subepicardial network. Fistulas are caused by the persistence of intratrabecular spaces in embryonic sinusoids. (1)

Coronary artery fistulas can be acquired and appear in tumors such as hemangiomas, in rheumatic or iatrogenic heart disease, after cardiac surgery, in transplant patients or they can also be post-traumatic or secondary to invasive cardiac procedures (implantation of pacemaker, endomyocardial biopsy or coronary angiography). (2) Nearly half of patients with coronary fistulas remain asymptomatic, while the other half develop congestive heart failure, infective endocarditis, myocardial ischemia induced by coronary steal or rupture of the aneurysmal fistula. (3) Its incidence is 0.2-0.6% in angiographic series and 0.002% in the general population. (1)

Frequently, coronary artery fistulas are found in patients aged between 30 and 76 years, with a mean of 71±14 years, which may be related to the age at which coronary angiography is most commonly performed, with a male-female ratio of 1.9:1. (4) They can also be associated with other congenital anomalies. Although there is no uniform consensus on the most common site of origin and termination, reports describe that the left coronary artery is involved in 35% of cases, while the right coronary artery is involved in 55% of cases, and both in 5%. (5) It can be drained to another blood vessel or cardiac chamber, more frequently to the right cavities (90% of the cases), and to the left ventricle in only 3% of the cases. (1)

CASE PRESENTATION

This paper reports the case of 52-year-old male patient, from Bogotá D.C., without ethnicity, and architect for profession. He presented with a history of dyslipidemia, and consulted due to a 6-month history of episodes of sharp retrosternal chest pain that radiated to the back and neck, lasting less than 5 minutes, associated with moderate efforts and attenuation at rest. He also showed progressive deterioration of his functional class. Physical examination was normal and electrocardiogram showed sinus rhythm with a heart rate of 70 bpm, with changes compatible with necrosis in the lower and lateral sides. Transthoracic echocardiogram showed left ventricular ejection fraction of 58%, with segmental alterations in contractility due to severe hypokinesis in the apical lateral, apical infarction and concentric remodeling of the left ventricle with a non-mobile image of an 11x9mm calcium refringence suggestive of a small organized thrombus. For this reason, a myocardial perfusion with pharmacological stress (dipyridamole) was performed, which was negative for myocardial ischemia, with

lower wall necrosis in the middle and distal segments. Figure 1 shows a severe perfusion defect in the middle and distal segments of the inferior wall, not reversible, and with mild hypokinesia; the estimated area of necrosis is 5-7% of the total myocardial mass.

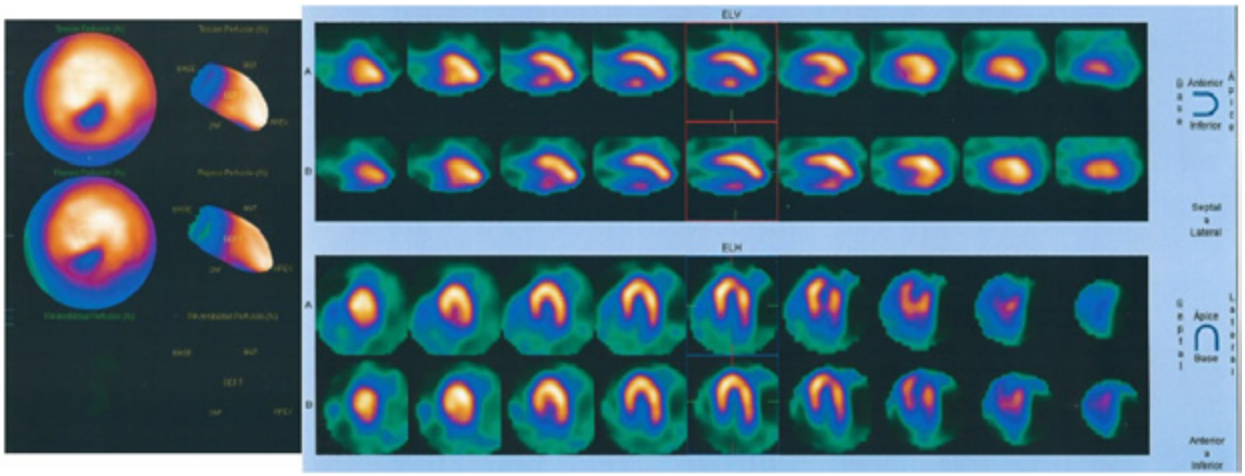

Figure 1. Myocardial perfusion test with pharmacological stress.
Source: Document obtained during the study.

Then, invasive stratification was performed by left ventriculogram and selective coronary angiography (Figure 2 and 3), in which a dominant right coronary system with epicardial coronary arteries, without obstructive lesions and presence of a fistula of the distal anterior descending artery to the left ventricle was found.

Figure 2 shows extravasation of contrast medium into the apical territory irrigated by the anterior descending artery, while, in Figure 3, diagnostic injection on the left coronary artery shows posteroanterior projections (ARC 18°, RAO 25°) (Figure 3A), left oblique with caudal angulation (CAU 20°, LAO 49°) (Figure 3B) and left oblique with skull (CRA 18°, LAO 8°) (Figure 3C). Extravasation of contrast medium is also observed from the anterior descending artery to the left ventricle (black arrow).

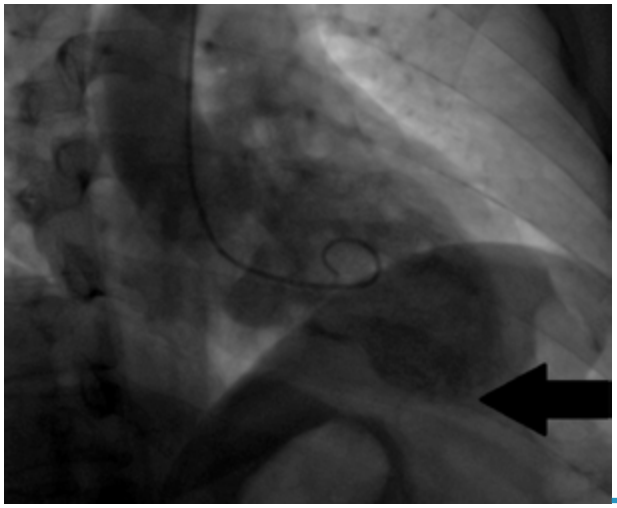

Figure 2. Left ventriculogram.
Source: Own elaboration.

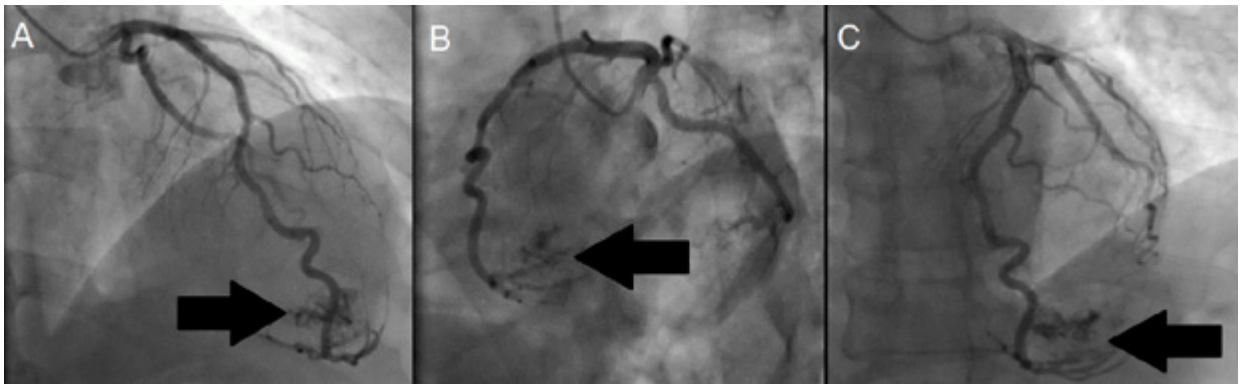

Figure 3. Coronary angiography of the left coronary artery.
Source: Own elaboration.

Considering that the findings ruled out significant coronary lesions, the patient was discharged the same day and cardiac nuclear magnetic resonance was requested as a complementary study for better anatomical characterization of the coronary fistula, in order to define management. The patient did not attend follow-up consultations.

DISCUSSION

This case is reported given the low frequency of this pathology and its form of presentation: precordial pain similar to angina, with infarction, epicardial coronary arteries without obstructions, and coronary fistula of the anterior descending artery to the left ventricle by means of coronary angiography.

Coronary fistulas that cause coronary disease or result in myocardial infarction are rare. The most prevalent symptom is angina pectoris; heart failure is less frequent and can cause infective endocarditis, thrombosis, embolism or arrhythmia. (6,7)

In the study by Wilde & Watt (8), 141 cases were reviewed, finding that 81 (57.4%) were asymptomatic, 35 (24.2%) presented dyspnea and 27 (18.4%) reported precordialgia. For Uyar *et al.* (9), the symptomatology of the fistulas that drain to the left ventricle can be similar to the symptomatology of aortic regurgitation.

Coronary fistulas can be congenital or acquired; they can also be associated with another congenital heart disease in 20-45% or be isolated in 55-80% of cases. (10) Studies have shown that its origin is the right coronary artery in 52-60% of the cases, the anterior descending artery in 30% and the circumflex artery in 18%. (11,12) Likewise, about 90% of the fistulas end up in the right cavities, being more frequent in the right ventricle (40% of the cases), followed by the right atrium, coronary sinus and pulmonary trunk. (12) The drainage of a coronary fistula to the left ventricle is very rare. (1,9)

The pathophysiological importance of coronary fistula relates to the volume of blood flowing and the pressure gradient through communication. Myocardial ischemia may occur due to decreased blood flow at points distal to the fistula or coronary steal. (6) If the fistulas are long or multiple, the intracoronary diastolic perfusion pressure could drop progressively below the critical level and a major short circuit may occur from left to right. When this occurs in situations such as physical activity, it leads to an increase of myocardial

oxygen demand, producing myocardial ischemia beyond the origin of the fistula; in other cases, signs of heart failure or pulmonary hypertension may be expected. (13) Coronary steal is the main cause of ischemia, but if there are high pressures in the left ventricle, it may not cause myocardial ischemia in relation to absence of elevated ventricular end-diastolic pressure. Yamanaka & Hobbs (14) found that myocardial infarction, seen in 9 of 51 cases, was caused by coronary fistulas.

Clinical symptoms and electrocardiogram may be helpful for diagnosis, especially in patients with long fistulas. Electrocardiographic signs may be similar to those of left ventricular overload or dynamic changes of the ST segment.

Doppler echocardiography in adults has low sensitivity, so most coronary artery fistulas are diagnosed incidentally during cardiac catheterization. Coronary angiography is not only useful to establish a diagnosis, but also to determine the type of intervention that may be necessary. (9) Some other diagnostic methods such as cardiac nuclear magnetic resonance, transesophageal echocardiography and multidimensional computerized coronary angiotomography have shown benefits. (14) Among them, multidimensional computerized coronary angiotomography has been widely used as it is non-invasive and provides three-dimensional visualization that helps delineate better the anatomy of the coronary arteries. Lim *et al.* (15) have shown that multidimensional computed coronary angiotomography detects anomalies in coronary arteries at a higher rate than traditional coronary angiography.

In children, spontaneous closure of coronary fistulas has been reported (16), being less frequent in adults. (17) In general, asymptomatic fistulas without association to other anomalies do not require immediate treatment, but fistulas with clinical relevance, symptomatic and large do require short-term treatment. (18) Indications for treatment include the presence of a large left-to-right short circuit, left ventricular volume overload, myocardial ischemia, left ventricular dysfunction, congestive heart failure, and prevention of endocarditis/endarteritis. (12)

The objective of the treatment is to provide normality in the coronary circulation by means of occlusion of the fistula. (3,6) Surgical closure methods are associated with low morbidity and mortality and good short and long term results have been described (18); however, myocardial ischemia or perioperative infarction has been described in 5% of cases. (9) For this reason, the use of surgical procedures has decreased considerably and percutaneous closure has become the alternative of choice. Occlusion of the fistula with coils, injection of alcohol and removable balloons are some of the percutaneous techniques. (9,15) The risks posed by the latter procedures are rare; however, periprocedural infarctions, migration of coils to the coronary circulation, deflation of removable balloons, transient changes in the T wave and transient branch hemiblock have been described. (10)

CONCLUSIONS

The presence of a coronary fistula may be an incidental finding in coronary angiography or aortogram in a patient with clinical manifestations of coronary insufficiency. Initial noninvasive complementary tests performed in patients with clinical signs of myocardial ischemia allow suspecting their presence in some cases.

To diagnose a coronary fistula, coronary angiography continues to be the most accurate diagnostic test; however, other non-invasive diagnostic methods have shown good results and could even replace this method in the future.

The therapeutic approach to coronary fistula should consider their anatomical and physiological characteristics to define whether they require management and whether it will be percutaneous or surgical. Short-term treatment benefits those patients who are symptomatic or at risk of complications such as coronary steal, aneurysm or significant intracavitary short circuit, with or without evidence of myocardial ischemia.

Findings of coronary artery fistula originating in the anterior descending artery and leading to the left ventricle are very rare in a coronary angiography, as described in the literature. In this case, without an MRI, closing the fistula by transcatheter aortic valve implantation would be recommended given the characteristics of the fistula in the angiography, because it is symptomatic and because of coronary steal. Collecting better casuistry for the study of this physiopathology, its presentation and results after treatment is expected in the future.

CONFLICT OF INTERESTS

None stated by the authors.

FUNDING

None stated by the authors.

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NORMAL ANION GAP METABOLIC ACIDOSIS SECONDARY TO TOPIRAMATE INTAKE: CASE REPORT

Keywords: Topiramate; Anticonvulsants; Renal tubular acidosis; Carbionic anhydrase; Intoxication.
Palabras clave: Topiramato; Anticonvulsivantes; Acidosis tubular renal; Anhidrasa carbónica; Intoxicación.

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ABSTRACT

Introduction: Topiramate is a drug used to treat various types of epilepsy and as prophylaxis in cases of migrainous headache. One of its mechanisms of action is the inhibition of carbonic anhydrase in the kidney that triggers the excretion of alkaline urine resulting in metabolic acidosis.

Case presentation: 17-year-old female patient from Mexico City who regularly uses topiramate, quetiapine and sertraline for the management of depressive disorder. She developed normal anion gap metabolic acidosis secondary to topiramate intake. As a result, she required invasive ventilatory support due to reduced consciousness and respiratory distress. Adequate response to management with laxatives and bicarbonate was achieved, with full renal and neurological recovery.

Discussion: Metabolic acidosis is the most common acid-base disorder observed in clinical practice. The difference between measurable cations and anions, known as anion gap, helps to classify the severity of acidosis. Bicarbonate losses or renal tubular disorders generate normal anion gap acidosis as opposed to acidosis resulting from an overproduction of endogenous acid or renal failure, which causes high anion gap. Topiramate is a little known cause of normal anion gap metabolic acidosis; by inhibiting carbonic anhydrase, it causes mixed renal tubular acidosis or type 3 acidosis, as a consequence of the inability to secrete hydrogen ions in the collecting tubule, and a limitation of bicarbonate reabsorption in the proximal tubule.

Conclusion: Topiramate, either in therapeutic doses or in overdose, can lead to normal anion gap metabolic acidosis due to the inhibition of carbonic anhydrase in the kidneys. It is usually reversible after starting bicarbonate.

RESUMEN

Introducción. El topiramato es un medicamento que se usa en el tratamiento de varios tipos de epilepsia y como profilaxis en casos de cefalea migrañosa. Entre sus mecanismos de acción, la inhibición de la anhidrasa carbónica en el riñón desencadena la excreción de orina alcalina ocasionando acidosis metabólica.

Presentación del caso. Paciente femenino de 17 años procedente de la Ciudad de México con antecedente de consumo de topiramato, quetiapina y sertralina para manejo de síndrome depresivo, quien desarrolla acidosis metabólica de anión restante normal secundaria a ingesta de topiramato. La joven requiere soporte ventilatorio invasivo por deterioro del estado de conciencia y síndrome de dificultad respiratoria y presenta adecuada respuesta a manejo con catártico y bicarbonato sin compromiso renal y sin secuelas neurológicas.

Discusión. La acidosis metabólica es la alteración ácido base más frecuente en la práctica clínica. La diferencia entre cationes y aniones medibles, conocida como anión restante o brecha aniónica, permite clasificar este tipo de acidosis. Las pérdidas de bicarbonato o trastornos de la función tubular renal generan acidosis de anión restante normal; por el contrario, la acidosis causada por sobreproducción de ácido endógeno o por insuficiencia renal genera anión restante elevado. El topiramato es una causa poco conocida de acidosis metabólica con anión restante normal; al inhibir la anhidrasa carbónica, se ocasiona una acidosis tubular renal mixta o tipo 3 debido a una in-

capacidad de secreción de hidrogeniones en el túbulo colector y una limitación en la reabsorción del bicarbonato en el túbulo proximal.

Conclusión. El topiramato en dosis terapéutica o en sobredosis puede generar acidosis metabólica de anión restante normal debido a la inhibición de la anhidrasa carbónica a nivel renal. Se trata de un cuadro reversible en el cual el manejo con bicarbonato ha mostrado buenos resultados clínicos.

INTRODUCTION

Metabolic acidosis is one of the most common conditions in patients admitted to the emergency room. In cases of normal anion gap metabolic acidosis, the most common causes are renal tubular acidosis, diuretic use, ureteroenterostomy, pancreatoenterostomy and acetazolamide or topiramate overdose. The following article presents, on the one hand, the case of a patient who develops metabolic acidosis secondary to topiramate intoxication and, on the other, a brief review of the literature on the subject.

CASE PRESENTATION

17-year-old female patient from Mexico City, residing at 2 250 m.a.s.l., currently unemployed and attending secondary school. The girl was found confused in her room, with spontaneous breathing, a lit cigarette and alcohol breath. The relative reported that she had taken 40 tablets of quetiapine, 20 of paroxetine and 20 of topiramate. She was last seen in normal neurological condition 5 hours before the incident.

The patient reported a history of major depressive disorder diagnosed 18 months earlier and attempt of autolysis, causing upper limb wounds with secondary hypovolemic shock, which required hospitalization for 20 days without admission to intensive care. Outpatient management was indicated with topiramate 50mg every 8 hours, paroxetine 20mg every 24 hours and quetiapine 100mg every 24 hours, with poor adherence. The patient indicated occasional tobacco consumption, alcohol intake of unquantified grammage, on a regular basis for a year, without drug use. She also reported menarche at age 14, irregular cycles and unknown date of last menstruation.

Physical examination showed blood pressure of 90/50 mmHg, mean blood pressure of 63 mmHg, heart rate of 100 beats per minute, respiratory rate of 30 breaths per minute, SpO2 of 89%, Glasgow Scale of 3/15, brain stem reflexes, mydriatic pupils, intercostal retractions, rhythmic heart sounds, rhonchi and bilateral basal rales, abdomen with diminished peristaltic-wave contractions, soft and depressed, without masses or peritoneal irritation data, and without pathological reflexes or murmurs. Paraclinical tests were requested and the results are presented in Table 1.

Table 1. Paraclinical tests.

Initial arterial blood gas Fraction of inspired oxygen: 100%	pH: 7.22 pCO_2: 33.4 mmHg pO_2: 78.4 mmHg SO_2: 94% HCO_3: 13.3 mEq/L BE: -11.7 Lactate: 4.5 Anion gap:11.7 PaO2/FiO2: 78.4
Hemogram	Leukocytes: 2 030 million/mm^3 Neutrophils: 1750/mL Linfocitos: 220 Hb: 12.8 gr/dL Ht: 37% Platelets: 171 000/mm^3
Renal function	Creatinine: 0.52 mg/dL BUN:12 mg/dl

Continues.

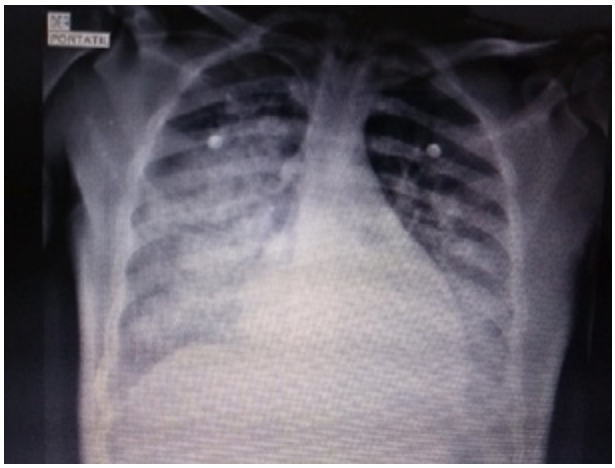
Liver function	Aspartate aminotransferase (AST):20 U/L Alanine aminotransferase (ALT):14 U/L Total bilirubin:0.6 mg/dL Direct bilirubin:0.3 mg/dL
Glucose	85 mg/dL
Serum albumin	3.7 g/ dL
Electrolytes	Calcium 8.4 mg/dl Chlorine 115 mEq/L Potassium 3 mEq/L Sodium 135 mEq/L
Enzymes	Creatine kinase (CK):59 U/L CK-MB:23 U/L Amylase:2178 U/L Lipase:18 U/L

AST: aspartate aminotransferase; ALT: alanine aminotransferase; CK: creatine kinase

Source: Own elaboration.

Chest x-ray showed bilateral alveolar opacities from the hilum towards the pleura in the lower two thirds of both lung fields, without images compatible with pleural effusion (Figure 1).

Figure 1. Chest x-ray.



Source: Document obtained during the conduct of the study.

The electrocardiogram recorded a frequency of 91 per minute, 30° axis, PR interval of 0.16 seconds, widened QRS complex (0.20 seconds) and prolonged QT interval (0.50 seconds); no ST segment alterations or branch block were observed.

Given the patient's neurological status, rapid intubation sequence was performed in the emergency room; she presented a convulsive crisis with generalized tonic-clonic seizure, controlled with diazepam 5mg IV. Arterial blood gases on admission showed mixed disorder: normal anion gap metabolic acidosis plus acute respiratory acidosis associated with hyperlactatemia type A; said hyperlactatemia is considered secondary to hypoperfusion subsequent to initial hypotension.

Neurological deterioration and electrocardiographic alterations secondary to overdose with antidepressant and topiramate were presumed in this patient. She also presented with hypotension and tachycardia attributable to the cardiovascular effects of drug overdose; in this case, despite the use of serotonin reuptake inhibitor, the patient did not show signs of serotonin syndrome.

Regarding the lungs, oxygenation disorder was diagnosed due to gasometry findings and radiographic images compatible with acute respiratory distress syndrome (ARDS). Management with crystalloids, cathartics, activated charcoal (1 g/kg) by nasogastric tube and sodium bicarbonate infusion at 1 mEq/kg was initiated, considering acidemia secondary to intoxication.

The patient was taken to the intensive care unit where hemodynamic condition improved without requiring vasopressors; lactated ringer's crystalloid with potassium chloride 2 mEq/hour was administered for management of mild hypokalemia. Invasive mechanical ventilation was initiated based on a diagnosis of ARDS due to radiological signs and PaO_2/FiO_2 ratio alteration. Possible bronchoaspiration was

considered due to the compromise of the state of consciousness, which also conditioned ventilatory deterioration. She also presented difficulty in ventilatory coupling requiring neuromuscular block and deep sedation.

Control arterial blood gases showed persistent normal anion gap metabolic acidosis within the first 24 hours, which was corrected subsequently (Table 2). Control electrocardiogram was performed without vasopressor or inotropic support, as well as QRS complex line and normal QT interval, maintaining sinus rhythm. Renal function was preserved without seizures; ventilatory function improved when sedation was discontinued without neurological sequelae, tolerating extubation on the fifth day. Finally, she was assessed by psychiatry, and management with paroxetine and quetiapine was restarted. The patient was discharged after 10 days without sequelae.

Table 2. Gasometric evolution during the first 24 hours*.

Date Hour	pH	pCO2	pO2	SpO2	HCO3	Lactate	Anion gap	BE	Na	K	Cl
13/07/15 20:08h	7.22	33.4	78.4	94%	13.3	4.5	12	-11.7	135	3	115
14/07/15 2:00 h	7.22	25.6	106	97%	10.2	7.3	11.8	-16	137	3.5	118
14/07 /15 5:30h	7.29	25.9	334	100%	14	4.3	11.7	-12.3	137	3.8	115
14 /07/15 19:00h	7.44	21.4	128	99%	17.5	1.8	12.4	-6.6	139	3.9	112
15/07/15 20:30h	7.45	30	105	96%	20.3	1.3	15.6	-4.2	140	4.0	110

* Reference values for arterial blood gases in Mexico City:
altitude: 2 250 m.a.s.l.; pH: 7.41±0.03; PaO_2:62.8±4.3 mmHg; $PaCO_2$: 35.2±4.7 mmHg; HCO_3: 22±2.5 mEq/L; SO_2: 91.6±4%; BE: 0±2.
Source: Own elaboration based on Vázquez-García & Pérez-Padilla (1).

DISCUSSION

Acid-base homeostasis is essential for the maintenance of life and is maintained mainly by the bicarbonate/carbonic acid buffer system interaction, which is characterized by the presence of an acid as a donor and a base as an acceptor of hydrogenions. Physiologically, a primary change in the partial pressure of CO_2 causes an adaptive response in bicarbonate concentration and vice versa, while major changes lead to alterations in the acid-base balance. (2)

Metabolic acidosis is the most frequent acid-base alteration, caused by the increase in the concentration of hydrogenols or by the decrease of bicarbonate; these situations are conditioned by increased formation or alteration in the excretion of acids or by loss of bicarbonate as shown in Table 3. (2)

Table 3. Mechanisms of metabolic acidosis.

Mechanism of metabolic acidosis	Causes
Increase in acid formation	Lactic acidosis, ketoacidosis, medications
Decreased acid excretion	Renal failure, renal tubular acidosis type 1, renal tubular acidosis type 4
Loss of bicarbonate	Diarrhea, tubular acidosis type 2, ureterostomy

Source: Own elaboration based on Berend *et al.* (2).

Diagnostic approach to metabolic acidosis

Respiratory compensation should be determined in the presence of metabolic acidosis; Winter's formula is used to know if the expected pCO_2 has been reached. (3)

$$pCO_2e = 1.5 \times (HCO_3 + 8) +/- 2$$

If the result is greater than expected, then a decompensated metabolic acidosis with respiratory acidosis is established; if it is lower, it refers to decompensated metabolic acidosis with respiratory alkalosis. (2-4)

In general, in all acid-base disorders, compensatory responses that try to maintain pH normality and follow predetermined patterns are observed. Inappropriate compensations, by excess or defect, imply the existence of a mixed acid-base disturbance. (5)

ANION GAP

In 1939, Gamble stated that the principle of electroneutrality required that the positive and negative charges in serum must be balanced. Anion gap represents a variety of "unmeasured" anions such as albumin, phosphate and sulfate (6), and is calculated using the equation (2-4)

serum sodium - (serum chlorine + serum bicarbonate)

It excludes potassium anion because its value is relatively low with respect to the other ions.

Albumin is an anion and, unlike the other anions, it can be measured and fluctuate significantly in several diseases; consequently, it has been included to determine the anion gap. (6)

Hypoalbuminemia causes a decrease in the anion gap. In hypoalbuminemic patients with metabolic acidosis, the anion gap may be low or normal, so the calculation should be corrected for albumin concentration in order not to underestimate the magnitude of its increase in acidosis due to the gain of non-chlorinated organic and inorganic acids. For each gram of decrease in albumin concentration, 2.5 are added to the anion gap that has been calculated. (6) Using the Figge formula, the anion gap corrected for albumin is AGAP + {0.25 x (4.4-albumin [g/dL])}. The normal anion gap values are 12 ± 4 mmol/L. (4)

The main causes of high anion gap metabolic acidosis are ketoacidosis, methanol, acetylsalicylic acid, L-lactate, D-lactate, glycoles (ethylene and propylene), 5-oxoproline (associated with chronic use of paracetamol), paraldehyde, ethylene glycol and chronic kidney disease. (7)

Normal anion gap metabolic acidosis

Hyperchloremic acidosis is caused by the inability to excrete hydrogen bonds or by the

loss of bicarbonate ions. (3) In normal anion gap acidosis, organic acids are not formed, so the calculation of the urinary anion is measured to determine whether the etiology is renal with positive urinary anion gap or non-renal with negative urinary anion gap. The most common etiologies related to potassium concentrations are shown in Table 4.

Table 4. Causes of normal anion gap metabolic acidosis.

Hypokalemia	Normokalemia - hiperkalemia
Renal tubular acidosis type 1 and 2	Renal tubular acidosis type 4
Carbonic anhydrase inhibitors	Early acute renal failure (IGF 20-50 m/min)
Urinary diversion	Hydronephrosis
Diarrhea	Hyporeninemic hypoaldosteronism
Surgical fistula drainage	Potassium-sparing diuretics
Posthipocapnic acidosis	Sulphide poisoning

Source: Own elaboration based on Rice *et al.* (3).

Approved in 1996 as a second-line anticonvulsant and prophylactic medication for migraine attacks, topiramate is a little-known cause of normal anion gap metabolic acidosis. (3) The mechanisms of action are blockade of sodium channels, potentiation of gamma aminobutyric acid (GABA), glutamate acuity and inhibition of carbonic anhydrase.

Carbonic anhydrase catalyzes the ionization of carbon dioxide to form carbonic acid, a reaction that develops continuously in the absence of the enzyme, but slowly in its presence. Balance is reached in less than 1 second, producing a proton (H+) and a bicarbonate anion. (3,4) Carbonic anhydrase is divided into 4 subgroups and 16 isoenzymes, which have a wide tissue distribution; therefore, their kinetic properties differ depending on the tissue where they are located. (8)

Topiramate has a sulfa fraction that binds to the zinc ion of carbonic anhydrase; this isoform of anhydrase is determinant in bicarbonate reabsorption in the proximal tubule and in acidification in the distal tubule. (5) Topiramate shares a very similar molecular morphology with acetazolamide; the latter is the reference drug for the inhibition of carbonic anhydrase. (9,10)

Carbonic anhydrase isoforms II, IV and XII are the most prevalent in the kidneys. (8) Topiramate is a high-potency inhibitor of type II, moderate potency inhibitor of type IV and mild potency inhibitor of type XII. The sulfamide analog present in this drug may be responsible for inhibiting the isoform II. (11,12)

In this context, the polymorphism of type XII anhydrase is studied as a target in the formation of renal tubular acidosis. (8)

Mirza *et al.* (9) state that susceptibility to develop acidosis is caused by genetic differences, finding two single nucleotide polymorphisms known as rs2306719 and rs4984241 in the gene of carbonic anhydrase type XII, which is significantly associated with lower values of serum bicarbonate.

Renal tubular acidosis induced by topiramate

Renal tubular acidosis is characterized by limited excretion of hydrogen ions in the kidney and the reabsorption of urinary bicarbonate. (10) In renal tubular acidosis type 1 (distal),

the secretion of hydrogen bonds through the collecting tubule is limited, and therefore a low concentration of bicarbonate in plasma is found. (13) On the other hand, in renal tubular acidosis type 2 (proximal), there is inability to absorb bicarbonate in the proximal convoluted tubule and 85% of the filtered bicarbonate is reabsorbed there. (13)

In the context of topiramate intake, metabolic acidosis is associated with alkaline urine, positive urinary anion gap, b2 microglobinuria with serum bicarbonate, urinary citrate, low urinary pH and urinary bicarbonate, and increased fractional excretion of bicarbonate. (14)

These findings are related to mechanisms of proximal and distal renal tubular acidification, that is, a combination of renal tubular acidosis type 1 and 2 that some authors call mixed or renal tubular acidosis. (14)

Reabsorptive limitation in renal tubular acidosis type 2 is the result of a large number of molecular defects, for example, a defect in the co-transporter Na-HCO_3 gene (SLC4A4). On the other hand, alteration in the secretion of hydrogen ion in renal tubular acidosis type 1 is due to several conditions in which there is a functional alteration of the expression of the exchanger gene Cl-HCO_3. (15)

Other reviews state that renal tubular acidosis type 4 can be caused by limited sodium reabsorption and decreased secretion of hydrogen and potassium in the distal tubule leading to normal anion gap metabolic acidosis, hyponatremia, hyperkalemia and low urinary ammonium concentrations. (3,7) This condition occurs in patients with obstructive uropathy, interstitial tubule diseases, diabetic nephropathy and users of potassium-sparing diuretics. It is common to see a slight decrease in the concentration of bicarbonate, but there are reports in the pediatric and adult population of concentrations of 10 mEq/L. (3,8) The differences between the different types of renal tubular acidosis are summarized in Table 5.

Table 5. Characteristics of the types of renal tubular acidosis.

Characteristics	*Renal tubular acidosis type 1*	*Renal tubular acidosis type 2*	*Renal tubular acidosis type 4*
Disorder	Distal acidification	Proximal absorption of altered HCO_3	Resistance to aldosterone
Serum bicarbonate	<10 mEq L	12-20 mEq L	>17 mEq/L
Serum potassium	Low	Low	High
Urinary pH	>5.3	<5.3	<5.3

Source: Own elaboration based on Rice *et al.* (3).

Some studies have shown that topiramate reduces serum bicarbonate levels. A study in 54 patients taking topiramate showed that 48% had metabolic acidosis with an average bicarbonate concentration of 18.8 mEq/L (range 13-21mEq/L). (16)

Topiramate, besides being a potential generator of metabolic acidosis, can also cause central neurogenic hyperventilation, perhaps due to its inhibitory effect of carbonic anhydrase in the brain and subsequent CSF acidosis. (17)

Possible adverse effects of metabolic acidosis include hyperventilation, fatigue, nausea and anorexia, all reported in case series of topiramate-induced metabolic acidosis. The most

severe cases may include respiratory failure, heart failure and coma; however, no correlation has been found between adverse effects and drug dosage. (7) Respiratory failure has been reported in a patient with therapeutic dose intake requiring mechanical ventilation. (18)

While status epilepticus, hypotension, severe metabolic acidosis and coma have been reported in overdose, neurological alterations may occur not only as a consequence of the adverse reaction to topiramate, but because of the association with valproic acid and benzodiazepine drugs. (19,20)

Case reports have shown that acute metabolic acidosis attributed to topiramate has been reversed between 6 and 30 days after drug intake has been suspended. (21,22)

A study in children receiving therapeutic doses between 8.2 mg/kg and 26 mg/kg found that metabolic acidosis persisted even 6 months after the initiation of topiramate treatment. This chronic acidosis can manifest itself with delayed growth, headache, diarrhea, hyperventilation, osteomalacia and osteoporosis in the adult population. (22,23)

Renal clearance mechanisms are activated leading to renal hypertrophy and accelerating renal failure in patients with previous kidney disease, promoting nephrocalcinosis and nephrolithiasis secondary to the difficulty of the renal system of acidifying urine. (10,19) In addition, chronic metabolic acidosis contributes to the generation of hypoalbuminemia, as well as to the decrease in insulin resistance; these effects can even be seen in mild metabolic acidosis. (24)

Other adverse effects reported as secondary to the intake of topiramate are nausea, ataxia, fatigue, weight loss, open-angle glaucoma and psychiatric symptoms such as hallucinations in 1.5-6.3% of cases. (19,25)

The initial treatment is the use of activated carbon, which has shown a good in vitro adsorption effect. The use of hemodialysis is reserved for severe metabolic acidosis and hypotension refractory to initial treatment. (19)

In this case, the patient was admitted with deteriorated state of consciousness associated with the consumption of quetiapine, topiramate and paroxetine, with hemodynamic instability that led to systemic hypoperfusion and subsequent hyperlactatemia. Stabilization of vital signs was achieved with crystalloid fluids. The patient also presented with adequate SpO_2; however, she developed early oxygenation disorder with radiological signs of ARDS secondary to possible bronchoaspiration, which had a favorable evolution after 5 days of mechanical ventilation. At the cardiovascular level, prolongation of the QT segment was considered acquired and probably secondary to the consumption of quetiapine in association with antidepressants; this temporary condition did not generate electrical instability or conversion to torsade de pointes.

The presence of a mixed base-acid disorder with normal anion gap metabolic acidosis and associated respiratory acidosis is particularly striking since topiramate, besides inducing hyperchloremic metabolic acidosis, also causes central neurogenic hyperventilation by inhibiting carbonic anhydrase as previously discussed. The initial pCO_2 level was expected to be low; however, when applying Winter's formula, it was found that the pCO_2 level was above as a result of respiratory compensation in the presence of metabolic acidosis. Therefore, this sign indicates that there was respiratory depression attributable to the intake of the other medications used and that said depression could suppress the respiratory compensatory effect secondary to the metabolic acidosis produced by topiramate.

Despite fluid therapy and the management of topiramate overdose, the acid-base status was normalized after 24 hours. Management with bicarbonate was initiated considering the widening of the QRS complex and hyperchloremic metabolic acidosis, which, according to the Stewart model, is explained by the decrease in the difference of strong ions whose main components are sodium and chlorine and whose value must range between 40 mEq/L and 44 mEq/L. Bicarbonate allows the stabilization of the donation of the water molecule in the formation of radical hydrogenions and, in addition, can reverse the membrane depressant effects by increasing the extracellular concentrations of sodium and by direct effect of pH on fast sodium channels.

The most probable cause of normal anion gap metabolic acidosis in this case may be the intake of topiramate, which inhibits carbonic anhydrase, generating renal tubular acidosis type 1 due to the inability to secrete hydrogenolions in the collecting tubule and the limitation of the bicarbonate reabsorption in the proximal tubule. There was no elevation of azotees or transaminases and leukopenia, at the expense of lymphocytopenia; this was correlated with the intake levels of quetiapine.

CONCLUSIONS

Topiramate causes normal anion gap metabolic acidosis by inhibiting carbonic anhydrase. This condition occurs even at therapeutic doses. Genetic influence has been identified as an important factor for metabolic acidosis by topiramate. Regarding treatment, bicarbonate, cathartics and activated charcoal are used.

CONFLICT OF INTERESTS

None stated by the authors.

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KARTAGENER SYNDROME, CURRENT DATA ON A CLASSICAL DISEASE. CASE REPORT

Keywords: Kartagener Syndrome; Primary Ciliary Dyskinesia; Cilia; embryology; Situs Inversus.
Palabras clave: Síndrome de Kartagener; Discinecia ciliar primaria, Cilios; Embriología; Situs inversus.

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ABSTRACT

Introduction: This article addresses the general aspects (pathophysiology, embryology, clinical presentation and prognosis) of the Kartagener syndrome (KS).

Case presentation: 26-year-old male patient, with a history of complicated sinusitis with cerebral abscess and secondary epilepsy, who consulted to the Hospital Universitario Nacional de Colombia due to headache, fever and mucus expectoration. The presence of situs inversus, chronic sinusitis and bronchiectasis suggested a diagnosis of primary ciliary dyskinesia and KS.

Discussion: Differential diagnoses of KS should be framed in its possible causal relationship with primary ciliary dyskinesia and other diagnoses associated with secondary ciliary dysfunction, such as cystic fibrosis, immunodeficiency and anatomical-functional conditions with rhinosinusitis and pulmonary infections involvement. Clinical suspicion of KS occurs when the heart is auscultated on the right and the liver is palpated on the left. Confirmation is achieved through imaging methods that prove visceral heterotaxia, indirect methods related to scan of ciliary malfunction (nasal nitric oxide, video microscopy) and ciliary biopsy that demonstrates the defect of the ciliary ultrastructure.

Conclusions: Respiratory infectious involvement in patients with KS is explained by the alteration of the cilia, which leads both to the malposition of some organs and to the structural and functional alteration of others.

RESUMEN

Introducción. El presente artículo aborda los aspectos generales (fisiopatología, embriología, presentación clínica y pronóstico) del síndrome de Kartagener (SK).

Presentación del caso. Paciente masculino de 26 años, con antecedente de sinusitis complicada con absceso cerebral y epilepsia secundaria, quien consulta al Hospital Universitario Nacional de Colombia por cefalea, fiebre y expectoración mucosa. La presencia de situs inverso, sinusitis crónica y bronquiectasias sugieren diagnóstico de discinesia ciliar primaria y SK.

Discusión. Los diagnósticos diferenciales del SK deben enmarcarse en la relación de causalidad posible con la discinesia ciliar primaria y de otros diagnósticos asociados a disfunción ciliar secundaria como fibrosis quística, inmunodeficiencia y condiciones anatómicas-funcionales con compromiso rinosenopulmonar. La sospecha clínica del SK se da cuando se ausculta el corazón a la derecha y se palpa el hígado a la izquierda. Su confirmación es mediante métodos de imagen que comprueban la heterotaxia visceral, por métodos indirectos de mal funcionamiento del barrido ciliar (óxido nítrico nasal, video microscopia) y por biopsia ciliar que demuestra el defecto de la ultraestructura ciliar.

Conclusiones. El compromiso infeccioso respiratorio presentado por los pacientes que cursan con SK se explica por la alteración en la cilia, que conlleva tanto a la malposición de algunos órganos como a la alteración estructural y funcional de otros.

INTRODUCTION

The Kartagener syndrome (KS) comprises a triad of situs inversus, bronchiectasis and paranasal sinusitis, which is named after Dr. Manes Kartagener (1), who described the presence of paranasal sinusitis in patients in association with situs inversus and bronchiectasis observed by Siewert in 1904. (2)

The KS is a rare entity that was described almost a century ago. (2) Several reports and case series have been published on this matter, although its physiopathology has only been clarified in light of recent advances in molecular and genetic biology, which explain its symptoms and signs. (3)

The incidence of primary ciliary dyskinesia (PKD) is estimated at 1 case per 10 000 to 20 000 births (based on surveys of situs inversus and bronchiectasis); however, its frequency is difficult to determine due to the diagnostic difficulty related to nonspecific clinical pictures. (4)

Sometimes, the diagnosis is suspected prenatally when situs inversus is documented in obstetric ultrasound (5); however, most cases are diagnosed during childhood due to repeated respiratory infections, when the clinician listens to heart sounds in the right hemithorax and chest x-ray, complemented with abdominal and paranasal sinuses imaging, shows dextrocardia. (4) Treatment is symptomatic and requires antibiotic therapy for associated infectious processes. (4)

CASE PRESENTATION

26-year-old, mestizo, male patient from Pacho (Cundinamarca, Colombia), biller, middle class, who consulted due to a global tension headache of 5 days of evolution, which was classified as very severe. He also presented unquantified fever; coughing with greenish expectoration; exertional dyspnea; odynophagia; generalized arthralgia; nasal congestion, and asthenia. The patient reported a history of symptomatic focal epilepsy secondary to brain abscess at age 23 as a consequence of a previous sinus complication (the etiology was not proven). Abscess required surgical drainage and antibiotic therapy (no data were available on the procedure or antibiotic management administered). Additionally, a tomography showed findings that suggested bilateral maxillary antrostomy by endoscopic intervention.

On physical examination, the patient was in good general condition, alert, hydrated, afebrile, with oxygen saturation of 84%, without respiratory difficulty and normal blood pressure, heart rate and respiratory rate. Erythematous oropharynx was observed along with whitish plaques, heart sounds in the right hemithorax, decreased vesicular breath sounds in both lungs, occasional wheezing in the right lung and bibasal stertors.

Symptomatology was interpreted as an infectious picture of low respiratory tract origin and possible bacterial sinusitis, for which antibiotic management was initiated with ampicillin sulbactam. Further paraclinical tests included a chest x-ray that showed dextrocardia, with no signs of consolidation or pleural effusion. This was complemented with high-resolution computed tomography (HRCT) (Figures 1 and 2) and a computed tomography (CT) of the paranasal sinuses (Figure 3).

After finding dextrocardia, it was necessary to ascertain visceral situs (normal, inverted, ambiguous). A simple tomography documented pulmonary bronchiectasis, as well as liver on the left side (Figure 4), leading to suspect KS; this was confirmed with findings of chronic sinusitis in paranasal sinus tomography. In addition, HRCT showed tomographic signs of infectious bronchiolitis.

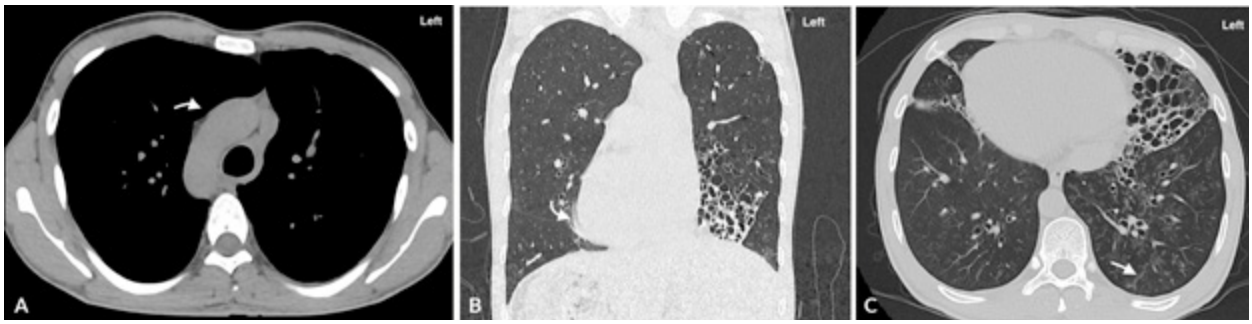

Figure 1. High-resolution computed tomography of the chest on 80-channel tomograph. A) right aortic arch; B) cardiac apex to the right of the midline with multiple cylindrical and sacular bronchiectasis; C) multiple micronodules with a "tree-in-bud" pattern suggesting infection.

Source: Document obtained during the study.

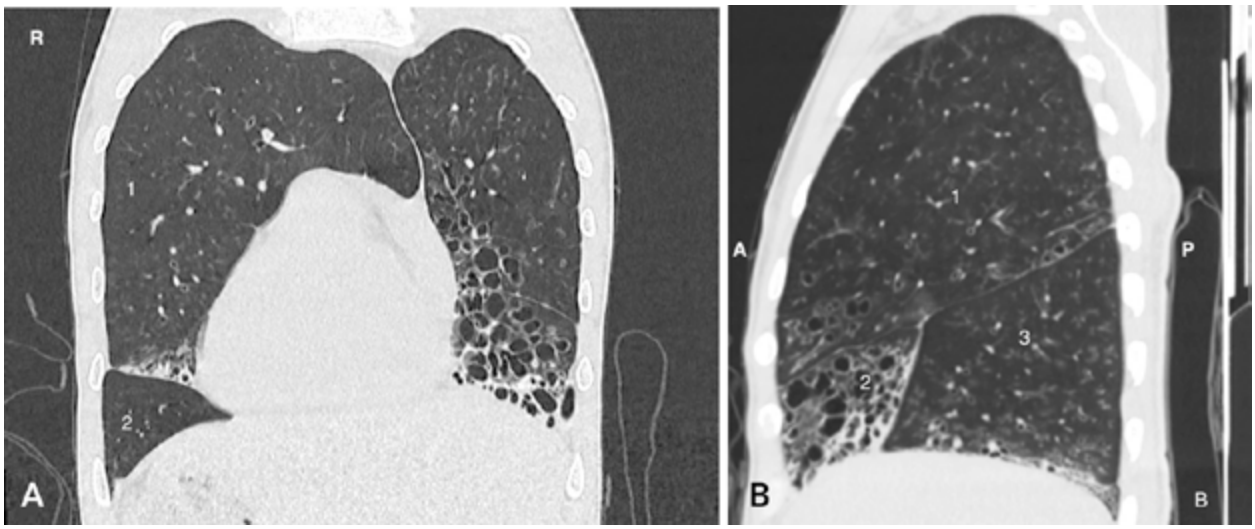

Figure 2. High-resolution computed tomography of the chest with isomerism of the bronchial branching pattern. A) coronal view of bi-lobed right lung; B) sagittal view of tri-lobed left lung.

Source: Document obtained during the study.

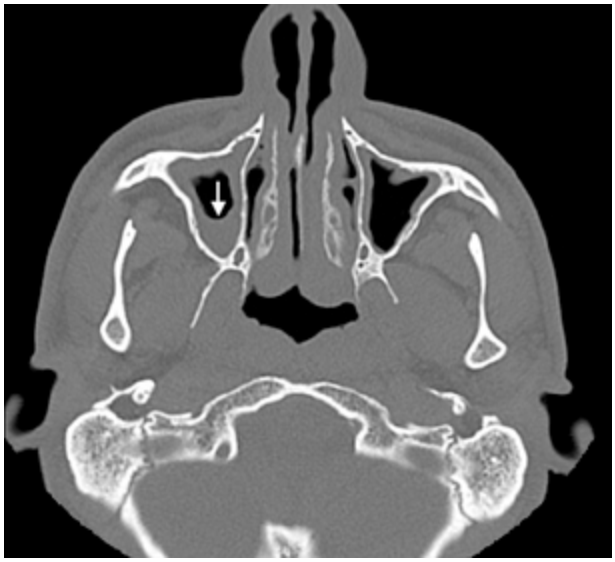

Figure 3. Paranasal sinus tomography with thickening of the mucosal lining, partially occupied by a soft tissue density mass.
Source: Document obtained during the study.

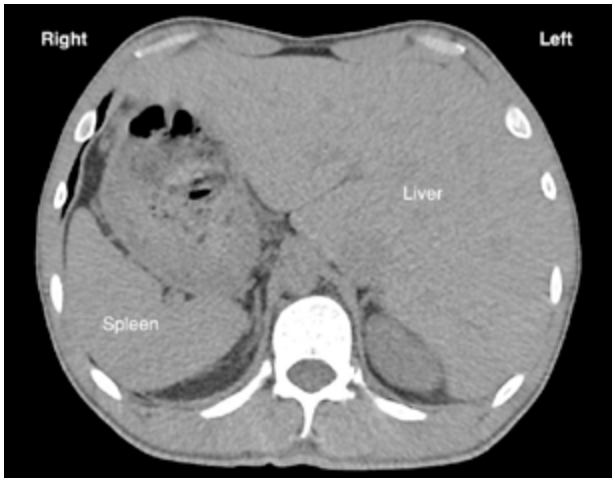

Figure 4. Simple tomography showing that the liver (H) is to the left of the midline and the spleen (B) to the right.
Source: Document obtained during the study.

Once the over-aggregated infectious process was confirmed in a patient with risk factors for pseudomonas infection, antibiotic therapy was adjusted with piperacillin tazobactam 4.5 gr IV every 6 hours for 7 days, with adequate tolerance and without complications secondary to treatment. The patient presented satisfactory clinical recovery and was discharged from the institution after completing the antibiotic scheme, with precise indications of outpatient controls by pulmonology. No images or control laboratory exams were made.

DISCUSSION

KS is part of the PKD spectrum related to an autosomal recessive genetic disorder that affects ciliary motility and predisposes to problems of laterality, rhinosopulmonary infections and impaired fertility. (4) Between 65% and 70% of patients with this disease have 2 or more mutations in at least 1 of the 35 identified PKD genes. (4) 50% of patients with PKD have situs inversus, while 20% of patients with situs inversus have KS. (6)

The positions of the organs are known as situs solitus (left heart, right liver), situs inversus (right heart, left liver) or situs ambiguus (some organs in an abnormal position, with others in normal position). Alterations in the genes that cause PKD lead to random situs (half of the individuals with situs inversus and the other half with situs solitus). (4)

Situs is regulated by a cascade of transcription factors on the right side of the embryo that are not expressed on the left side; this was described using an animal model and was discovered more than 20 years ago by Dr. Levin. (7) To this day, the more relevant genes are SSH (which is one of the first to activate on the left side and start a whole cascade of transcription, which is not expressed on the right side) and activin β-B (which initiates the

cascade on the right side and is not expressed on the left side).

Laterality depends on the movement of the cilia present in the primitive node, which are oriented upwards and immersed in extraembryonic fluid; they also move to any side of the extraembryonic fluid that contains multiple substances, contributing to gene expression. The movement of the fluid allows for different substance concentrations (which accumulate on one side only) and, therefore, for the expression of different genes in each hemi-embryo.

Ciliary movement depends on the normal configuration of the cilia, which is formed by arrangements of ten pairs of microtubules, assembled by various proteins such as dynein and others. Altered dynein in animal models, known as left-right dynein and encoded by gene IV (inversus viscerum), causes situs ambiguus.

The clinical manifestations for which patients consult do not depend on the position of the organs, since the picture of a child born with KS is given mostly by pulmonary symptoms that usually appear within 12-24 hours after birth, leading to neonatal respiratory distress syndrome in 40-80% of cases. Typical symptoms are persistent moist cough, sputum production, nasal congestion and chronic wheezing, with recurrent ear, nose and throat (ENT) infections, being the most frequent reason for consultation. (8) Respiratory symptoms are explained by the altered ciliary structure and function that prevents sweeping respiratory mucous secretions.

PKD diagnosis is confirmed by the presence of one or more of the criteria proposed by the European Society of Pneumology: low levels of nasal nitric oxide, frequency of ciliary oscillation ≤-11Hz by high speed videomicroscopy from ciliary biopsy or more than 20-30% of ciliary ultra-structural abnormalities by electron microscopy (Table 1). (9)

Table 1. Sensitivity and specificity for diagnosing primary ciliary dyskinesia.

Test	Sensitivity	Specificity
Nasal Nitric Oxide	0.90-0.99	0.75-0.97
High-speed video-microscopy	0.96-1.00	0.93-0.95
Electron microscopy	0.71-1.00	0.92-1.00

Source: Own elaboration based on Lucas *et al.* (9).

The differential diagnoses that should be considered depend on the moment of symptom onset: in newborns, it manifests with transient tachypnea, while cystic fibrosis and other causes of bronchiectasis and rhinosinusitis and pulmonary infections suppuration, including humoral immunodeficiencies, chronic granulomatous diseases, allergic bronchopulmonary aspergillosis, vasculitis, severe asthma and allergic rhinitis with unusual chronic sinusitis, are observed children and adults. (8,10)

Genetic diagnosis is available and multigene panels include most of the genes related to PKD. However, a negative result does not rule out this disease, as not all the genes involved are known to date. A positive result can detect up to 70% of all PKD cases. (11)

Imaging plays a key role in proving the anatomical findings that support KS. However, the diagnostic precision of PKD is achieved with the elements mentioned above, all of which are difficult to access. Inadequate sweeping of pulmonary secretions causes bronchial dilatations or bronchiectasis that are observed as tubular opacities or ovoids of variable sizes in chest x-ray, a less sensitive method for its detection with respect to HRCT. (12)

On the other hand, thin-section chest CT is the gold standard to detect bronchiectasis, although thick-section CT can also be used. The bronchial artery index is used to identify it and should normally be close to 1; however, it may increase during vasoconstriction or be normal during pulmonary hypertension. Therefore, the

cardinal sign of bronchiectasis on a CT scan is the observation of bronchioles less than 1cm from the pleural silhouette (Table 2). (12)

Table 2. General distribution of bronchiectasis disease.

Bilateral upper lobes	CF/ABPA
Unilateral upper lobe	TB
Middle lobe and lingula	KS/YS
Lower lobes	Childhood viral infections

ABPA: allergic bronchopulmonary aspergillosis; CF: cystic fibrosis; TB: tuberculosis; YS: Young's syndrome.

Source: Own elaboration based on Adam *et al.* (13) and Pappas *et al.* (14)

According to the classification proposed by Reid (15), bronchiectasis is divided into cystic, cylindrical and varicose. Its characterization, in the case of this patient, was carried out by means of a CT scan that showed a predominantly cystic pattern. According to another case report (16), the three types of bronchiectasis have been described in patients with KS in equal proportions.

Situs inversus abnormalities can be recognized by conventional radiography and ultrasound. CT provides good anatomical detail of the specific condition, while MRI can be useful to assess patients with cardiac abnormalities. (6,17)

Both sinus radiographs and CT scans of patients with KS may show thickening of the mucosa, opacified paranasal sinuses and hypoplastic frontal sinus.

Finally, prognosis depends on lung involvement. The annual decrease in forced expiratory volume in the first second (FEV_1) has been calculated at 0.8% to 3% of the predicted value. (18) Life expectancy in patients with PKD is close to the normal population, depending on the care provided in specialized centers and early diagnosis. (10)

CONCLUSION

The infectious respiratory compromise presented by patients with KS can be explained by cilia alteration, which leads to the malposition of some organs, as well as to structural and functional alteration of others. If a person with recurrent respiratory infections attends consultation, and also presents structural alterations in the lungs, PKD should be considered.

Situs and the fact that the organs are usually located to the right or left do not have yet a satisfactory explanation regarding their correlation with KS, and new theories have been proposed in this regard. For some authors, laterality is determined even during oogenesis when the chromatids separate; in any case, their clinical implication is not clear.

CONFLICT OF INTERESTS

None stated by the authors.

FUNDING

None stated by the authors.

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POST-POLIO SYNDROME REPORT OF TWO CASES

Keywords: Poliomyelitis; Post-Polio Syndrome; Electromyography; Fatigue; Muscle Weakness.
Palabras clave: Poliomielitis; Síndrome pospoliomielitis; Electromiografía; Fatiga; Debilidad muscular.

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ABSTRACT

Introduction. Post-polio syndrome (PPS) is a neurological syndrome that appears decades after an acute episode of polio. This condition decreases functional capacity until completing affecting daily activities. This event occurs in 20-80% of the people who were affected by the polio virus. It is more frequent in women and a direct correlation between the risk of developing this syndrome and the severity of the sequelae of polio has been reported.

Case presentation. The objective of this article is to present two clinical cases of patients who developed post-polio syndrome approximately forty years after the initial infection.

Discussion. This article seeks to question the concept of polio as a static disease, since it is a process difficult to diagnose and treat, as in both cases presented here.

Conclusion. The psychological and functional impact of this disease on patients is regarded as a challenge for the health professional, since clinical needs must be identified and current barriers care reduced.

RESUMEN

Introducción. El síndrome pospoliomielitis se reconoce como un trastorno neurológico que aparece décadas después de un episodio agudo de poliomielitis y disminuye la capacidad funcional hasta afectar las actividades cotidianas. El evento ocurre en un 20-80% de las personas que fueron afectadas por el virus de la poliomielitis, es más frecuente en las mujeres y existe una relación directa entre el riesgo de padecer este síndrome y el grado de severidad de las secuelas de la polio.

Presentación del caso. El objetivo de este artículo es la presentación de dos casos clínicos de pacientes que presentaron este síndrome después de cerca de cuarenta años de haber presentado un episodio de poliomielitis.

Discusión. Se cuestiona el concepto de la poliomielitis como una enfermedad estática; además, en los casos presentados esta patología constituye un proceso de difícil diagnóstico y manejo.

Conclusión. El impacto psicológico y funcional en los pacientes se asume como un reto para el profesional de salud, puesto que se deben identificar las necesidades clínicas y reducir las barreras asistenciales existentes en la actualidad.

INTRODUCTION

In 1875, M. Raymond described the onset of progressive muscle atrophy and weakness in a series of survivors of acute poliomyelitis during childhood. At that time, Jean-Martin Charcot stated that the initial infection may make the neurons of these individuals more sensitive, so that spinal diseases occurred subsequently, resulting in a new weakness as a consequence of the overuse of the affected muscles. In 1979, after the publication of a report made by an elderly patient about the motor difficulties he developed after suffering from polio in his childhood, a significant increase of the amount of individuals with similar clinical pictures was observed. The term post-polio syndrome (PPS) was finally established around the 1980's. (1-3)

Although this is a little known entity, PPS can affect between 20% and 85% of the population with new neuromuscular symptoms that occur at least 15 years after achieving stability in patients with previous acute paralytic

poliomyelitis. (4) In 2000, the first diagnostic criteria were described (3,5), which included 1) suffering from paralytic poliomyelitis with evidence of motor neuron loss, confirmed by clinical history, and symptoms and signs of chronic denervation in electromyographic study (EMG); 2) partial or complete recovery of the acute disease, accompanied by a period of about 15 years of stable neurological function; 3) sudden or gradual onset of muscle weakness or abnormal, persistent and progressive fatigue, atrophy or muscle or joint pain; and 4) persistent symptoms for at least a year.

Other neurological, medical or traumatic causes that explain the clinical picture should be excluded, and some exclusion criteria should be considered, such as symptoms secondary to oropharyngeal or respiratory complications, structural radiculopathies, compressive neuropathies, degenerative arthropathies, joint instability, scoliosis and psychopathological symptoms such as anxiety syndrome, depression and sleep disorders. (6,7)

Likewise, exploration should consider the presence of flaccid and asymmetric weakness with hyporeflexia in the affected areas, without associated sensory alterations. As part of the complementary studies, it is worth noting that there is no biochemical or physiological marker that allows for the unambiguous characterization of patients with PPS, so they are used mainly to identify or rule out other diseases. (1,8) Neither the analysis of the cerebrospinal fluid (CSF) nor blood analyses show alterations, although an increase in serum creatine kinase levels may be observed in a small number of patients, which is explained by muscle overstress. EMG shows signs of long-standing neurogenic involvement with loss of motor units that show an increase in polyphasia and amplitude, with giant potentials; even though this study identifies alterations compatible with previous poliomyelitis, it does not differentiate patients who report new symptoms. (9) In short, these studies are not useful to diagnose PPS, but to confirm that there are sequelae of polio and to rule out other pathologies such as neuropathies, radiculopathies and myopathies. (10-12)

On the other hand, it is also possible to request a biopsy of the affected muscles, which can histologically show regrouping by types of fibers, atrophic angulated fibers and fibers with hypertrophy, which are characteristic of possible denervation or reinnervation. However, it is not usually useful for diagnosis. (13)

Scientists from the National Institute of Neurological Disorders and Stroke (NINDS) and other institutions have shown, through several studies, that the weakness caused by PPS is a slow-evolving condition characterized by periods of stability, accompanied by a sudden deterioration in the ability to carry out daily activities. (14)

The purpose of exposing the following cases is to present different associated diagnoses, clinical and diagnostic evidence, and an interdisciplinary management approach to this pathological entity.

CASE PRESENTATION

Case 1

59-year-old female patient, mixed race, from Popayán (Colombia), middle class, with a history of idiopathic scoliosis and polio during childhood, lumbar arthrodesis 26 years before consultation and dysplasia of the right hip. Pharmacological management of the patient included pregabalin and tramadol for chronic pain for 2 years. A recent clinical picture of 15 days of intense pain in the lumbar region that limits sitting and supine position

and radiates to the lower left limb was reported, which is atrophic as a sequel to the childhood syndrome (Figure 1), with presence of lower extremity strength of 3/5 and positive reflexes. On admission to the emergency service, a foreign body sensation was reported in the right dorsal region, possibly associated with the history of arthrodesis.

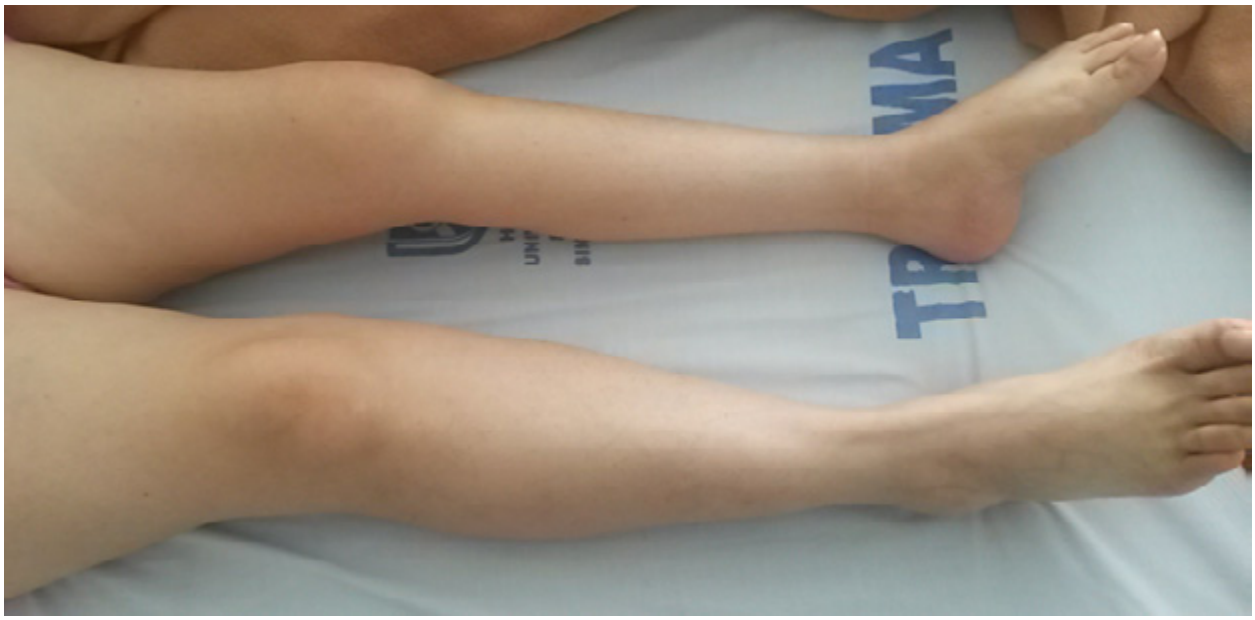

Figure 1. Significant atrophy of the left lower limb.
Source: Document obtained during the study.

Spine radiography was requested, revealing Harrington rod instrumentation without evidence of corrosion, left convex scoliosis in the lumbar spine, and wires and sublaminar hooks placed from T12 to S1. In addition, an electromyogram was indicated with nerve conduction velocities that show a chronic axonal injury in the lower limbs (Figure 2). The patient did not show signs of acute denervation or sensitive involvement, although muscle and joint pains persisted. The findings allowed ruling out radiculopathy and compressive neuropathy.

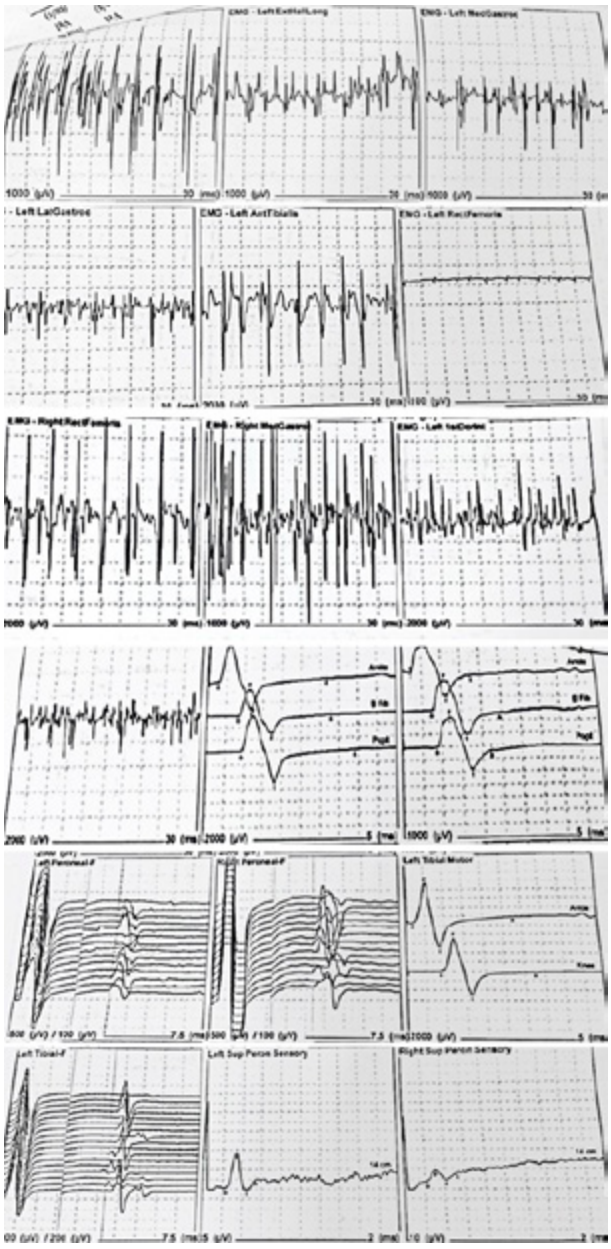

Figure 2. Electromyogram report.
Source: Document obtained during the study.

Figure 2 shows normal motor conduction velocities and amplitudes of motor evoked potentials, although the amplitude was lower in the left peroneum than in the right side by 50%, in spite of having normal parameters. The muscles of the upper limbs and the distal and dorsal latencies were normal; the amplitude and sensory conduction velocities of sensory potentials were also normal. The EMG showed signs of bilateral chronic denervation in the lower limbs, with a decrease in the recruitment of potential motor units and some polyphasic potentials.

After conducting clinical and paraclinical studies, it was determined that the symptomatology was associated with PPS since the necessary clinical diagnostic criteria were observed, as well as signs of chronic denervation in the lower limbs as reported by the EMG bilaterally, with a decrease in motor unit recruitment and some polyphasic potentials. Therapeutic management with prednisone was initiated and a slight improvement of the symptoms was reported. Follow-up was performed for the following 2 months.

Case 2

47-year-old male patient, mestizo, from Popayán (Colombia), middle class, with a history of childhood poliomyelitis at age five, who consulted the emergency service due to sensation of hyperthermia, dyspnea and oppressive chest pain. Additionally, he presented cough with purulent expectoration, for which a chest X-ray was taken, finding consolidation in the left lung base. Possible left basal pneumonia was considered and management with ampicillin/sulbactam was initiated.

In addition to the initial symptoms, the patient reported fatigue when walking and myalgias with weakness in the left lower limb. Upon exploration of lower limbs, evidence of negative Patrick's test, intense muscular atrophy in the gastrocnemius and tibialis anterior muscles (with normal knee joint balance), lower

extremity strength of 4/5, positive reflexes and preserved sensitivity were observed (Figure 3). Clinically, possible hip and sacroiliac joint pathology was ruled out. Although EMG was not performed, clinical differential diagnoses, such as a lumbar hernia, were ruled out through spinal magnetic resonance, which in turn ruled out nerve root compression.

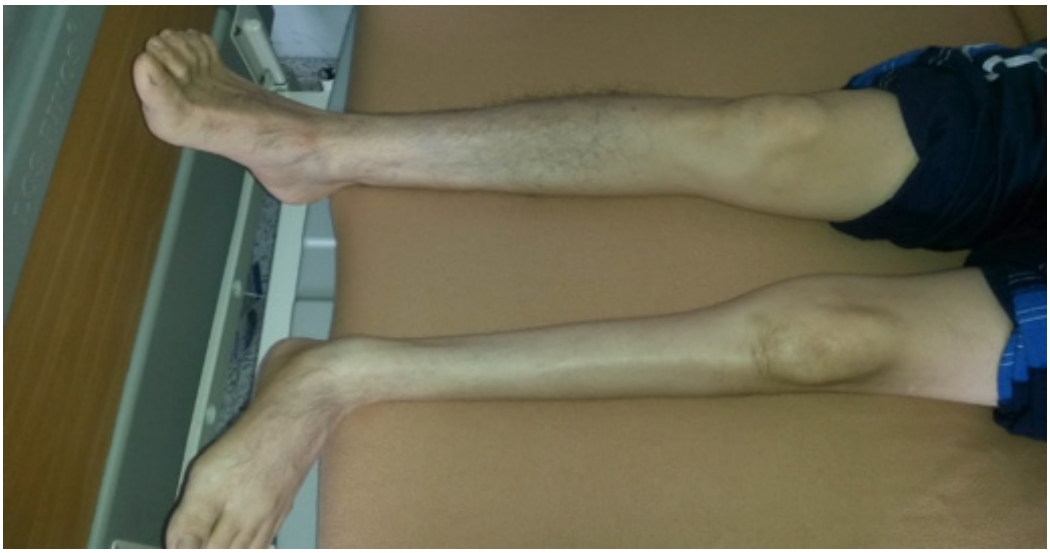

Figure 3. Significant atrophy of the left lower limb.
Source: Document obtained during the study.

Interconsultation with neurology was indicated, determining that the symptoms presented by the patient were associated with PPS after conducting clinical and paraclinical analyzes. Regardless of the lack of an EMG study, the diagnosis was achieved based on clinical findings, which are mandatory for this entity. Simultaneous symptomatic management with NSAIDs and therapies with physiotherapist were formulated, and the patient was monitored for the following 2 months. Adequate pain modulation and clinical evolution were evident at follow-up.

DISCUSSION

It should be noted that both patients gave their consent for conducting this academic and clinical study. It is possible to observe that the chronic pain presented by the patients had an adequate and satisfactory evolution, with clear and objective evidence of asymmetric muscle group atrophy with respect to the contralateral side. The current components of this clinical picture include progressive muscle weakness on the side of atrophy and generalized fatigue; these manifestations are compatible with PPS, which occurred approximately 40 years after the onset of the disease in both patients. (15-18)

PPS should not be considered a sequel to polio. A sequence of a mutated genome in the poliomyelitis virus may be observed in the CSF of some patients; consequently, the presence of a chronic infection in infected neurons that prevails over the years is considered a mechanism. Although they are not the same entity, the most common complains about this syndrome

include myalgias or muscle pains and arthralgias, as well as fatigue and low resistance to exertion. Diagnosis is difficult to achieve since the symptoms can be misinterpreted as related to the normal aging process. (19)

Individuals with a history of poliomyelitis and suspected PPS should be referred to a specialist in neuromuscular disorders, preferably with experience in the treatment of people with post-polio. These specialists include, among others, neurologists, psychiatrists (rehabilitation specialists) and orthopedists. For a definitive diagnosis, different pathological entities should be ruled out, such as Parkinson's disease, cerebrovascular disease, multiple sclerosis, amniotrophic lateral sclerosis, radiculopathy, spinal cord tumors, comprehensive neuropathy, myasthenia gravis, muscular dystrophy, post-surgical processes, heavy metal poisoning, depression, among others. Likewise, a complete physical examination, such as that performed on the patients reported here, should be done —although only positive aspects were described—, as well as complementary tests. Although all the necessary tests were not carried out in these subjects, great value was given to data collection and clinical analysis, which allowed discarding a certain number of additional possibilities.

Differential diagnoses allow, in a certain way, to provide an accurate diagnosis at the moment of categorizing a pathology. For PPS, different tests should be considered, such as antinuclear antibodies to rule out an ongoing autoimmune process; cytochemical CSF study and viral panel to rule out herpetic encephalitis; electrophysiological study of the peripheral nerve; electromyography to rule out acute denervation processes such as radiculopathies or pathologies such as amyotrophic lateral sclerosis; magnetic resonance of the spine to rule out compressive lumbar hernias; simple computerized axial tomography of the skull to rule out ischemic strokes; and toxicological tests, since it is worth discarding heavy metal poisoning depending on the approach.

In short, the most useful way to approach this pathology is by building a good clinical history, including physical examination based on interdisciplinary approaches that allow understanding the patient at the time of requesting paraclinical test to discard any condition.

Most researchers agree that when the infectious event occurs, the motor neurons initiate cell death and, as a consequence, loss of innervation and motor function of the muscle fibers occurs, thus giving way to flaccid paralysis, as in the case of the clinical pictures of these patients during childhood. Then comes a phase in which new axonal buds appear, reincarnating the affected muscle fibers and restoring all or part of their function. Not all axonal buds have complete stability; for this reason, they begin to die after a few years, generating new denervation of muscle fibers and the onset of PPS symptoms. (12)

Furthermore, persistent inflammatory changes since the presentation of the initial picture during childhood have been described, considering that there has been an increase in several cytokines, mainly proinflammatory such as INF-γ and TNF, both in the spinal cord and in the CSF of patients with PPS.

Recent proteomics research show increased concentrations of protein fragments and proteins related to inflammation and cell death mechanisms, such as apoptosis, in the CSF of patients with PPS. A possibility is raised of a late aberrant response to the original infection or a persistent immune response due to the persistence of viral particles or an immune response to a neurodegenerative process caused by other factors. (3,20) Although there are no major paraclinical contributions, the evolution, symptomatology and chronic pain of the patients tell the story of an event that develops over the years and that should not go unnoticed in patients who have a history of poliomyelitis in their childhood.

Regarding management, an interdisciplinary approach is suggested, including a neurologist, a rehabilitator, a physiotherapist, an occupational therapist and nursing professionals with experience in rehabilitation of patients with the symptoms related to this syndrome and in psychiatric aspects to allow them to establish management for long-term disability (Table 1). (21-25)

Table 1. Main symptoms of post-polio syndrome and their management.

Symptom	Management
Weakness	▪ Avoiding excessive use of muscles ▪ Losing weight ▪ Strengthening weakened muscles with prostheses and assistive devices
Fatigue	▪ Establishing regular rest periods during the day ▪ Changing lifestyle ▪ Improving sleep through relaxation techniques and medications
Pain	▪ Making lifestyle changes with less activity ▪ Stretching muscles ▪ Using ice or moist heat and assist devices ▪ Using medications: traditional non-steroidal anti-inflammatory drugs and cyclo-oxy-genasa-2 inhibitors; using opioids is not advisable
Respiratory problems	▪ Using pneumococcal vaccine and annual flu shots ▪ Using non-invasive methods: complementary oxygen
Dysphagia	▪ Change of diet ▪ Using special swallowing techniques
Psychosocial difficulties	▪ Conducting an interdisciplinary approach with a psychologist, a social worker and a psychiatrist

Source: Own elaboration.

Finally, the rehabilitation phase should be considered, especially if it is carried out during the acute phase of the disease. When rehabilitation is carried out late, an evaluation should be made that includes muscle, orthopedic, trophic, respiratory and functional examination. The techniques are chosen according to the findings. The duration of the rehabilitation should be adapted to a precise objective and it is only extended in particular cases. (26)

CONCLUSIONS

PPS is a clinical entity difficult to diagnose and treat that requires an interdisciplinary plan to achieve improvement of the initial symptomatology. Based on the fact that management is symptomatic, an improvement in the patient's lifestyle should be achieved to secure a good quality of life. In order to diagnose this entity, the person's childhood history must be kept in mind and the medical history of the past year should be analyzed to determine if the symptomatology has prevailed over time. Although it is incurable, prognosis is positive as long as good therapeutic and symptomatic management is carried out.

Current studies seek to determine if there is an immunological component in PPS, since evidence has shown a correlation with the immune response to inflammation around motor neurons or muscle fibers. This opens a window for young researchers to propose projects that allow searching for alternatives for this type of clinical entities.

CONFLICT OF INTEREST

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