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STREPTOCOCCAL TOXIC SHOCK SYNDROME AND CLARKSON'S DISEASE: CASE REPORT

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INTRODUCTION

In 1987, Cone described for the first time in the literature two cases of patients who had streptococcal cellulitis caused by group A Streptococcus, with clinical presentations similar to the toxic shock syndrome caused by Sthaphylococcus aureus. Two years later, Stevens, in 1990, reported a series of 20 patients who had infections which were confirmed with the identification of group A streptococcus. Streptococcus pyogenes, or group A beta-hemolytic streptococci (GAS), are gram-positive bacteria that cause a wide range of infections. They are normally found in the throat and on the skin of healthy people, without causing any disease.

Occasionally, these bacteria can cause streptococcal pharyngitis and/or skin infections such as cellulitis and scarlet fever. However, they can cause more serious conditions, such as an invasive group A streptococcal infection, necrotizing fasciitis, septic arthritis, toxic shock syndrome, among others. In addition, in rare presentations, the patient may develop Systemic Capillary Extravasation Syndrome, also known as Clarkson's Disease. In this case, the patient manifests with hypotension, hypoalbuminemia and hemoconcentration, which occur due to an extension of the endothelial lesion and loss of plasma and proteins into the interstitial compartment.

OBJECTIVE

To describe a clinical case of a patient with Streptococcal Toxic Shock Syndrome, who evolved with Systemic Capillary Extravasation Syndrome, and its importance in early diagnosis with immediate therapy, in order to obtain better clinical outcomes.

METHOD

This paper is a descriptive clinical case report based on the patient's clinical history and medical records. In addition, the report is based on a bibliographic review of the subject in the main databases, such as PubMed, UpToDate, Scielo and the National Institute of Health (NIH),

CASE REPORT

This was a 35-year-old male patient from Bragança Paulista, in a situation of social vulnerability, previously under lockdown, currently homeless and with a history of untreated tuberculosis. He was admitted by the general surgery team at the Hospital Universitário São Francisco (HUSF) in Bragança Paulista. O he patient came to the emergency room due to a fall from a height of approximately one meter, evolving with a complaint of progressive low back pain, intense myalgia, prostration and fever that had not been measured for 5 days. He was conscious, oriented, in good general condition, slim and did not require ventilatory support. However, within a few hours of admission, the patient's general condition worsened, and he became confused, obese, hypotensive and hemodynamically compromised. As a result, the patient's level of consciousness dropped and orotracheal intubation and mechanical ventilation were chosen. The patient progressed rapidly, with hypotension and tachycardia, requiring volume expansion and a progressive increase in the doses of vasoactive drugs. On physical examination, hematomas were found on the back, but there were no other alterations,

Laboratory tests revealed metabolic acidosis with increased lactate (146mg/dL), normocytic and normochromic anemia (Hb: 12.5g/Dl, HT 35.8%; VCM 88fL; HCM 30.7pg; RDW 12.6%), leukopenia with neutropenia and lymphopenia (Leukocytes 2700 mm^3 ;

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neutrophils 1890mm^3 and lymphocytes of 567 mm^3), an increased C-reactive protein (CRP) (284 mg/dL), indicators of liver damage (TGO 505 U/L and TGP of 249 U/L). The patient had been anuric for the last 12 hours, with renal dysfunction (Creat 1.4 mg/dL, urea 87 mg/dL), hypoalbuminemia (1.2 g/dL albumin). He maintained an average blood pressure of 65 mmHg at the expense of noradrenaline, vasopressin and adrenaline in optimized doses and corticotherapy. During the laboratory investigation, serologies were investigated and the diagnosis of HIV (human immunodeficiency virus) was made. In the imaging tests, the bedside Pocus revealed pericardial effusion and right ventricular dysfunction. A CT scan of the thoracic spine revealed edema of the paravertebral fatty muscles on the right and a CT scan of the lumbar spine revealed areas suggestive of intramuscular hematomas on the right. The chest CT scan showed images suggestive of granulomatous disease, the main hypothesis being tuberculosis and pleural effusion on the right. The abdominal CT scan showed fluid extending from the peri-hepatic region to the pelvis and subcutaneous edema on the right flank and back. During the current hospitalization, the skin in the patient's thoracic region took on a purple-erythematous hue, becoming hardened, swollen, shiny and with an increased temperature. It evolved with the eruption of vesicles and the formation of blisters, and consequently skin gangrene.

Given the patient's clinical condition, with a previous history of possible exposure to opportunistic diseases such as tuberculosis, in a situation of social vulnerability such as homelessness and possible drug use (unconfirmed), as well as previous trauma, the hypothesis of distributive shock, such as septic shock or SIRS, was raised. In addition, the scenario of a patient who, despite volume expansion, was poorly distributed with loss of volume in the third space, led to the possibility of Clarkson's disease. To corroborate our hypothesis, the patient had hypoalbuminemia (serum albumin of 1.2). This was not consistent with the patient's physical biotype and there was no previous history to justify this loss of albumin, other than in an acute form. Therefore, the hypothesis of invasive infection by Group A *Streptococcus pyogenes* (GAS) was put forward, causing the toxic shock and capillary extravasation responsible for the hypoalbuminemia, hemoconcentration and hypovolemic shock. Subsequently, infection with Group A *Streptococcus pyogenes* (GAS) was confirmed in positive blood cultures.

Figure 1

Source: own archive.

DISCUSSION AND RESULTS

Streptococcus pyogenes (GAS) is an aerobic, coccal, gram-positive species that belongs to the beta-hemolytic genus of Lancefield's group A. It is commonly associated with cases of pharyngitis and non-necrotizing skin infections. It is commonly associated with cases of pharyngitis and non-necrotizing skin infections, in some scenarios, especially in the presence of risk factors, it is responsible for invasive infections, such as necrotizing soft tissue infection, pregnancy-associated infection, bacteremia and respiratory tract infections and in two thirds of cases, it complicates with Streptococcal Toxic Shock Syndrome. Its ability to trigger serious clinical conditions is directly associated with its various virulence factors, such as the presence of M and M-like proteins in its cell wall, which are responsible for facilitating adhesion and invasion of the bacteria. These proteins prevent the opsonization of the bacteria by component 3 (C3) of the complement system, so that prevents phagocytosis of the invader. In addition, GAS is capable of synthesizing Spe (streptoococcal pyrogenic exotoxins) A, C and G, which act as superantigens, i.e. they are capable of directly stimulating the MHC class II receptors of T lymphocytes, regardless of the antigenic presentation made by the antigen-presenting cells. In this context, there is an intense production of cytokines by activated lymphocytes, as this mechanism is capable of initiating a massive proliferation of T lymphocytes, which triggers a large release of cytokines, especially tumor necrosis factors (TNF) alpha and beta, interleukins (IL)-1 and IL- 2 and interferon (IFN)-gamma.

Secondary to this storm of inflammatory cytokines, there is an increase in capillary permeability and systemic tissue damage. These and other virulence factors make GAS an important bacterium in our environment. For this reason, in 2022 the Pan American Health Organization issued an Epidemiological Alert due to the growing number of invasive diseases caused by group A streptococcus. Among the risk factors for developing an invasive GAS infection are traumas, especially those that result in bruising or muscle distension, chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), recent surgery, HIV infection, intravenous drug use, homelessness, postpartum status, burns and others. Its form of invasive infection, in the absence of shock, includes necrotizing soft tissue infection, pregnancy-associated infection, bacteremia and pneumonia. Necrotizing soft tissue infection leads to involvement of the epidermis, dermis, subcutaneous tissue, fascia and muscle.

These presentations can be complicated by the appearance of Streptococcal Toxic Shock Syndrome. This is characterized by intense capillary leakage and tissue damage due to the presence of streptococcal toxins, which trigger shock and multiple organ failure. It is an extremely critical scenario, in which the patient may present with severe hypotension, which persists despite drug therapies, tachycardia, fever, multiple organ and system involvement, with renal failure, liver failure, acute respiratory distress syndrome and disseminated intravascular coagulation. Some patients may report pain at the site of the trauma, which usually precedes localized edema and local erythema, which can evolve with ecchymoses and peeling of the skin and eventually develop into necrotizing fasciitis in a short space of time. In the clinical case reported, a systemic disease, its hyperacute evolution, the hypotensive condition, refractory to vasopressor drugs and, in addition to the dermatological manifestation, added to the marked risk factors for the development of Streptococcal Toxic Shock Syndrome, the suspicion that it was an infection caused by streptococcus was discussed. Therefore, in order to reach a diagnosis, blood cultures were requested after the patient's hospitalization, which came back positive for Group A *Streptococcus pyogenes* (GAS).

Despite the appropriate treatment for the case, the skin lesions and the patient's condition intensified. This led the team to suspect Capillary Extravasation Syndrome, which is caused by two different mechanisms. In this patient, the dermatological lesions caused intense protein expenditure, predisposing the patient to hypoalbuminemia, as seen in the tests. In addition to the fact that the infection caused by *Streptococcus pyogenes* led to significant endothelial damage due to the presence of cytokines, interleukins, tumor necrosis factor, among others, as already mentioned in this discussion. These increased vascular permeability and the loss of protein-rich fluid from the intravascular space to the interstitial space, thus causing volume depletion and worsening the case with the development of Clarkson's disease. A significant protein loss is seen, which generates compensatory hypermetabolism and a vigorous increase in metabolic rate, leading to accelerated blood flow, which can predispose to hypothermia and an inability of the patient to respond to vasoconstriction and/or vasodilation in an attempt to maintain body vascular resistance.

Systemic Capillary Extravasation Syndrome, or also known as *Clarkson's disease*, is characterized by a condition in which there is an intense loss of protein content from the intravascular to the interstitial space and an increase in capillary permeability, which leads to a loss of intravascular volume. Consequently, the patient develops hypovolemic shock. The syndrome was described in 1960 by physician Bayard Clarkson, in which his patient presented with a low-grade fever, hypotension and edema of the face, arms and legs. She progressed rapidly with unexplained shock and anasarca, dying of pulmonary edema and heart failure. At the time of this case, Dr. Clarkson's studies showed that his patient was the victim of a syndrome that leads to rapid plasma extravasation due to an intense increase in capillary permeability, followed by hemoconcentration and vascular collapse. This syndrome can occur idiopathically, where crises occur at regular intervals and are triggered by menstruation, allergies and sinusitis. It can be associated with skin diseases such as erythroderma and psoriasis, as well as the drug-induced form, such as granulocyte colony-stimulating factors.

Early and careful administration of intravascular fluids is the most important component in the therapy of patients with capillary leak, which can stabilize blood pressure and improve patient dynamics. In cases refractory to volume resuscitation, vasopressors are necessary, always remembering that volume resuscitation is the priority. Although the administration of albumin seems a viable choice to complement volume expansion, in these patients, the continuous loss of damaged endothelium attenuates the effectiveness of albumin. For this reason, it is extremely important to implement specific therapy for the underlying disease in order to reduce the production of cytokines that cause endothelial damage and reverse capillary leakage.

CONCLUSION

Given the clinical case presented, with the diagnosis of Streptococcal Toxic Shock Syndrome leading to the development of Capillary Extravasation Syndrome. The extremely rapid deterioration of the patient, even with appropriate treatment, highlights the hemodynamic aggressiveness of these syndromes. In addition, there is a lack of literature on Capillary Extravasation Syndrome that discusses its diagnosis and treatment. It is therefore important that it is a diagnosis considered in any patient presenting with shock, such as sepsis, even if there is no infectious focus identified. A better awareness of its pathology can lead to early identification of the case, allowing for better treatment.