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CASE STUDY OPEN ACCESS

BROCQ-LYELL SYNDROME INDUCED BY PHENYTOIN. CLINICAL CASE

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ABSTRACT

Stevens Johnson Syndrome (SJS) has been defined as a vesiculobullous multiforme erythema of the skin and other organs. It is considered to be the initial stage of a skin reaction which most severe form of presentation is Toxic Epidermal Necrolysis (TEN), characterized by intense pain and loss of the epithelial surface (greater than 30% of the body surface), compromising the vital functions of the organism, that produced electrolyte imbalance, kidney and ocular involvement, with high catabolism and potential risk of sepsis. Etiologically it is related to the use of drugs in 80% of cases. The treatment includes several immunomodulators, among which are systemic corticosteroids, cyclosporine, intravenous immunoglobulin, cyclophosphamide, plasmapheresis and inhibitors of tumor necrosis factor alpha. We reported a case of a 27-year-old woman with anticonvulsant treatment with phenytoin, who developed a NET which she survived due to the multidisciplinary approach in the hospital unit.

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INTRODUCTION

Stevens Johnson Syndrome (SSJ) was described in 1922 by Stevens and Johnson as a febrile illness accompanied by stomatitis, purulent conjunctivitis and skin lesions (Aviakian, 1991 and Ortiz, 2001). It is defined as a generalized bullous multiforme erythema that compromises skin and mucous membranes. Currently, it is considered as the initial stage of a dermal reaction whose most severe presentation is the Toxic Epidermal Necrolysis (NET), acute systemic inflammation that compromises the skin, mucous membranes and respiratory and intestinal epithelia. They are synonymous with NET, Lyell or Brocq-Lyell syndrome, large-burn syndrome and disseminated acute epidermal necrosis type 3 (Roujeau, 1995). Its distribution is worldwide, affecting all races, ages and both sexes.

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The annual risk is 0.4 to 2 cases per million inhabitants. Mortality can reach up to 70% in cases of NET (Roujeau, 1994 and Crosi, 2004). In the etiology of this entity, the use of various pharmacological groups has been implicated in more than 80% of the cases studied; cases are described after the use of anticonvulsant treatments in 15% (Diphenylhydantoins, Carbamazepines, Lamotrigine), non-steroidal anti-inflammatories and Alopurinol in 33%, as well as antibiotics that represent the largest proportion with 34 to 80% of cases (Sulfamides, Aminopenicillins, Quinolones and Cephalosporins) (Pacheco, 2001 and Ortiz, 2001). In the pathophysiology of the disease, it suggests that the active metabolites of the drugs behave like haptens attached to proteins in the basement membrane and in the bridging of the epidermal cells mediated by T lymphocytes (cytotoxic) and macrophages with cytokine release. This generates toxic reaction and direct cellular necrosis that induces expression of keratinocyte apoptosis promoter proteins, with extensive separation of the epidermis and mucous membranes (Magnelli,

and Estrella-Alonso, 2017). The typical case of NET described by Lyell, takes place in 3 phases: prodromal, necrolysis and reepithelialization. The first phase is characterized by a catarrhal prodrome, with a fever of 39-40º C, asthenia, headache, odynophagia, nausea, vomiting, myalgia and arthralgia, with a variable duration generally of 48-72 hours, but it can last for weeks (Estrella-Alonso, 2017). The second phase is characterized by the appearance of papular, erythematous, target-shaped skin lesions (white, "bulleye" or "target"), painful, initially on the face and trunk, which then extends to the extremities. Subsequently, vesiculobullous lesions appear in the mucosa of the conjunctiva, nasal, oral, as well as vulvovaginal, anorectal and urethral regions, with formation of pseudomembranes and thus compromising important functions of the individual such as food and urination (Estrella-Alonso, 2017). Photophobia also appears with bilateral catarrhal conjunctivitis, purulent and even corneal ulcers and hemorrhagic areas that leave serious sequelae. The severity of the condition is proportional to the necrotic extension of the skin and is both an important prognostic factor for survival. The potential bacterial colonization, together with a diminished immune response, increases the risk of sepsis. There is a massive loss of transepidermal fluids associated with a hydroelectrolytic imbalance and the appearance of prerenal insufficiency is also common; A frequent complication in these patients is the establishment of a hypercatabolic state with inhibition of insulin secretion and resistance to it and, less frequently, diffuse interstitial pneumonitis that can lead to acute respiratory failure syndrome. Due to the great similarity between the clinic of the SSJ and NET, Bastuji-Garin et al. conducted a study in 1993 in which criteria were defined for the classification of both diseases, determining as SSJ cases with an epidermal compromise less than 10% of body surface area (SC) affected and as NET cases with a condition greater than 30% of SC affected. Cases between 10 and 30% of affected CS would be established as a superposition of both pathologies. In atypical or doubtful cases, skin biopsy is useful, which will reveal varying degrees of keratinocyte necrosis, surrounded by lymphocytes, edema of the papillary dermis, poor perivascular lymphohistiocytic infiltrate and subepidermal blistering (Bastuji-Garin, 1993 and Zhang, 2019).

The differential diagnosis is faced with various dermal reactions, mainly with those of desquamative and exfoliative type such as Scalded Skin Syndrome, Pemphigus vulgaris, Bullous Pemphigoid, Herpetiform Dermatitis, Impetigo and Kawasaki Syndrome, among others. In NET it is important to remember the increased skin sensitivity and the positive Nikolsky sign as diagnostic keys for its distinction. As for the treatment, the identification and suspension of the drugs potentially responsible for the pathology is essential, as well as the treatment of precipitating infections. In patients with extensive conditions, their attention should be considered in an Intensive Care Unit or in a Burned Unit. Being an immunological reaction, human immunoglobulin (0.5 to 1 g / kg / day) is used intravenously, with favorable results due to its immunomodulatory effects. Corticosteroids, in short treatments at the onset of the disease, are also beneficial, as well as cyclosporine, intravenous immunoglobulin, cyclophosphamide, plasmapheresis and alpha tumor necrosis factor inhibitors, may be favorable, although ideal therapy remains a matter of debate. Among the most common causes of death are; sepsis, acute respiratory failure syndrome and multiple organ failure (Gupta, 2016). Survival of SSJ / NET has increased considerably in recent years, but long-term sequelae remain frequent. The regeneration of the epidermis or reepithelialization period occurs within 3 weeks, being the last to regenerate the periorificial and pressure areas (Ortiz, 2001).

Clinical case

A 27-year-old female patient, from the urban environment of the state of Guerrero, with a history of esquirlectomy and dura mater plasty on February 20, 2019, secondary to a gunshot wound in the skull, lower jaw and right shoulder, with sequelae of monoparesis of the left upper limb, he required during transfusion hospitalization of 4 erythrocyte concentrates, with a 7-day hospital stay, graduated phenytoin-based antiepileptic contracting (100mg every 8hrs) and broad-spectrum antibiotic therapy (ofloxacin 400 mg orally every 8 hours). After 4 days of outpatient management, he presented with hyporexia, poor general condition, erythematous labial mucosa, hyperemic conjunctiva, presence of herpetic oral pain lesions, painful, with abundant sialorrhea and odynophagia, for which hospital admission was decided in the department of Internal Medicine section of Dermatology. On physical examination, patient in poor general condition, tachycardia, febrile (39 ° C), hypertensive, with the appearance of a large burn (80% of total body surface). It is managed intrahospitally with intravenous antibiotic therapy (Ceftriaxone). Additionally, general supportive care was established, diphenylhydantoin and NSAIDs were suspended due to the possible diagnosis of erythroderma by medication. During the first 24 hours of his admission, she attended with greater clinical deterioration with toxic appearance, edema in the mouth and lips, rash installed in the maculopapular cephalo-caudal direction, not pruritic, with a positive Nikolsky sign in the extremities and thorax, subsequently added bladder irritation data. Medical treatment with methylprednisolone and consecutively prednisone was initiated.

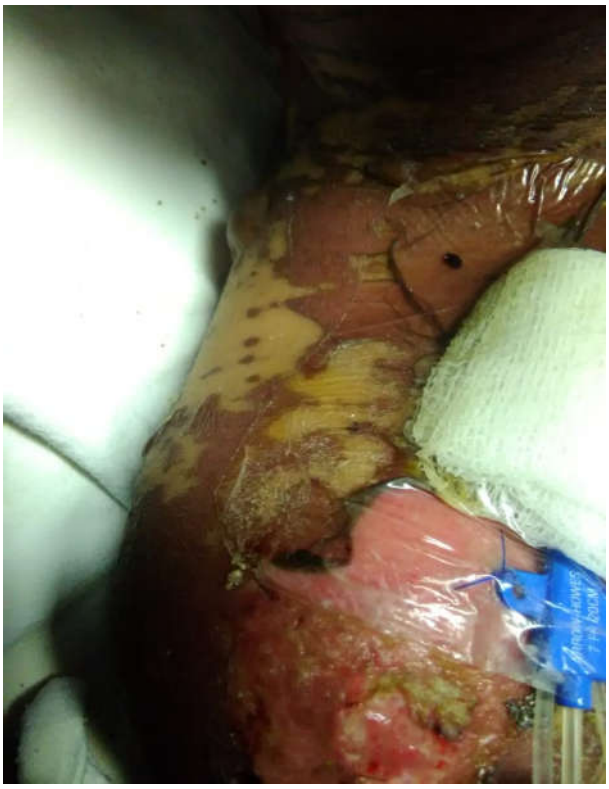

Figure 1. Nikolsky's sign in Lyell syndrome. Epidermal detachment when rubbing with the finger

At 48 hours after admission, confluent vesicles and scaling appeared, with a serous fluid content, with a burning sensation to the touch, these in the anterior and posterior thorax, cheeks and ear pavilions, bleeding lips, oral cavity with cheilitis and limitation of opening, ulcerations in palate, cheeks, tongue and gums, as well as facial edema. At the pulmonary level, thick transmitted crackleswere auscultated, presence ofacrocyanosis and respiratory distress characterized by intercostal and subcostal circulation, nasal flutter, with 95% pulse oximetry saturation, which is why it is managed with supplementary low flow oxygen.

Figure 2. Oral and conjunctival mucosa involvement. A) Oral mucosa lesions initially characterized by vesicles that eroded forming hemorrhagic ulcerations. B) Conjunctiva involvement with bilateral and purulent conjunctivitis

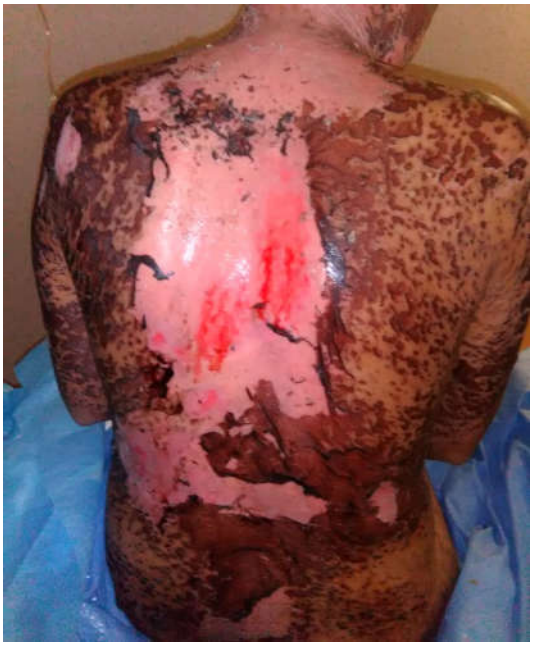

Figure 3. Necrosis phase. Generalized dermatosis that affects> 30% of body surface with a predominance in the face and trunk characterized by purpuric lesions that give rise to large blisters which evolve leaving areas of denuded skin with the appearance of "great burn"

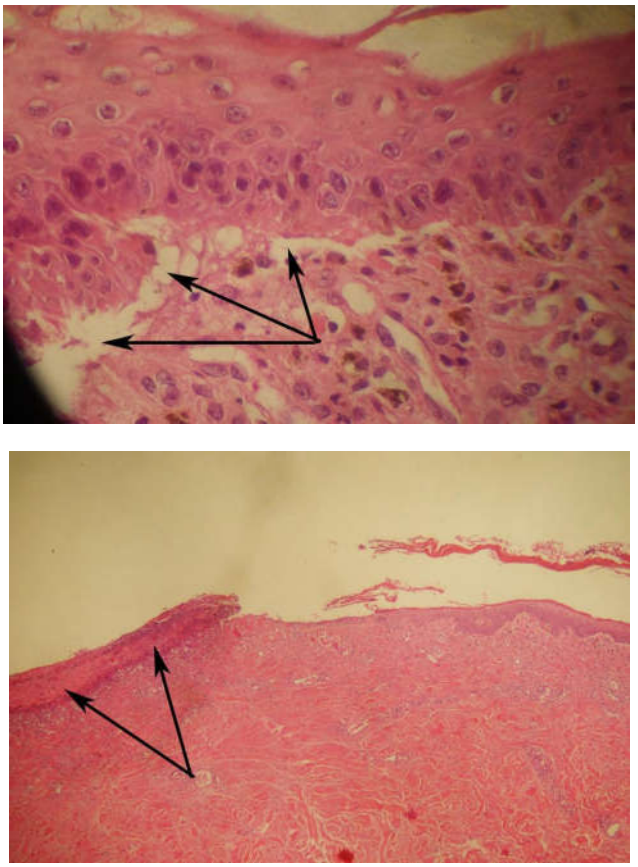

Figure 4. Intraepidermal spongiosis and vacuolization of the basement membrane are observed with an inflammatory infiltrate of diffuse lymphocytic predominance in the dermis. The biopsy shows multiple apoptotic keratinocytes

In the third and fourth days of hospitalization, an important epidermis aspect was observed, mainly in the face, loss of eyelashes, mucosa of cheeks and back-lingual mucosa, of anterior and posterior thorax, upper abdomen, upper portion of both arms, calculating 95% of affected body surface. The hydroelectrolytic contribution was increased, a 3-way central venous catheter was placed in the right subclavian area in addition to analgesia with nalbuphine and Tramadol. Figure 3

Laboratory test

Hematic Biometrics: Hb: 10.59 g/dL, Hto. 31.3%, VCM 88.6 fL, HCM 30.4 pg, Leukocytes 7 K/uL, Lymphocytes 21 %, Eosinophils 3 %, Segmented 66 %, Bands 0 %, Monocytes 5 %, Platelets 233,000 K/uL

General urine test: Density 1.015, Ph 7.5, Yellow color, Leukocytosis 364 / field / piocytes, Moderate bacteria and Moderate epithelial cells. Negative rest.

Electrolytes: Na 133 mEq, K 3.9 mEq, Cl 102 mEq.

Blood chemistry: Glucose 155 mg / dL, urea: 23.5 mg / dL; BUN: 11 mg / dL; Cr: 0.6 mg / dL, uric acid 2.2 mg / dL

Liver function tests: Total bilirubins 0.20 mg/dL, indirect bilirubin: 0.1 mg / dL, Total proteins 5.4 g/dL, Albumin 2.4 g/dL, Globulins 3.0 g/dL, Alkaline phosphatase 51 U/L, ALT 24 U/L, AST 26 U/L, Glycemia 80 mg / dL and Creatinine 0.43mg/dL.

Arterial blood gas with pH 7.45; PCO2: 24.2 mmHg; PO2: 64.1 mmHg; SO2%: 94.4; FIO2: 21%; HCO3: 16.6 mmol/L; base (Ecf): –6.6mmol / l, and PO2 / FiO2: 305 mmHg

A skin biopsy was taken in the right inguinal region that confirmed the structural alterations as a severe form of Erythema multiforme of the Toxic Epidermal Necrolysis type, probably secondary to drugs (Anticonvulsants). The bloody areas extended to 90% of SC as well as the oral and perianal mucosa, with easy bleeding, which were covered with Lassar paste and mupirocin ointment. Local medication based on ophthalmic drops with Chloramphenicol ointment and eye lubricant was placed on both corneas. Serial mechanical washes were performed under sedation and analgesia, the wounds were covered with hydrocolloid dressings and lesions were reepithelialized until the second week. Its evolution was towards the improvement of the general state, without recurrence of the systemic inflammatory response and improved biochemical tests, was discharged after 12 days of hospitalization and continued in medical treatment in outpatient clinic. It currently has sequelae due to skin dyschromia and starts walking with help, as well as tolerance to food by mouth.

DISCUSSION

Stevens Johnson Syndrome and Toxic Epidermal Necrolysis, two rare, but severe forms of presentation of mucocutaneous bullous diseases, which share similar clinical and histopathological characteristics, but differ in the extent of dermal involvement (Garcia, 2000 and Bastuji-Garin, 1993). The acute inflammatory reaction associated with drugs is caused by immune disorders. Viral infections and drug interactions act as a cofactor or as predisposing or precipitating factors and the genetic load is responsible for the specific metabolism against drugs and also for susceptibility to adverse reactions. We describe a clinical case of NET in a 27-year-old woman, with the use of anticonvulsant drugs (phenytoin) as a possible etiological factor involved in this entity. It is estimated that 5% of patients treated with these drugs have some type of these reactions. In the case we present, phenytoin therapy for 11 days seems to be an influential and determining factor in the appearance of the dermal reaction (Pacheco, 2001). There is no unified treatment in the world due to the low incidence of NET, resources in different parts of the world are variable and the therapeutic approach depends on the inputs available6. Treatment with methylprednisolone and prednisone steroids, general measures and dermal care, led to a satisfactory resolution of the condition, with involution of the lesions at 12 days, without the need for surgical management of the lesions and recovery of the integrity of their skin, but with dyschromia in previously affected areas. The most common poor prognostic factors are anemia and lymphocytopenia[10,16]; but to standardize the degree of severity and at the same time the prognosis, the SCORTEN scale has been designed, which evaluates parameters such as: age, malignancy, tachycardia, initial body surface affected, BUN, glucose and bicarbonate, which must be calculated within the 24 hours after admission and on the third day[11,14,15]. Our patient presented a score of 2 points, during the first and third day of hospital stay, corresponding to an estimated mortality> 12.1%. The definitive diagnosis was made with the histological examination that reported necrotic epidermis, early, necrosis with intensely eosinophilic cells in the epidermis, poor mononuclear infiltrate in the dermis and, late, extensive confluent necrosis of the entire epidermis. In addition, subepidermal blisters and an inflammatory infiltrate are observed which, depending on its extension, is related to mortality: if the infiltrate is mild, the mortality is 27%; if it is moderate, mortality is 53% and if it is severe, mortality is 71% (Quinn, 2005).

Conclusion

The skin and mucous membranes are the most affected in an allergic reaction. However, only a small percentage of skin reactions pose a vital risk or lead to significant sequelae. Treatment is limited to the early recognition of symptoms, withdrawal of the medication involved and life support measures. Clinicians should carefully evaluate all adverse skin reactions and quickly discontinue dispensable medications, especially when there are signs or symptoms that may indicate the onset of a serious skin reaction, as it was in the case presented.

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