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CASE REPORT

Etanercept associated with pulse therapy with corticosteroids in toxic epidermal necrolysis: case report

Etanercept associado a pulsoterapia com corticoesteroides na necrólise epidérmica tóxica: relato de caso

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Abstract

Toxic epidermal necrolysis (TEN) is a rare dermatological disease characterized by necrolysis of the epidermis on more than 30% of the body surface, which occurs days or weeks after the use of a medication or the causative disease. This report is about a case of TEN related to the use of allopurinol in a 61-year-old female patient admitted to a burn intensive care unit, in which she received multidisciplinary care. There are several treatment options; however, there is no gold standard. In this paper, the patient was treated primarily with corticosteroid pulse therapy, and then, with the administration of etanercept, there was a significant and rapid improvement in the lesions. This drug reduces mortality and reduces the time for re-epithelialization. Although etanercept is a promising treatment, as a monotherapy and in combination therapy, high-level evidence is still needed to support its routine use.

Keywords: Drug-related side effects and adverse reactions. Etanercept. Stevens-Johnson syndrome.

Resumo

A necrólise epidérmica tóxica (NET) é uma doença dermatológica rara, caracterizada pela necrólise da epiderme em mais de 30% da superfície corpórea, que ocorre dias ou semanas após o uso de uma medicação ou doença causadora. Este relato é sobre um caso de NET relacionada ao uso de alopurinol, em uma paciente do sexo feminino, de 61 anos, internada em uma unidade de terapia intensiva de queimados, em que recebeu cuidado multidiscplinar. Existem diversas opções de tratamento direcionado, no entanto, não há um padrão-ouro. Neste caso, a paciente foi tratada primariamente com pulsoterapia com corticoesteroide e, em seguida, com a admistração de etanercept, houve expressiva e rápida melhora das lesões. Esta droga cursa com redução da mortalidade e diminuição do tempo para reepitelização. Embora o Etanercept se mostre promissor, tanto como monoterapia quanto como terapia combinada, evidências de alto nível ainda são necessárias para apoiar seu uso rotineiro.

Palavras-chave: Etanercepte. Efeitos colaterais e reações adversas relacionados a medicamentos. Síndrome de Stevens-Johnson.

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Introduction

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are rare medication-induced conditions characterized by skin necrosis and mucocutaneous involvement associated with severe systemic symptoms. SJS and TEN appear, most commonly, between 1 and 4 weeks after drug exposure[1].

In addition to cutaneous involvement, there is mucosal involvement in 80% of cases. Oral mucosa is more commonly involved. SJS's total body surface area is < 10%, whereas TEN involves more than 30%, and SJS/TEN overlaps between 10% and 30%. The diagnosis is based on clinical and histological criteria[2].

High-dose systemic corticosteroids (CS) have been standard therapy for over 20 years. However, no treatment has been shown to be effective. Recent studies demonstrate that treatment with tumor necrosis factor-α (TNF-α) antagonists, such as etanercept, reduces mortality and decreases re-epithelialization time[3].

Case report

J.A.P.L, 61-year-old female patient, resident of Curitiba, Paraná, Brazil, with a history of hypertension and hypothyroidism, using enalapril, hydrochlorothiazide, and levothyroxine, was admitted in July 2024 to a burn intensive care unit (ICU). The patient presented with widespread cutaneous involvement characterized by epidermal detachment and necrosis, resembling a large burn, affecting both upper and lower extremities, the chest, back, and facial region; Nicolsky sign was positive. The clinical picture was suggestive of TEN.

The patient initially presented prodromal symptoms including fever, asthenia, pruritus, and upper respiratory tract manifestations. Due to respiratory complaints, medical attention was sought, and amoxicillin was prescribed. Cutaneous lesions developed 3 days after the initiation of antibiotic therapy. Notably, the patient had also been on allopurinol 300 mg daily, initiated approximately 1 month before the onset of skin involvement. Causality assessment using the algorithm of drug causality for epidermal necrolysis scoring system indicated a higher probability that allopurinol was the culprit drug, with a score of 6, consistent with a "very probable" association.

On admission to the ICU, SCORTEN was calculated, a score to calculate the severity and mortality rate of patients with TEN, which scored 4, predicting a mortality rate of 60%. On the 1st day of ICU admission, a lesion biopsy was performed, and the anatomopathological examination suggested TEN.

As initial therapy, a pulse of methylprednisolone (1 g every 24 h, for 3 days) was administered, without significant improvement in the condition. One day after the end of pulse therapy, treatment with etanercept was started: four doses of 50 mg were administered subcutaneously, in regions unaffected by the lesions, with a 3-day interval between them.

During treatment with etanercept, the patient showed progressive improvement of the lesions (Figs. 1 and 2). At the end of the four doses, she presented erythematous scaly plaques on her arms bilaterally, back, and legs, and erythematous erosion plaques on her buttocks; 16 days after the last dose, the patient had significant improvement.

Ten days after hospital discharge, lesions had almost completely regressed, presenting only violet plaques on the trunk and upper and lower limbs, without epidermal detachment or bullous lesions, and with small pustules on the limbs.

During her hospitalization, she underwent seven debridements of devitalized tissue by the plastic surgery team in the surgical center, with dressings made with rayon, Vaseline, collagenase, wadding, and bandage.

At the time of the patient's admission to the ICU, laboratory evaluation revealed hemoglobin of 11.8 g/dL, leukocyte count of 7250/mm^3 with 71% segmented neutrophils, platelet 237,100/mm^3, urea 115 mg/dL, creatinine 1.60 mg/dL, aspartate aminotransferase 29 U/L, alanine transaminase 115 U/L, total bilirubin 1.11 mg/dL, alkaline phosphatase 140 U/L, and C-reactive protein (CRP) 28.46 mg/L. Serologic testing for hepatitis B and C, human immunodeficiency virus, and syphilis was negative, as were autoimmune markers including antinuclear antibodies and anti-Ro antibodies.

At the time of ICU discharge, following completion of treatment with etanercept, laboratory tests showed hemoglobin of 9.4 g/dL, leukocyte count of 7200/mm^3 with 62% segmented neutrophils, platelet 348,600/mm^3, and CRP 2.55 mg/L. Liver and renal function markers had normalized, and all blood cultures obtained throughout hospitalization remained negative. The patient remained hospitalized for a total of 17 days, 15 of which were spent in an intensive care bed.

Discussion

The main medications associated with TEN are allopurinol, antiepileptics (carbamazepine, phenytoin, phenobarbital), antibiotics (sulfamethoxazole, β-lactams,

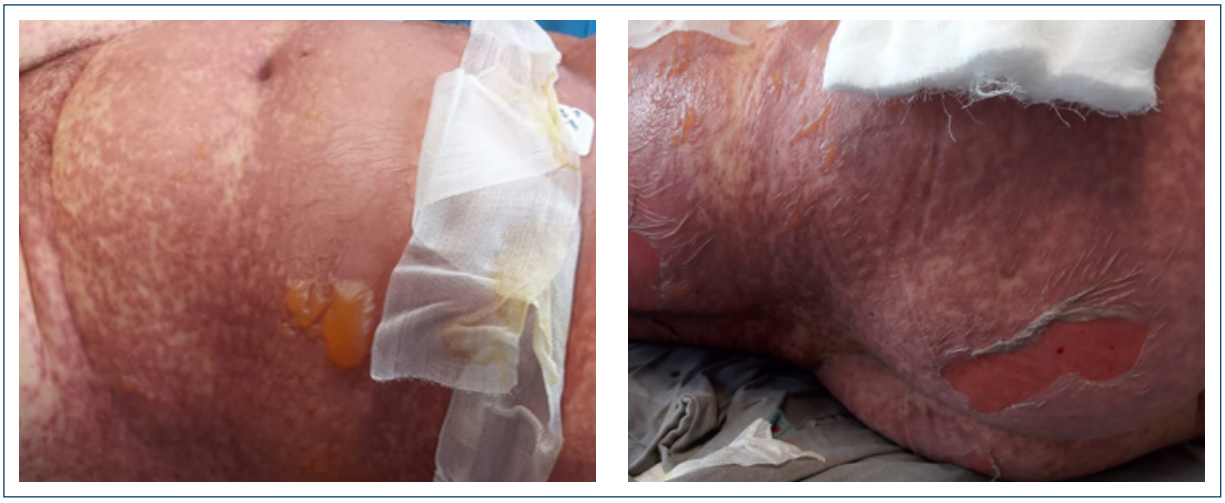

Figure 1. Initial progression of the exanthema with coalescence of lesions, blister formation in the abdomen, and early epidermal detachment (left) on the dorso. Final progression to extensive sheet-shaped epidermal detachment (right).

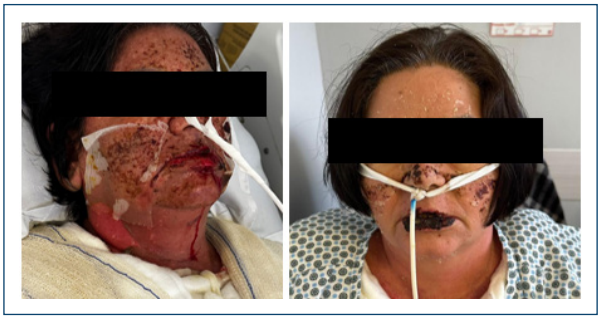

Figure 2. Involvement of the oral mucosa, conjunctiva, and face before starting Etanercept (left) and a few days after starting Etanercept (right).

and quinolones), and antiretrovirals (abacavir and nevirapine), among others[4].

The diagnosis of TEN is based on clinical and histological criteria. Histological findings include full-thickness epidermal necrosis, lymphocytic infiltrate at the dermal-epidermal junction, CD4+ T cells in the dermis and CD8+ T cells in the epidermis, and endothelial apoptosis[5].

Regarding supportive treatment, it should preferably be conducted in a specialized burn center, where there is multidisciplinary management and professionals specialized in dealing with life-threatening wounds. Furthermore, suspending causative medication, protecting the airways if necessary, replacing fluids, performing early enteral nutrition, dressing wounds, and arranging an emergency ophthalmological consultation are essential. Moreover, close monitoring for infections – one of the most common and serious complications of NET – is crucial to ensure timely intervention and improve patient outcomes[1].

Several adjuvant therapies have been used, including high-dose CS, intravenous immunoglobulins (IVIG), plasmapheresis, cyclophosphamide, cyclosporine A, and TNF-α inhibitors (etanercept and infliximab). However, there is a lack of consensus regarding the appropriate management of SJS and TEN[1].

The choice of therapy for SJS/TEN should be based on an individualized assessment of the patient, considering factors such as disease severity, comorbidities, response to previous treatments, and risk of adverse effects[6]. In our case, corticosteroid pulse therapy was used combined with etanercept.

The pathophysiology of TEN is not yet clear. However, studies show increased levels of TNF-α in skin biopsy samples or blister fluid and serum from patients with TEN. Therefore, biological therapies with TNF-α antagonists – infliximab and etanercept – are being further studied[3,7].

TNF-α inhibitors have demonstrated therapeutic potential in various inflammatory dermatoses, including cutaneous polyarteritis nodosa (CPAN), where TNF-α contributes to vascular inflammation and ulcer formation. Despite differing etiologies, TEN and CPAN exhibit TNF-α–driven inflammation, supporting its role as a shared therapeutic target. These observations highlight the need for further studies to validate the efficacy of TNF-α blockade in severe cutaneous inflammatory diseases[8].

Etanercept has been shown to reduce mortality rates and shorten the re-epithelialization time in TEN[3,7]. In a randomized study involving 96 patients with SJS-TEN, etanercept demonstrated superior clinical outcomes compared to CS. In addition, etanercept significantly decreased levels of TNF-α and granulysin in both blister fluids and the plasma of patients[7].

In the article by Ao et al., with a sample of 25 patients, the duration of the acute phase, time of CS use, length of hospitalization, and re-epithelialization were compared between a group that used methylprednisolone and another that used Etanercept plus methylprednisolone. The combined therapy performed better in all parameters[9].

There is also the possibility of using topical and systemic therapies, with particular emphasis on the use of 0.5% silver nitrate applied to denuded areas in combination with a single subcutaneous dose of etanercept. In a pilot series involving seven adult patients with SJS, this approach led to significant clinical improvement within 1 week and complete resolution of mucocutaneous lesions within 2 weeks, with a favorable safety profile[10].

According to the S3 Guideline "Diagnosis and Treatment of Epidermal Necrolysis" which is based on a systematic review aimed at providing an evidence-based framework for clinical decision-making in TEN, there is currently no high-quality evidence to support or refute the use of combination therapy with CS and etanercept. Furthermore, no statistically significant differences in mortality were observed when comparing CS plus etanercept to CS alone or CS combined with IVIG[6].

Although there is no established gold standard for the treatment of TEN, this case report highlights a potentially effective therapeutic approach. Despite the poor initial prognosis, the patient responded favorably to treatment, with successful re-epithelialization and complete recovery without residual disability. The combination of etanercept and CS appears to be a promising therapeutic option for TEN, as supported by emerging evidence. However, larger, randomized controlled trials are needed to further validate its efficacy and safety.

Conclusion

Toxic epidermal necrolysis (TEN) is a life-threatening condition associated with high morbidity and mortality rates, and currently, there is no established gold-standard treatment. However, the combination of systemic corticosteroids and etanercept has shown promising therapeutic outcomes. Despite these encouraging results, further studies are needed to validate its efficacy and support its routine use in clinical practice.

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None.

Conflicts of interest

None.

Ethical considerations

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

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

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

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