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Stevens-Johnson syndrome in a patient with rheumatoid arthritis during long-term etanercept therapy

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Abstract

Background: Etanercept and other anti-TNF-alpha agents have been indicated as a therapeutic option in severe drug reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Etanercept has been shown to quickly reduce the detachment of the epidermis and shorten healing time. Cases of etanercept-induced severe adverse drug reactions were also described.

Main observations: A 27-year-old woman with a 4-year history of etanercept and sulfasalazine treatment for rheumatoid arthritis was admitted with Stevens-Johnson syndrome. The patient received one dose of an OTC drug containing acetaminophen, phenylephrine and pheniramine two days prior to developing fist mucocutaneous symptoms. The most probable causative agent was paracetamol. Throughout the successful routine therapy of Stevens-Johnson syndrome etanercept therapy was continued. Sulfosalazin administration was stopped and administered again after recovery with no recurrence of the skin and mucosal symptoms.

Conclusions: This case indicates that there is no justification for discontinuation of long-term anti-TNF-alpha treatment in patients who develop Stevens-Johnson syndrome / toxic epidermal necrolysis. (*J Dermatol Case Rep*. 2016; 10(1): 14-16)

Introduction

Stevens-Johnson syndrome (SJS) is a type of acute, severe drug reaction that typically involves the skin and the mucous membranes. Several investigators propose that Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) represent the same disease at different levels of severity. Both diseases are characterized by necrosis of the epidermis, leading to the formation of blisters with detachment of skin and mucosa.[1] Although several classification schemes have been reported, the simplest one is defined as the maximum degree of detachment of the epidermis: SJS is recognized with less than 10% body surface area, but TEN more than 30%. By contrast, involvement of 10-30% of the body surface area is treated as an overlapping SJS/TEN.[2,3,4] The incidence of SJS is estimated at 1,2-6 per million patient years.[2,3] Mortality rate is approximately 1-5%, while the TEN — even 25-35% and it is higher in the elderly.[4] Various etiologic factors have been implicated as causes of Stevens-Johnson syndrome: drugs, infections, malignancy-related diseases. Drugs most commonly are the causative factors. The substances which most often cause symptoms of both diseases (SJS and TEN) are: sulfonamides (TMP-SMX), anticonvulsants (carbamazepine, phenytoin, lamotrigine), non-steroidal anti-inflammatory drugs (oxicams) and nevirapine and allopurinol.[2,3,4]

Case report

A 27-year-old patient, female, with a 4-year history of etanercept and sulfasalazine treatment because of a severe course of rheumatoid arthritis was admitted to Department of Dermatology, Sexually Transmitted Diseases and Clinical Immunology because of SJS symptoms. The patient took one

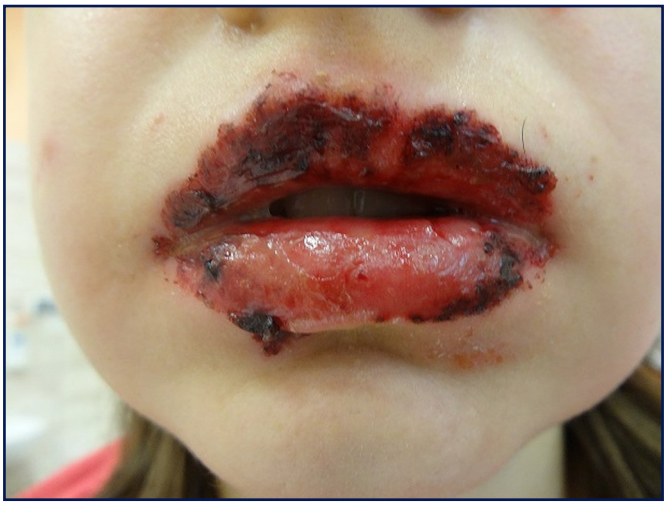

Figure 1
Hemorrhagic crusting of the mucous membranes.

sachet dose OTC drug containing acetaminophen, phenylephrine and pheniramine because of malaise and chills, two days before the appearance of symptoms. A dermatological examination revealed erosions, covered with dark red scabs, localized on vermilion and oral mucosae, mild erythema on hands and feet. The laboratory tests revealed normocytic, normochromic anemia (RBC 3.60 10^{12}/L, Hgb 10.8 g/dL), elevated markers of inflammation (ESR 22 mm/h, CRP 35.50 mg/L). The urine analysis showed erythrocyturia and leucocyturia, but in urine culture no bacteria was found. The patient was treated with GKS intravenously — dexamethasone 12 mg/day, doxycycline 200 mg/day, acyclovir p.o 2 g/day (in five doses a day), fluconazole 100 mg/day, and intensive topical treatment: brushing the oral suspension of nystatin 5 times a day, wraps with KMnO4, and skin with 5% urea ointment, 0.5% hydrocortisone ointment. In addition, she was on a liquid diet. Sulfosalazin administration was stopped, but the patient was still treated with etanercept. After recovery, the patient received sulfosalazin again with no recurrence of the skin and mucosal symptoms.

Discussion

Paracetamol (acetaminophen) is a popular OCT drug used as an analgesic and antipyretic. It is considered a relatively safe drug, recommended by doctors in case of intolerance of aspirin and other NSAIDs. Sometimes it may provoke urticaria, angioedema, and even anaphylaxis.[1] In the literature there are descriptions of systemic reactions, including vasculitis, hepatitis with glomerulonephritis, toxic epidermal necrolysis and Stevens-Johnson syndrome.[1,5] The risk of developing SJS or TEN after taking paracetamol is depending on geographic region. In France, on the basis of the cases described in the literature, there were no such cases. In other European countries (Germany, Italy, Portugal) this kind of relationship was found in adults and children.[6,7,8,9,10] Hindu *et al.* reported that the drug is an etiological factor for more than 6% of cases in their region.[11] Additionally, there is a difficulty to determine the etiologic agent is because paracetamol is often used for the treatment of prodromal symptoms SJS/TEN, which as the beginning are often interpreted as a viral infection.[7] Furthermore, the World Health Organization (WHO) recommends paracetamol in children with a temperature higher than 38.5°C, which increases its probability as a causative factor in the pediatric population.[6] Symptoms develop after at least a few days after the first administration of the drug responsible for the development of SJS/TEN. Interestingly, in cases provoked by paracetamol, the symptoms will appear just in two to three days after admission.[1,6,12] Just as in our patient.

For additional components of the drug taken by the patient, phenylephrine and pheniramine, the FDA reported 18 cases in which provocation SJS was very likely, 59 with low probability and 8 cases of possible association. In the available literature there are limited data regarding such cases.[13]

In our patient SJS/TEN occurred in the patient during treatment with etanercept. The drug wasn't suspected as an etiologic agent, because the patient has received it for four years and she continued to do so during illness and still, after recovery. Furthermore, etanercept or other anti-TNF drugs are used in the treatment of severe drug reactions.[14,15] The available literature describes several cases of TEN patients treated with etanercept successfully. Etanercept can quickly reduce the detachment of skin symptoms, shorten healing time and should be considered an anti-TNF preparations as first-line drugs.[14,15] However there are also descriptions of cases where these drugs caused SJS or TEN.[16,17]

The first step in the treatment of patients with drug-induced SJS is immediate to withdrawal of the drug which is suspected of the reaction.[12] The Garcia-Doval *et al*. described that earlier provoked-drug withdrawal the better prognosis. In the case of exposure to agents with longer half-lives the risk of mortality is higher.[12,18]

Conclusions

Paracetamol is considered as a safe and well tolerated drug. Unfortunately, in each case of severe drug reaction, we should also take into account that it can be a potential causative agent. The underlying viral infection may change immune response and tolerance to the drug. The etiology of paracetamol as the causative agent is difficult to prove because of the risk of provoking re-development of SJS or TEN.

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