

Fever in Steven Johnson Syndrome, a case report

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Abstract

Steven Johnson syndrome is a life threatening clinical condition that is usually manifested with fever, rash, bullous formation, oral and ocular lesions and genital and anal lesions. This syndrome, in majority of cases begins with influenza-like symptoms and continues with a red rash and blisters. Then the top layer of the affected skin dies and sheds.[1,2] This case report is about a 28 year old male patient who was referred to the Infectious Disease Hospital of University Hospital Center Mother Theresa Tirana with the suspected diagnosis of Hemorrhagic Fever. The patient referred 5 days of continuous fever, malaise, rash, myalgia, headache, and nausea. As soon as the patient was admitted, we immediately performed specific serologic tests, therapeutic regimen for the suspected diagnosis of hemorrhagic fever and complementary examination. During the first 10 hours, we noticed that the rash became more intense and other skin lesion and bullous formation appeared. The patient was admitted in ICU and initial diagnosis of Steven Johnson Syndrome was made. This case report elaborates the particular clinical appearance and the misdiagnosis that was associated with Steven Johnson Syndrome.[3] Specific conditions as the prolonged prodromal phase of SJS, the strong epidemiological data for hemorrhagic fever, the absence of information for misuse of drugs led us towards a “sure diagnosis” in the first place. However, the close follow-up in the ICU revealed new clinical signs and rapid differential diagnosis was done. Due to the intensive care therapy, which was applied for Hemorrhagic fever at first place, we managed to overcome complications and save the patient life.[4]

Introduction

The Stevens-Johnson syndrome (SJS) is a rare immune complex-mediated hypersensitivity disorder which affects approximately 2 per million persons.[5] The syndrome was initially described in 1922 and Alan Lyell provided an early description of TEN in 1956. Both, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) represent the spectrum of severe cutaneous adverse reactions (SCAR) affecting skin and mucous membranes. Steven Johnson Syndrome, clinically appears in three different forms which reflect the same condition: a mild form, called erythema multiforme (where < 10% TBSA is affected), the main form (between 10 and 30%), and the severe form, called toxic epidermal necrolysis) [6]

The most important clinical signs and symptoms of SJS are the following:[7,8,9]

- prodromal signs: 2-3 days of malaise, rash, fever, cough, arthralgia, myalgia, rhinitis, headache, anorexia, and nausea and vomiting, with or without diarrhea
- conjunctivitis, usually occurring 1-3 days before the skin lesions appear
- intense erythema, progressing rapidly to epidermolysis and ceasing in 2-3 days
- blisters
- mucous membrane erosion
- hemorrhagic crusting of the lips
- epidermal detachment
- extreme pain
- dehydration, which may lead to hypovolemic shock and death

Stevens-Johnson etiology is mainly a reaction to medication. Several drugs have been identified during the last decade as a triggering cause: NSAIDs, especially ibuprofen, anticonvulsants (phenytoin, valproic acid,

phenobarbital, carbamazepine), antibiotics (sulphonamides, aminopenicillins, quinolones, cephalosporins, tetracyclines, imidazole antifungal agents and allopurinol. [10,11] Generally, when BSA sloughing is less than 10%, the mortality rate is approximately 1-5%. When more than 30% BSA is present, the mortality rate is between 25 and 35%. The severity score called SCORTEN relates to several variables of mortality.[12]

The exact mechanism of Stevens-Johnson syndrome and toxic epidermal necrolysis is unknown; however, one theory holds that altered drug metabolism (eg, failure to clear reactive metabolites) in some patients triggers a T-cell-mediated cytotoxic reaction to drug antigens in keratinocytes. CD8+ T cells have been identified as important mediators of blister formation.

Recent findings suggest that granulysin released from cytotoxic T cells and natural killer cells might play a role in keratinocyte death; granulysin concentration in blister fluid correlates with severity of disease. Another theory is that interactions between Fas (a cell-surface receptor that induces apoptosis) and its ligand, particularly a soluble form of Fas ligand released from mononuclear cells, lead to cell death and blister formation. A genetic predisposition for SJS/TEN has been suggested.

The treatment of the syndrome follows the basic treatment criteria:[13]

- early transfer of patients to an intensive care unit
- placement of a central intravenous line
- rapid detection and withdrawal of all potential causative agents
- monitoring of fluids and electrolytes.
- parenteral nutrition by a nasogastric tube in patients
- placement of a Foley catheter
- irrigation of the eyes every hour
- mouth washes frequently, and topical anaesthetic for buccal pain
- patient placed in a heated environment
- anticoagulant therapy - heparin for prophylaxis of thromboembolic events
- blood transfusions if anaemia is present
- corticotherapy
- systemic antibiotics (either for documented infection or prophylactic)
- pain relief with analgesics

Material and method

A 28-yr-old male, was referred to the Infectious Disease Hospital, as a suspected Hemorrhagic fever, from the regional hospital of Kukes where he had been hospitalized for 2 days. In admission the patient referred 5 days of continuous fever, malaise, rash, arthralgia, myalgia, headache, and nausea. The patient worked as a stockbreeder and he had had frequent contact with ticks. In the objective examination (performed in both hospitals during 48 hours) the patient presented continuous fever (with no response to antipyretics) generalized macular rash, conjunctivitis and oral mucous erosions. He referred no drug misuse of antipyretics, except for paracetamol, which according to the patient information was not overdosed. Ten hours after the admission in our hospital the patient presented in the first place a more intense erythema and a bullous formation in the left hand which rapidly involved all the body surface. Within few hours we encountered positive Nikolsky sign, hemorrhagic crusting of the lips and conjunctivitis. Considering the latest clinical manifestation, the allergologist and dermatologist were asked for a consult and the diagnosis of Steven Johnson Syndrome was established in the first place.

The following figures demonstrate the characteristic erythema and skin lesions in different days of hospitalization.

Fig 1. Day 1 of hospitalisation (consequitive skin lesion in admittion and 10 hours later)



Fig 2. Day 4- 13 of hospitalisation



Fig3. Day of Dehospitalisation



As for the patient's clinical course, the fever continued with the profile continuous and high for 7 days after the appearance skin lesions and never dropped below 38 °C .

At first he was tachypneic, with acid-base disorders, but hemodynamically stable. He needed no oxygen support.

Lab tests during the first week produced the following findings:

- white blood cells : 3.400
- red blood cells:4.650.000
- hematocrit : 42.7%
- platelets 123.000
- C-reactive protein : 23.8 mg/dl
- Creatin kinase: 467Ui/L
- AST 123
- ALT 120
- lactic dehydrogenase : > 625 IU/l
- albumin 2.9 g/dl
- total protein :5.3 g/dl
- sodium : 126mmol/l

Serologic tests for Hemorrhagic fever (CCHF and HFRS) resulted negative

The blood cultures resulted negative

Chest x rays evidenced no respiratory tract infection

The patient was treated as a burn patient with 100% BSA, as follows:

- a central intravenous catheter was placed and the patient was given fluids according to the modified Parkland formula during the first day and hydro electrolytic balance in the following days
- vital signs were monitored every hour
- nasogastric tube was placed because during the first days
- a Foley catheter was placed to measure urine output
- a termostabel environment was provided
- fresh frozen plama (twice daily)
- antiseptic solution applied on affected areas every 2 h The response to therapy was immediate after resuscitation
- Corticosteroids were administered in high doses; 200mgx 2 /day
- Antibiotics were administered because of prolonged fever, not as a prophylactic measure but mainly as a therapeutic measure.

The patient fully recovered after 20 days of hospitalization and left the infectious disease hospital in a good clinical condition

Conclusions

Improved treatment techniques and critical burn care have decreased the mortality and morbidity of the Stevens Johnson syndrome. Prompt recognition of the disease and treatment of patient according to strict therapeutic regimens in the ICU contributed to the successful treatment of these patients.

Discussion

SJS and TEN have been traditionally related with fever. Fever up to 40°C (104°F) or even higher occurs in nearly all patients with SJS/TEN and is independent of the cause (drug vs. infection)

In this case report, we encountered continuous fever with high intensity in the prodromal phase (this type of fever profile and the clinical and epidemiological data strongly suggested for Hemorrhagic fever). In the following clinical stages the fever profile manifested almost the same features with gradual diminution of intensity.

Stevens-Johnson syndrome commonly affects multiple organs, and esophageal strictures develop in some patients. In 70% of SJS cases, drugs are found to be the causative agents and about 25% derive by bacterial and viral infections. Neoplasms and collagen diseases have also been pointed out as possible causes. In the end, the cause of SJS is unknown in one quarter to one half of cases.[14,15]

Sometimes, here are no specific clues or enough evidence to point out a possible causative agent.

In our case there was no evidence of drug misuse or any precedent of drug reaction.

Beside this, this syndrome has also been linked to herpes simplex virus, mycoplasma bacterial species, and measles vaccine. [16]

Skin biopsy is an additional final examination and reveals necrosis in all layers of the epidermis caused by apoptosis of keratinocytes and epidermal detachment, while the dermis displays minimum inflammatory changes. Serum levels of tumor necrosis factor-alpha and soluble IL-2, IL-6 and C-reactive protein receptors are typically elevated in patients with SJS, although none of these serological tests are used routinely for diagnosis in our midst. [20,21]

Finally, it has been reported that immunochromatographic test for serum granulysin is useful for the prediction of Stevens-Johnson syndrome and toxic epidermal necrolysis (showing that serum granulysin levels are elevated (cut off: 10 ng/mL) in patients with SJS/TEN before generalized blisters form.

Given the fact that our patient had strong epidemiological data and clinical features that could be correlated with haemorrhagic fever, the Steven Johnson syndrome was not suspected in the first place.

Specific therapies for SJS and TEN have not yet reached evidence-based acceptance standards. The low prevalence of the disease and its lethal potential make it difficult to perform randomized clinical trials. Some reviews concluded that steroids do not shorten the duration of disease and may also increase the risk of infections and worsen healing. Many authors do not recommend the routine use of systemic steroids in the treatment of SJS/TEN but some centers advocate an early pulse (first 48 hours).

Studies have suggested benefit of plasmapheresis for the treatment of SJS/TEN; however, there are reports showing that its use did not significantly affect mortality and length of hospital stay in some cases.

Cyclosporin is an immunosuppressive medication with anti-apoptotic activity and has been considered as a potentially useful drug for treatment; however, its usefulness is not well defined. reported that commercial preparations of intravenous immunoglobulin contained natural anti-Fas (anti-CD95) antibodies that blocked Fas to FasL binding, thus intervening in disease pathogenesis. The studies show mixed results. Successful treatment depends on the dose and its early use.

The criteria for diagnosis of SJS in this case were based on the clinical ground (dynamic changes of cutaneous elements reaching the epithelial detachment within 24 hours) and history of drug exposure to antipyretics (Paracetamol), even though there were no evidence of drug misuse.

No skin biopsy was recommended by the allergologists and dermatologist as the clinical manifestation, its evolution were strong enough evidences for diagnosis.

The treatment of patient was done in the Intensive Care Unit, applying the supportive regimens, antibiotics and corticosteroids.

We noticed a relevant improvement after the first 24 hours of therapy with corticosteroids to continue the treatment just in terms of steroids.

In this specific case, our results suggest that early steroid therapy should be performed along with other supportive management, preferably in an intensive care unit, the sooner possible.[23]

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