68

A 31-Year-Old Woman from Malawi With a Generalized Mucocutaneous Rash

CAMILLA ROTHE

Clinical Presentation

History

A 31-year-old woman presents to a hospital in Malawi with a generalized skin rash. The rash started 3 days before on the trunk, and then spread to the extremities and the mucosal membranes involving lips, oral mucosa, conjunctivae and genital mucosa.

There is also a productive cough with whitish sputum that started 1 day before the rash appeared, and she also reports a sore throat and dysuria for the past 2 days.

The patient had been found to be HIV positive 2 months earlier, when she was hospitalized with cryptococcal meningitis. She was treated with high-dose oral fluconazole, because amphotericin B and flucytosine were unavailable. She improved and was discharged home on a maintenance dose of fluconazole. Antiretroviral treatment with stavudine (d4T), lamivudine (3TC) and nevirapine (NVP), as well as co-trimoxazole prophylaxis, were started 1 month previously.

The rest of the medical history is unremarkable and there are no known allergies.

Clinical Findings

Her temperature is 37.7°C (99.9°F), blood pressure 120/68 mmHg, pulse 90 bpm and respiratory rate 24 breath cycles per minute. There is a generalized, non-itchy maculopapular rash involving the skin and mucous membranes but sparing the palms and soles. There is bilateral conjunctivitis. The eyelids and lips are covered with haemorrhagic crusts (Fig. 68.1). The lips are swollen and she can hardly open her mouth; talking and eating are difficult and painful. The chest is clear.

Questions

1. What is the most likely diagnosis and what is it caused by?
2. How would you approach the patient?

Discussion

A young Malawian woman presents with a generalized rash involving her skin and mucous membranes. She also complains of a productive cough of short duration, dysuria and dysphagia.

The patient is HIV positive. Within the past month she commenced treatment with co-trimoxazole and an

• **Fig. 68.1** The face of the patient, showing bilateral swelling of the eyes with conjunctivitis and swollen lips with haemorrhagic crusts. The maculopapular rash was non-itchy and spared the scalp.

antiretroviral triple therapy with d4T, 3TC and NVP. She has a low-grade fever, but her chest is clear.

Answer to Question 1

What is the Most Likely Diagnosis and What is It Caused By?

The most important diagnosis to consider is Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis. This potentially life-threatening mucocutaneous hypersensitivity reaction is most commonly caused by drugs. Its incidence is much higher in HIV-positive than in HIV-negative patients. If SJS involves more than 30% of the skin surface, it is called toxic epidermal necrolysis (TEN). SJS/TEN may lead to widespread epidermal detachment and erosions of the mucous membranes. Non-specific prodromal symptoms such as cough, sore throat, fever, headache and myalgias usually precede the rash by several days and may be mistaken for a bacterial or viral infection, or for malaria in a tropical setting.

Answer to Question 2

How Would You Approach the Patient?

SJS/TEN is a clinical diagnosis. Once suspected, all potentially causative drugs should be immediately withdrawn. If in doubt, all drugs need to be stopped. In general, medications initiated 2 to 4 weeks prior to the onset of symptoms are usually responsible. In this patient's case, the major culprit drugs were nevirapine and co-trimoxazole.

The patient at this stage only had a maculopapular rash. However, patients with SJS/TEN often develop large bullous skin lesions. Once they break open, this leads to considerable loss of serous fluid, similar to a burn. Therefore, patients with SJS/TEN ideally should be managed in a burns unit. Topical antiseptics will reduce skin colonization; however, wound debridement is not recommended. Steroid eye drops should be given in case of conjunctivitis, and early ophthalmological review should be sought to prevent conjunctival scarring and blindness. Patients need careful management of fluids and electrolytes and high caloric nutrition. A nasogastric (NG) tube is often helpful until the mucosal lesions have healed. Fever may be part of the clinical picture and there is no role for prophylactic antibiotics unless there are signs of sepsis. Vital signs need to be checked regularly, and blood cultures and full blood count taken repeatedly.

A urinary catheter should be inserted to prevent urethral strictures. Skin and mucosal lesions in SJS/TEN are very painful. Often, opioids are necessary to control the pain.

Upon discharge, patients should be urged to avoid the culprit drug and this should be clearly stated in the patient's documents.

The Case Continued…

Antiretroviral drugs and co-trimoxazole were stopped on admission. Because the patient was febrile, blood cultures and a rapid malaria test were taken and both came back negative. She received IV fluids and a urinary catheter. The patient and her family declined an NG tube, because they had observed that patients who had an NG tube or oxygen probes were more likely to die than patients who did not have such devices.

• **Fig. 68.2** The right leg of another patient with SJS/TEN showing extensive epidermal sloughing and large areas of denuded dermis.

The patient was given 0.9% normal saline as mouthwash and dexamethasone eye ointment. Fever and cough settled spontaneously. She was discharged after 10 days in hospital.

When all lesions had completely healed, she was started on a new antiretroviral combination therapy and nevirapine was replaced by efavirenz. Co-trimoxazole was not replaced because there were no alternative drugs available. The new drug combination was tolerated well and no further rash occurred.

SUMMARY BOX

Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

SJS is a life-threatening mucocutaneous hypersensitivity reaction. It is most commonly caused by drugs. In SJS, less than 10% of the total body surface is involved. If more than 30% is affected, it is called toxic epidermal necrolysis (TEN). Between 10% and 30% it is classified as 'SJS/TEN overlap'. The extent of skin involvement is a major determinant for prognosis.

In Western industrialized countries, SJS/TEN is considered rare, with an estimated incidence of 1 to 7 per million per year. However, it is about 1000 times more common in HIV-positive individuals, and clinicians working in sub-Saharan Africa and other high-prevalence settings need to be aware of this condition.

The drugs most commonly implicated in SJS/TEN are antibiotics (in particular sulfonamides, but also other classes), the antiretroviral nevirapine, anticonvulsants and allopurinol.

Infectious agents (e.g. *Mycoplasma pneumoniae* and HSV) may also be responsible. Host genetic factors also seem to play a role.

The pathophysiology is yet to be fully elucidated. Because of an unknown mechanism there is widespread apoptosis of keratinocytes and subsequent epithelial necrosis.

SJS/TEN often starts with non-specific, flu-like symptoms. After several days a morbiliform rash sets in that becomes more and more confluent. The epidermis may slough, giving rise to flaccid bullae, leaving a characteristic denuded dermis (Fig. 68.2), which causes intense pain. Conjunctivitis is common and may lead to scarring and blindness. Involvement of the oral mucosa and haemorrhagic crusting of the lips make it difficult for the patient to eat, drink and talk. Involvement of the urogenital mucosa is very painful and may lead to urethral strictures. The oesophagus and trachea may also be affected.

Diagnosis can often be made clinically. Skin biopsies may help rule out the major differential diagnoses such as staphylococcal scalded skin syndrome, toxic shock syndrome, exfoliative dermatitis, autoimmune bullous diseases and acute paraneoplastic pemphigus.

All potentially causative drugs need to be withdrawn immediately. Treatment is supportive and there is no clear benefit of any other disease-modifying interventions. Systemic corticosteroids do not seem helpful and the use of IV immunoglobulins is disputed. However, data from large controlled clinical trials are lacking.

According to literature from the developed world, the case fatality rate of patients with SJS is up to 5%; in TEN it is 30% on average. Primary causes of death are infection and multi-organ failure.

A severity-of-illness score (SCORTEN) has been published to predict the lethality of patients with SJS/TEN. Its use in resource-constrained setting is limited, because it requires laboratory results (urea, bicarbonate, glucose) that may be difficult to obtain.

Further Reading

1. Gerull R, Nelle M, Schaible T. Toxic epidermal necrolysis and Stevens–Johnson syndrome: a review. Crit Care Med 2011;39(6):1521–32.
2. Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. Lancet 2017;390:1996–2011.
3. Hoosen K, Mosam A, Dlova NC, Grayson W. An update on adverse cutaneous drug reactions in HIV/AIDS. Dermatopathology 2019;6:111–25.
4. Hazin R, Ibrahimi OA, Hazin MI, et al. Stevens–Johnson syndrome: pathogenesis, diagnosis, and management. Ann Med 2008;40(2):129–38.
5. Schulze Schwering M, Kayange P, Rothe C. Ocular manifestations in patients with Stevens-Johnson syndrome in Malawi – a review of the literature illustrated by clinical cases. Graefes Arch Clin Exp Ophthalmol 2019;257(11):2343–8.