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Case Report

Cefotaxime-induced Stevens–Johnson syndrome: a case report

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ABSTRACT

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis are two forms of a life-threatening skin condition, in which cell death causes the epidermis to separate from the dermis. The syndrome is thought to be a hypersensitivity complex that affects the skin and the mucous membranes. The most well-known causes are certain medications, but it can also be due to infections, or more rarely, cancers. SJS usually begins with fever, sore throat, and fatigue, which is commonly misdiagnosed and therefore treated with antimicrobials. Ulcers and other lesions begin to appear in the mucous membranes, almost always in the mouth and lips, but also in the genital and anal regions. Conjunctivitis of the eyes occurs in about 30% of children who develop SJS. A rash of round lesions about an inch across arises on the face, trunk, arms and legs, and soles of the feet, but usually not the scalp. SJS is a medical emergency that usually requires hospitalization. Treatment focuses on eliminating the underlying cause, controlling symptoms and minimizing complications. Recovery after SJS can take weeks to months, depending on the severity of the condition. If it was caused by a medication, then the medication and others closely related to it has to be avoided permanently. An 18-month-old male child was admitted to a private health setup in Kolar with the complaints of peeling and discoloration of the skin, ulcerations in the oral cavity, eyelids, and genitalia. The parents gave the history of cefotaxime injection being administered to the child for treating typhoid 20 days back. Seven days after the administration of cefotaxime, the child had developed maculo-papular lesions all over the body. Later on there was peeling and discoloration of the skin. Itching was present. Ulcerations in the oral cavity, eyelids and genitalia were also noticed by the parents, who then brought the child to the health care center. According to the Naranjo's adverse drug reaction probability scale, there is a possible relation between this adverse drug reaction (SJS) and cefotaxime.

Keywords: Cefotaxime, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Hypersensitivity, Medical emergency, Macula-papular lesions, Ulcers, Conjunctivitis, Naranjo's causality scale, Possible

INTRODUCTION

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis are two forms of a life-threatening skin condition, in which cell death causes the epidermis to separate from the dermis. The syndrome is thought to be a hypersensitivity complex that affects the skin and the mucous membranes. The most well-known causes are certain medications, but it can also be due to infections, or more rarely, cancers.

SJS usually begins with fever, sore throat, and fatigue, which is commonly misdiagnosed and therefore treated with antimicrobials. Ulcers and other lesions begin to appear in the mucous membranes, almost always in the mouth and lips, but also in the genital and anal regions. Those in the mouth are usually extremely painful and reduce the patient's ability to eat or drink.

Conjunctivitis of the eyes occurs in about 30% of children who develop SJS. A rash of round lesions about an inch across arises on the face, trunk, arms and legs, and soles of the feet, but usually not the scalp.[1]

SJS is a medical emergency that usually requires hospitalization. Treatment focuses on eliminating the underlying cause, controlling symptoms and minimizing complications. Recovery after SJS can take weeks to months, depending on the severity of the condition. If it was caused by a medication, then the medication and others closely related to it has to be avoided permanently.

Cefotaxime is a third-generation cephalosporin antimicrobial. Like other third-generation cephalosporins, cefotaxime is a broad-spectrum antimicrobial with activity against numerous Gram-positive and Gram-negative bacteria. It is on the World Health Organization's list of Essential Medicines, the most important medications needed in a basic health system.[2]

A possible association between cefotaxime and SJS has been reported.[3]

CASE REPORT

An 18-month-old male child was admitted to a private health setup in Kolar with complaints of peeling and discoloration of the skin, ulcerations in the oral cavity, eyelids, and genitalia. The parents gave the history of cefotaxime injection being administered to the child for treating typhoid 20 days back. Seven days after the administration of cefotaxime, the child had developed maculo-papular lesions all over the body. Later on there was peeling and discoloration of the skin. Itching was present. Ulcerations in the oral cavity, eyelids and genitalia were also noticed by the parents, who then brought the child to the health care center.

The parents said that the baby had cough with expectoration 4 days after the administration of cefotaxime. A day prior to admission the baby had a fever. A history of burning micturition was reported.

Treatment given was piperacillin and the tazobactam injection, hydrocortisone injection, paracetamol syrup, intravenous (i.v) multiple electrolytes, i.v dextrose normal saline, fusidic acid skin cream. Eye management: benzalkonium eye drops twice daily, lubricating eye drops (I-Dew DS) containing carmellose sodium thrice daily, moxifloxacin eye drops thrice daily (Figure 1).

DISCUSSION

SJS is a rare condition, with a reported incidence of around 2.6-6.1 cases/million people per year. The condition is more common in adults than in children. Women are affected more often than men, with cases occurring at a two to one ratio.

Figures 1: (a and b) Cefotaxime induced Stevens–Johnson syndrome.

SJS is an immune-complex - mediated hypersensitivity complex that typically involves the skin and the mucous membranes. Although several classification schemes have been reported, the simplest classification breaks the disease down as follows:[4]

- SJS: a minor form of toxic epidermal necrolysis, with <10% body surface area (BSA) detachment
- Overlapping SJS/toxic epidermal necrolysis: detachment of 10-30% of the BSA
- Toxic epidermal necrolysis: detachment of more than 30% of the BSA
- These conditions were first recognized in 1922.[5]

The SJS was first described in 1922, when the American pediatricians Albert Mason Stevens and Frank Chambliss Johnson reported the cases of two boys aged 7 and 8 years with "an extraordinary, generalized eruption with continued fever, inflamed buccal mucosa, and severe purulent conjunctivitis." Both cases had been misdiagnosed by primary care physicians as hemorrhagic measles.

All three are part of a spectrum of severe cutaneous reactions (SCAR) which affect the skin and mucous membranes.[6]

The skin pattern most commonly associated with SJS is widespread, often joined or touching (confluent), papuric spots (macules) or flat vesicles or bullae, which may also be confluent.[6] These occur primarily on the torso.[6]

SJS, toxic epidermal necrolysis (TEN), and SJS/TEN overlap can be mistaken for erythema multiforme.[7] Erythema multiforme, which is also within the SCAR spectrum, differs in clinical pattern and etiology.[6] Although both SJS and TEN can also be caused by infections, they are most often adverse effects of medications.[6]

Generally, SJS begins with a nonspecific upper respiratory tract infection. This usually is part of a 1-14-day prodrome during which fever, sore throat, chills, headache, and malaise may be present. Vomiting and diarrhea are occasionally noted as part of the prodrome. Mucocutaneous lesions develop abruptly. Clusters of outbreaks last from 2 to 4 weeks. The lesions are typically non-pruritic. A history of fever or localized worsening should suggest a superimposed infection; however, fever has been reported to occur in up to 85% of cases. Involvement of oral and/or mucous membranes may be severe enough that patients may not be able to eat or drink. Patients with a genitourinary involvement may complain of dysuria or an inability to void.

A history of the previous outbreak of SJS or of erythema multiforme may be elicited. Recurrences may occur if the responsible agent is not eliminated or if the patient is reexposed.

Typical prodromal symptoms are cough productive of a thick purulent sputum, headache, malaise, and arthralgia. Patients may complain of a burning rash that begins symmetrically

on the face and the upper part of the torso. This may be accompanied by ocular symptoms.

In addition to the skin, lesions in SJS may involve the following parts of the body: oral mucosa, esophagus, pharynx, larynx, anus, trachea, vagina, and urethra.

Ocular symptoms include red eye, tearing, dry eye, pain, blepharospasm, itching, grittiness, heavy eyelid, foreign body sensation, decreased vision, burn sensation, photophobia, and diplopia.

Delineation of a drug exposure timeline is essential, especially in the 1-3 weeks preceding the cutaneous eruption. An idiosyncratic, delayed hypersensitivity reaction has been implicated in the pathophysiology of SJS. Certain population groups appear more susceptible to develop SJS than the general population. Slow acetylators, patients who are immunocompromised (especially those infected with HIV),[8,9] and patients with brain tumors undergoing radiotherapy with concomitant antiepileptics are among those at most risk.

Antigen presentation and production of tumor necrosis factor - alpha by the local tissue dendrocytes results in the recruitment and augmentation of T-lymphocyte proliferation and enhances the cytotoxicity of the other immune effector cells.[10] A "killer effector molecule" has been identified that may play a role in the activation of cytotoxic lymphocytes.[11] The activated CD8+ lymphocytes, in turn, can induce epidermal cell apoptosis via several mechanisms, which include the release of granzyme B and perforin. In 1997, Inachi et al. demonstrated perforin-mediated apoptosis in patients with SJS.[12] Perforin, a pore-making monomeric granule released from natural killer cells and cytotoxic T-lymphocytes, kills target cells by forming polymers and tubular structures not unlike the membrane attack complex of the complement system.

Apoptosis of keratinocytes can also take place as a result of ligation of their surface death receptors with the appropriate molecules. Those can trigger the activation of the caspase system, leading to DNA disorganization and cell death.[13] The death of keratinocytes causes separation of the epidermis from the dermis. Once apoptosis ensues, the dying cells provoke recruitment of more chemokines. This can perpetuate the inflammatory process, which leads to extensive epidermal necrolysis.[14]

Higher doses and rapid introduction of allopurinol[15] and lamotrigine[16] may also increase the risk of developing SJS/TEN. Risk is lessened by starting these at the low doses and titrating gradually.[17] There is evidence that systemic lupus is a risk factor as well.[18]

Although SJS can be caused by viral infections and malignancies, the main cause is medications.[6] SJS may be caused by vancomycin, allopurinol, valproate, levofloxacin, diclofenac, etravirine, isotretinoin, fluconazole,[19] valdecoxib, sitagliptin, oseltamivir, penicillins, barbiturates, sulphonamides, phenytoin, azithromycin, oxcarbazepine, zonisamide, modafinil,[20] lamotrigine, nevirapine, pyrimethamine, ibuprofen,[21] ethosuximide, carbamazepine, bupropion, telaprevir[22] and nystatin.[23,24]

Medications that have been traditionally known to lead to SJS, erythema multiforme, and toxic epidermal necrolysis include sulfonamide antimicrobials, penicillin antimicrobials, cefixime, barbiturates, lamotrigine, phenytoin, and trimethoprim. Combining lamotrigine with sodium valproate increases the risk of SJS.

NSAIDs are a rare cause of SJS in adults; the risk is higher for older patients, women, and those initiating treatment. In general, the symptoms of drug-induced SJS arise within a week of starting the medication. Similar to NSAIDs, paracetamol has also caused rare cases of SJS. People with SLE or HIV are more susceptible to drug-induced SJS.

In this event, causalty assessment using Naranjo's scale revealed that cefotaxime was a possible cause for the adverse drug reaction.

Treatment

SJS constitutes a dermatological emergency. Initially the treatment is similar to that for patients with thermal burns and continued care can only be supportive like i.v fluids and nasogastric or parenteral feeding and symptomatic like analgesic mouth rinse for mouth ulcer. There is a certain amount of disagreement as to whether the skin should be debrided or not between the dermatologists and surgeons. Treatment with corticosteroids is controversial. I.v immunoglobulin treatment has shown some promise in reducing the length of the reaction and improving the symptoms. Topical anesthetics, antiseptics and i.v analgesics may be used. Those with chronic ocular surface disease caused by SJS can often find relief of their symptoms and improved eyesight with prosthetic replacement of the ocular surface ecosystem treatment.

SJS has a mortality of around 5%. The mortality for TEN is 30-40%. The risk of death can be estimated using the SCORTEN scale, which takes a number of prognostic indicators into account. Other outcomes include organ damage/failure, cornea scratching and blindness.

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