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SJS/TENS

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Introduction:

Hello everyone! My name is Moyin Onasanya, I am a fourth-year medical student at the University of Saskatchewan. Today's PedCases podcast was created with the guidance and support of Dr. Loretta Fiorillo, the divisional director of pediatric dermatology at the University of Alberta.

In this episode, we will discuss a critical condition in pediatric dermatology: Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN). SJS/TEN is a life-threatening condition that needs to be identified and treated quickly to avoid devastating outcomes.

Learning Objectives:

By the end of this podcast, you should be able to:

1. Define SJS/TEN and recognize its clinical presentation.
2. Discuss the pathophysiology of SJS/TEN.
3. Identify the etiology and common triggers of the condition.
4. Discuss appropriate management and treatment options for patients with SJS/TEN.
5. List potential acute and chronic complications and outcomes associated with SJS/TEN.

Clinical Case

Let's start with a clinical case.

You are working in the pediatric ER. At 2:00 p.m., a 9-year-old boy named Andrew presents to the ED with his mother who states that Andrew developed a diffuse full-body rash 6 hours ago. The rash started abruptly this morning beginning on his trunk and spreading to his chest and face. Initially, the rash looked like flat "targets" on the skin, but now his mother has noticed some blisters and skin peeling. Andrew also complains

that he feels like his whole body is burning. Prior to the rash, Andrew had a 3-day history of fever, sore throat, cough, myalgias, and arthralgias.

Andrew was previously a healthy 9-year-old, however, three weeks ago he was diagnosed with epilepsy and was started on carbamazepine. He is of Han Chinese descent.

On examination, Andrew appears very fatigued and ill. His vitals are: BP 98/60, HR 135, T 39°C, RR 22, and O2 sats 98% on room air. He is Fitzpatrick skin type 4. On the chest, abdomen, back, and face, you notice dusky red edematous patches and macules with overlying widespread blisters, bullae, and skin sloughing. There are also mucosal erosions and crusting around his lips. You estimate that the rash covers about 10% of Andrew's body surface area (BSA). You apply slight pressure on an area of normal-appearing skin on his right arm and the skin peels right off. The team calls the ICU for consultation.

What is SJS/TEN?

SJS/TEN are acute dermatological emergencies characterized by diffuse, rapidly progressing cutaneous necrosis often caused by an adverse reaction to a medication (1). SJS and TEN are on the same disease spectrum but the difference between the two is based on the extent of BSA involved. SJS involves 10% or less of the body surface area, TEN affects 30% or more, and cases involving 10%-30% of the BSA are referred to as SJS/TEN (1,2).

For children above the age of 14, BSA can be calculated using the general Rule of Nines**,** which divides the body into sections approximating 9% of the body's surface area. With this rule, the entire head and neck encompasses 9%, the front torso 18%, the back torso 18%, each arm 18%, each leg 18%, and the groin 1% (3). However, for children under the age of 14, the proportions of their body parts are different as their heads are proportionally larger compared to the rest of their bodies (3). In these pediatric cases, the Lund and Browder chart can be used (3). This chart provides age-specific approximations of body surface area to be more accurate, such as attributing 18% to the head and neck in infants, in contrast to 9% in adults (3).

Characteristic symptoms of this condition include fever, dusky erythema, skin sloughing, and atypical targetoid lesions (1). Atypical targetoid lesions differ from typical target lesions by lacking the three classical clear targets, instead presenting with two zones and/or poorly defined margins (4). Lymphadenopathy is also often present in SJS/TEN (1). A hallmark feature of SJS/TEN is mucosal involvement, including lesions in the mucosal lining of the mouth, genitals, and conjunctiva, occurring in about 90% of cases (1, 5). Ocular involvement is the most frequently affected mucosal site, with complications including corneal ulcers, scarring, and in severe cases, blindness (5). Mouth lesions are generally painful and can cause food refusal, while genital lesions

can lead to dysuria, urethritis, urinary retention, and genital scarring (4, 6). There is also a potential occurrence of gastrointestinal involvement, resulting in ulceration and perforation, and respiratory complications such as acute respiratory distress syndrome and emphysema (4).

The onset of SJS/TEN is often preceded by non-specific systemic symptoms including fatigue, fever, cough, and sore throat, typically lasting 1-3 days (5). Afterward, coalescing dusky red purpuric atypical targetoid lesions quickly develop on the face and upper body. This is followed by the formation of soft and large fluid-filled blisters (bullae) which can rupture with minimal trauma. The centers of these lesions become wrinkled and peel away due to necrosis and poor epidermal attachment, leaving raw areas of bright red dermis vulnerable to infection (1,5).

There are two diagnostic clinical signs of the disease, the Nikolsky and Asboe-Hansen's signs. The Nikolsky sign is characterized by the detachment of normal-appearing skin when slight twisting pressure is applied, and the Asboe-Hansen's sign is characterized by movement of fluid into normal-appearing skin when direct pressure is applied to a bulla (2).

Pathophysiology and Etiology

The pathophysiology of SJS/TEN is not fully understood but has been proposed to be caused by dysregulation of cellular immunity.

Medications are the most common trigger for SJS/TEN, accounting for approximately 90% of cases (7). The proposed mechanism of drug-induced SJS/TEN hypothesizes that the body has an impaired ability to detoxify toxic drug metabolites causing activation of cytotoxic T lymphocytes (1). These T-cells are believed to target keratinocytes (cells present in the epidermis) leading to their death through the release of granulysin, fas ligand, fas-ligand receptor, and perforin/granzyme B which are cytotoxic mediators. This leads to epidermal necrosis and detachment from the dermis (1,2,5). The acronym "The 5 A's" represents the likely causative medications of SJS/TEN: antibiotics (particularly sulfonamides and penicillins), allopurinol, anti-inflammatory drugs (NSAIDs), anticonvulsants (e.g. carbamazepine, phenytoin, phenobarbital), and antiretrovirals (particularly NNRTIs like nevirapine and efavirenz) (2,5).

Genetic predispositions such as the HLA-B*15:02 allele common in Southeast Asian populations (especially Han Chinese), can increase the risk of drug-induced SJS/TEN (1,7). This allele specifically makes affected Southeast Asian populations susceptible to carbamazepine (1). Other risk factors include immunocompromised states (e.g., HIV, malignancy), patients who have slow acetylator genotypes, and patients undergoing radiotherapy while on anticonvulsants (1).

<u>Differential Diagnosis</u>

The differential diagnosis for SJS/TEN includes erythema multiforme major, Reactive Infectious Mucocutaneous Eruption (RIME), drug-induced linear IgA bullous dermatosis, staphylococcus scalded skin syndrome, acute graft-vs-host disease, fixed drug eruption, pemphigus vulgaris, bullous pemphigoid, and DRESS (drug reaction with eosinophila and systemic symptoms) (1,2,5).

Erythema multiforme (EM) is commonly mistaken for SJS/TEN due to overlapping features (1). EM; however, is typically triggered by infections, most commonly herpes simplex virus (HSV) (1). EM is characterized by classic target lesions, minimal skin sloughing, and localized mucosal involvement (1). Systemic symptoms, such as fever, as also less prevalent in EM compared to SJS/TEN (1).

Reactive infectious mucocutaneous eruption (RIME) is a condition triggered by an infections that can closely resembles SJS (7). RIME is most commonly triggered by mycoplasma pneumonia infection and is sometimes described as as mycoplasma induced rash and mucositis (MIRM) (7). Other infectious triggers of RIME include Chlamydia pneumoniae, and viral respiratory infections including influenza and COVID. Unlike SJS, RIME typically presents with mucositis, has limited skin involvement, and has a negligible mortality rate (7).

Diagnosis and Investigations

The diagnosis of SJS/TEN is primarily clinical, meaning that it is based on history and physical examination. However, a skin biopsy can confirm the diagnosis.

Investigations should include routine bloodwork (CBC, electrolytes, liver function tests, renal function tests), lactate, CRP, and ESR to assess overall patient status (7). If you're considering RIME or EM on the differential diagnosis, serology and PCR for bacteria and viruses (e.g., mycoplasma pneumoniae, chlamydia pneumoniae, Epstein-Barr virus, cytomegalovirus, HSV) are also important (5,7). A chest x-ray may be necessary to rule out pneumonia or infectious triggers of RIME (7).

Treatment and Management

Treatment of SJS/TEN in children is emergent. If the disease is caused by a medication, the most important step is to immediately discontinue the offending drug. The Algorithm of Drug Causality in Epidermal Necrolysis (ALDEN) can help assess drug causality (7). There is also a prognostic score called the Score for Toxic Epidermal Necrolysis (SCORTEN) which predicts the morbidity and mortality risk of SJS/TEN (7). Patients should be admitted to the ICU or a burn center. Management is supportive, similar to treating a large body burn, and includes fluid and electrolyte management, prevention of hypothermia, wound care, analgesia, nutritional support, and prevention of secondary infections (2,5).

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Currently, intravenous cyclosporine is the preferred medical treatment (1). Recent studies have also found TNF-alpha inhibitors such as infliximab and etanercept, are useful for treating disease (5,7). The use of corticosteroids and intravenous immunoglobulin (IVIG) has been debated, and some believe the use of corticosteroids may worsen outcomes in some cases (5). Specialist referrals are important, particularly ophthalmology for ocular complications that can result in vision loss. Plastic surgery should also be consulted for wound care.

Appropriate and timely treatment of this disease is important because there is concern about mortality, especially when large areas of the BSA are involved. In children, the mortality rate for SJS is 1%, 1-4% for SJS/TEN, and up to 16% for TEN (7,8). The primary cause of death in these conditions is sepsis from secondary infection (7). Therefore, identifying and treating SJS/TEN as quickly as possible is important for favorable outcomes.

Conclusion

To summarize, the key learning points from today's episode are:

1. SJS/TEN are life-threatening dermatological emergencies characterized by rapid-onset blistering and skin sloughing and are often preceded by flu-like symptoms.
2. SJS/TEN are most commonly triggered by medications
3. The difference between SJS and TEN is based on BSA involvement: SJS affects less than 10%, TEN affects more than 30%, and cases between 10%-30% are termed SJS/TEN.
4. The most important management step is stopping the offending drug. Treatment is supportive, and cyclosporine and TNF-alpha inhibitors can be used as a medical treatment.
5. SJS/TEN has a high mortality risk, often related to sepsis from secondary infection. Other specialties that may need to be consulted include ophthalmology and plastic surgery

That concludes our podcast. Thank you for tuning in!

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