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Review Article

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Severe Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis Misdiagnosed as Varicella: A Case Report

Ànnia Puignau Pont

Estudiante En Universitat de Barcelona, Spain

Corresponding author
Ànnia Puignau Pont, Estudiante En Universitat De Barcelona, Spain.

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ABSTRACT

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening severe cutaneous adverse reactions with mortality rates ranging from 10% to 50%. Early recognition and prompt intervention are critical to improve outcomes, yet diagnostic challenges frequently lead to delayed treatment.

Case Presentation: We report the case of a 58-year-old male who developed SJS/TEN with over 30% body surface area involvement following carbamazepine initiation for trigeminal neuralgia. The patient presented with a progressive vesiculopustular rash initially misdiagnosed as an allergic reaction and subsequently as varicella, leading to inappropriate antiviral therapy. Clinical deterioration with extensive blistering and mucosal involvement eventually raised suspicion of SJS/TEN, which was confirmed by skin biopsy. Following transfer to a specialized burn unit and implementation of a multidisciplinary treatment approach, the patient achieved complete recovery.

Conclusion: This case highlights the diagnostic challenges of SJS/TEN, particularly when clinical presentation mimics more common conditions such as varicella or staphylococcal scalded skin syndrome. Early recognition, immediate withdrawal of the culprit drug, and specialized supportive care are essential to reduce morbidity and mortality in these severe cutaneous adverse reactions.

Keywords: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Carbamazepine, Severe Cutaneous Adverse Reactions, Diagnostic Delay, Case Report

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) represent a spectrum of rare but potentially fatal severe cutaneous adverse reactions (SCARs) characterized by extensive epidermal necrosis and detachment [1]. These conditions affect approximately 1 to 10 individuals per million population per year, with SJS defined as less than 10% body surface area (BSA) detachment, SJS/TEN overlap as 10-30% BSA detachment, and TEN as 30% or greater BSA involvement [2]. Despite their rarity, these conditions carry significant mortality rates, ranging from 10% for SJS to up to 50% for TEN, with overall in-hospital mortality of approximately 19%[1-3].

The pathophysiology of SJS/TEN involves drug-specific cytotoxic T-cell and natural killer cell-mediated keratinocyte apoptosis, typically occurring 4 to 28 days after drug exposure [1,4]. More than 100 medications have been implicated as triggers, with aromatic anticonvulsants (including carbamazepine, phenytoin, and phenobarbital), allopurinol, antibiotics, and nonsteroidal anti-inflammatory drugs being the most commonly associated agents [2,5,6]. Carbamazepine, in particular, has been identified as a high-risk medication with reporting odds ratios exceeding 24 times that of non-antiepileptic drugs [7].

The clinical presentation of SJS/TEN typically begins with a prodromal phase characterized by fever, malaise, and influenza-like symptoms, followed by the development of painful cutaneous lesions and mucosal involvement [1,4]. The initial eruption often manifests as erythematous, irregularly shaped, dusky-red macules with atypical target lesions, progressing to flaccid blisters and extensive epidermal sheets [1]. A positive Nikolsky sign—epidermal sloughing under lateral pressure—is characteristic of these conditions [1]. Mucosal involvement occurs in approximately 80% of cases and may precede cutaneous manifestations, affecting the oral cavity, eyes, genitalia, and respiratory tract [1].

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Despite well-described clinical features, SJS/TEN can be challenging to diagnose, particularly in the early stages when the presentation may mimic more common dermatologic conditions. Studies have shown that up to 72% of patients initially referred for suspected SJS/TEN are subsequently reclassified with alternative diagnoses [3]. Common mimickers include drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme major, acute generalized exanthematous pustulosis (AGEP), generalized bullous fixed drug eruption, staphylococcal scalded skin syndrome, and viral exanthems including varicella [1,8,9].

The diagnostic delay resulting from misdiagnosis can have serious consequences, as prompt withdrawal of the culprit medication is associated with decreased mortality compared to cases where the offending agent is continued [2]. Furthermore, early transfer to specialized care units and implementation of appropriate supportive measures are critical determinants of outcome [4-10].

We present a case of carbamazepine-induced SJS/TEN that was initially misdiagnosed as an allergic reaction and subsequently as varicella, illustrating the diagnostic challenges clinicians face when evaluating patients with severe cutaneous eruptions. This case underscores the importance of maintaining a high index of suspicion for SJS/TEN in patients presenting with progressive vesiculobullous eruptions, particularly in the context of recent medication initiation.

Case Presentation

A 58-year-old male with a medical history of hyperuricemia treated with allopurinol presented to the emergency department with a widespread rash affecting the thorax and abdomen. One month prior to symptom onset, he had been started on carbamazepine for the management of trigeminal neuralgia.

On initial presentation, the patient was diagnosed with an allergic reaction, attributed to recent mussel consumption, and was treated with antihistamines. However, his symptoms worsened over the following days, with progression of the rash prompting a return visit to the emergency department. At this time, he was administered adrenaline, systemic corticosteroids, and antihistamines for presumed anaphylaxis.

Three days later, the patient's condition deteriorated significantly. He developed pustular skin lesions that spread to involve both upper and lower extremities, accompanied by fever of 38°C. Given the clinical presentation of vesiculopapular erythema with fever, a broad differential diagnosis was considered, including infectious etiologies such as varicella and immune-mediated conditions. Serological testing was performed, and dermatology consultation was obtained. Based on the clinical appearance of the lesions, a presumptive diagnosis of varicella was made, and treatment with acyclovir was initiated.

Despite antiviral therapy, the patient experienced rapid clinical deterioration with the development of mucosal involvement. This progression raised concern for staphylococcal scalded skin syndrome, prompting the addition of vancomycin and clindamycin to his treatment regimen.

As the patient developed extensive blistering with progressive skin detachment, the diagnosis of Stevens-Johnson syndrome was suspected. High-dose methylprednisolone therapy was initiated. A skin biopsy was performed, which confirmed the diagnosis of SJS/TEN with histopathological findings consistent with full-thickness epidermal necrosis. Clinical assessment revealed greater than 30% body surface area involvement, meeting criteria for toxic epidermal necrolysis.

Given the temporal relationship between carbamazepine initiation and symptom onset, occurring approximately one month after starting the medication, carbamazepine was identified as the likely culprit drug and was immediately discontinued. The patient was transferred to a specialized burn unit for intensive supportive care.

With implementation of a multidisciplinary treatment approach including wound care, fluid and electrolyte management, nutritional support, infection prevention, and ophthalmologic care, the patient demonstrated progressive clinical improvement. Re-epithelialization proceeded steadily, and the patient achieved hemodynamic stabilization. Following an extended hospitalization, the patient made a complete recovery without significant long-term sequelae.

Discussion

This case illustrates several critical aspects of SJS/TEN diagnosis and management, particularly the challenges associated with recognizing this condition when it mimics more common dermatologic presentations. The initial misdiagnosis as an allergic reaction to food, followed by presumptive diagnoses of varicella and staphylococcal scalded skin syndrome, resulted in a delay in appropriate management and continuation of the offending medication.

Diagnostic Challenges and Differential Diagnosis

The differential diagnosis of vesiculobullous eruptions with fever and mucosal involvement is broad, and distinguishing SJS/TEN from clinical mimickers requires careful attention to specific clinical features. In a retrospective review of 208 patients with suspected SJS/TEN, only 28.4% ultimately received this diagnosis, with the most common alternative diagnoses being drug hypersensitivity syndrome (DRESS), morbilliform drug eruption, erythema multiforme, and AGEP [8]. Key distinguishing features that favor SJS/TEN include the presence of Nikolsky sign, atypical target lesions, fever, and lymphopenia [8].

Varicella, the initial presumptive diagnosis in our patient, can be distinguished from SJS/TEN by several features. Varicella typically presents with a characteristic progression from macules to papules to vesicles to crusts, with lesions in various stages of evolution simultaneously present. The distribution is typically centripetal, beginning on the trunk and face. In contrast, SJS/TEN presents with dusky-red macules that progress to flaccid blisters with positive Nikolsky sign, and the lesions tend to be more uniform in appearance [1]. Furthermore, varicella is uncommon in adults with prior immunity and typically occurs in the context of known exposure.

Staphylococcal scalded skin syndrome (SSSS), another consideration in this case, can be differentiated from TEN by

several features. SSSS typically occurs in young children and immunocompromised adults, presents with more superficial skin involvement (intraepidermal cleavage rather than full-thickness necrosis), and demonstrates rapid improvement with appropriate antibiotic therapy. Skin biopsy readily distinguishes these conditions, with SSSS showing subcorneal splitting and TEN demonstrating full-thickness epidermal necrosis [1].

Carbamazepine as a Culprit Drug

Carbamazepine is well-established as a high-risk medication for SJS/TEN. In a pan-European multicenter study, anticonvulsants accounted for 18.9% of SJS/TEN cases, with aromatic anticonvulsants (carbamazepine, phenytoin, and phenobarbital) documented in 87.5% of anticonvulsant-induced cases [5]. An analysis of the FDA Adverse Event Reporting System found that carbamazepine had a reporting odds ratio of 24.5 for SJS/TEN compared to non-antiepileptic drugs [7]. In a Chinese cohort, carbamazepine was identified as one of the most common individual causative drugs for SJS/TEN [6].

The timing of symptom onset in our patient—approximately one month after carbamazepine initiation—is consistent with the typical latency period for drug-induced SJS/TEN, which ranges from 4 to 28 days after continuous drug exposure [1,2]. This temporal relationship, combined with the absence of alternative explanations and the well-established association between carbamazepine and SJS/TEN, strongly implicates carbamazepine as the causative agent in this case.

Genetic susceptibility plays an important role in carbamazepine-induced SJS/TEN. A strong association has been established between the HLA-B15:02 allele and carbamazepine-triggered SJS/TEN in Han Chinese and other Asian populations, with nearly 100% of affected individuals carrying this allele. In patients of northern European and Japanese ancestry, the HLA-A[1]31:01 allele has been associated with carbamazepine-induced SCARs[1]. Current guidelines recommend HLA-B15:02 testing prior to initiating carbamazepine in patients of Chinese descent and other genetically at-risk populations [11].

Clinical Course and Prognosis

The extent of BSA involvement is a critical determinant of prognosis in SJS/TEN. Our patient had greater than 30% BSA involvement, meeting criteria for TEN, which carries the highest mortality risk within the SJS/TEN spectrum. The Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN) is widely used to predict in-hospital mortality and includes seven clinical and biological parameters: age greater than 40 years, malignancy, heart rate greater than 120 beats per minute, initial BSA detachment greater than 10%, serum urea greater than 10 mmol/L, serum glucose greater than 14 mmol/L, and serum bicarbonate less than 20 mmol/L[12,13]. SCORTEN scores of 2 or greater are significantly associated with increased mortality risk [5].

Recent data indicate that in-hospital mortality for TEN is approximately 30%, with overall one-year mortality reaching 40% when post-discharge deaths are included [3].The most common causes of death during the acute phase are sepsis, respiratory failure, and multi-organ dysfunction [1]. Long-term sequelae are common among survivors and include ophthalmologic complications (corneal scarring, symblepharon, dry eye), cutaneous manifestations (pigmentary changes, scarring), psychological sequelae (post-traumatic stress disorder), and chronic pulmonary disease [3].

Management Principles

The cornerstone of SJS/TEN management is immediate withdrawal of the culprit medication and transfer to a specialized care unit, preferably a burn center or intensive care unit with experience managing these conditions [4,10]. Prompt cessation of the offending drug is associated with decreased mortality compared to cases where the medication is continued [2].

Supportive care is universally recognized as essential and includes meticulous wound care, fluid and electrolyte management, nutritional support, temperature regulation, pain control, and prevention of secondary infections [4,10,14]. Ophthalmologic evaluation and care are critical to prevent vision-threatening complications, and all patients should receive specialized eye care during the acute phase and long-term follow-up [10-11].

The role of immunomodulatory therapies remains controversial due to the lack of high-quality randomized controlled trials. A Cochrane systematic review found very low-certainty evidence for most interventions, with etanercept showing potential mortality reduction compared to corticosteroids (low-certainty evidence) [14]. Systemic corticosteroids, intravenous immunoglobulin (IVIG), cyclosporine, and TNF-alpha inhibitors have all been used, but no single agent has demonstrated clear superiority [1,14,15,16]. Current practice varies widely across centers, with treatment approaches ranging from supportive care alone to various combinations of immunomodulatory agents [5-10].

A recent review of evidence from 2017-2023 concluded that high-quality studies assessing the efficacy of immunomodulating agents in accelerating healing and reducing mortality are still lacking, and that best supportive care in expert centers remains the cornerstone of treatment [10]. The multidisciplinary approach employed in our patient's care, combining specialized supportive measures with systemic corticosteroids and transfer to a burn unit, is consistent with current best practices.

Importance of Early Recognition

This case underscores the critical importance of early recognition of SJS/TEN. Diagnostic delay can result in continued exposure to the culprit medication, delayed transfer to specialized care, and inappropriate treatment that may worsen outcomes. Clinicians should maintain a high index of suspicion for SJS/TEN in patients presenting with:

1. Progressive vesiculobullous eruptions with mucosal involvement
2. Recent initiation (within 4-28 days) of high-risk medications
3. Prodromal symptoms of fever, malaise, and skin pain
4. Positive Nikolsky sign
5. Atypical target lesions with dusky centers
6. Rapid progression despite initial treatment
7. When SJS/TEN is suspected, immediate dermatologic consultation, skin biopsy for histopathologic confirmation, withdrawal of suspected medications, and transfer to a specialized care unit should be prioritized [8-10].

Conclusion

This case of carbamazepine-induced SJS/TEN initially misdiagnosed as varicella demonstrates the diagnostic challenges clinicians face when evaluating patients with severe cutaneous eruptions. The delay in diagnosis resulted from the similarity of early SJS/TEN manifestations to more common conditions, highlighting the need for heightened clinical awareness of this rare but life-threatening condition.

Key learning points from this case include: (1) SJS/TEN should be considered in the differential diagnosis of any patient presenting with progressive vesiculobullous eruptions, particularly in the context of recent medication initiation; (2) carbamazepine is a well-established high-risk medication for SJS/TEN, and genetic testing for HLA-B15:02 should be considered in at-risk populations prior to drug initiation; (3) early recognition and immediate withdrawal of the culprit drug are critical to improving outcomes; (4) transfer to specialized care units and implementation of multidisciplinary supportive care are essential components of management; and (5) despite diagnostic challenges, complete recovery is possible with appropriate and timely intervention.

As SJS/TEN remains a rare condition with high morbidity and mortality, continued education of healthcare providers regarding early recognition and appropriate management is essential. Future research should focus on developing validated diagnostic algorithms, identifying novel therapeutic targets, and conducting high-quality randomized controlled trials to establish evidence-based treatment protocols.

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