Clinical, diagnostic, and treatment comparisons between Stevens-Johnson syndrome and toxic epidermal necrolysis: review of the literature

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INTRODUCTION
Stevens-Johnson syndrome is a rare but serious medical condition, which is classified within the blistering diseases of the skin and mucous membranes. It is characterized by a severe and generalized immune-mediated inflammatory reaction, predominantly affecting the skin and mucous membranes, such as the eyes, mouth and genitalia.

This syndrome is considered an extreme form of a disease known as erythema multiforme, but is distinguished by its severity and extent. The exact etiology of Stevens-Johnson syndrome has not been fully established, but it is believed that it may be related to an autoimmune response triggered by certain medications, viral, bacterial or fungal infections, as well as other genetic and environmental factors.

On the other hand, toxic epidermal necrolysis (TEN) is an acute and severe dermatologic disease characterized by extensive sloughing of the epidermis, the outermost layer of the skin, over the entire body. It is considered a severe form of Stevens-Johnson syndrome and is associated with high morbidity and mortality.

The disease initially manifests with nonspecific symptoms such as fever, malaise and sore throat. Subsequently, characteristic skin lesions develop, including erythema (redness) and blisters in the form of rapidly spreading patches or plaques. These lesions may coalesce and form large areas of sloughing of the epidermis, leading to exposure of the underlying dermis. The affected skin may present a burned appearance and have a burn-like texture.

EPIDEMIOLOGY
The epidemiology of Stevens-Johnson syndrome (SJS) is characterized by its infrequent but significant nature in terms of morbidity and mortality. The annual incidence of SJS is estimated to range from 1.2 to 6 cases per million people, with a prevalence of about 1 case per 100,000 population. However, these figures may vary depending on the population studied and the risk factors present.

Stevens-Johnson syndrome affects both sexes equally and can occur in any age group, although it is seen more frequently in young adults and adolescents. There is a significant association between SJS and certain predisposing factors, such as the presence of certain histocompatibility antigen alleles, particularly the HLA-B1502 allele in individuals of Asian descent and the HLA-B5801 allele in individuals of Han Chinese and Thai descent.

In terms of mortality, Stevens-Johnson syndrome is considered a potentially fatal disease, with a case-fatality rate ranging from 5% to 10%. Serious complications associated with SJS include sepsis, multiorgan failure, metabolic...
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disorders, respiratory failure and water and electrolyte imbalances. Mortality tends to be higher in older patients and in those with extensive body surface area involvement, as well as in those with delayed diagnosis and initiation of appropriate treatment.

On the other hand, the epidemiology of toxic epidermal necrolysis (TEN) is characterized by its rarity and severity, making it a dermatologic disease of significant clinical importance. The incidence of NET varies widely according to geographic regions and population groups studied, with estimates ranging from 0.4 to 1.2 cases per million population per year.

NET can affect individuals of all ages, but shows a bimodal distribution with peaks of incidence in two main groups: children and older adults. In children, NET tends to be more common in those younger than 10 years, while in adults older than 40 years. The gender ratio may also vary, but a slight preponderance in males is observed in some studies.

The etiology of toxic epidermal necrolysis is closely related to the administration of drugs, which are responsible in most cases. Certain drugs, such as antiepileptic drugs (carbamazepine, lamotrigine, phenytoin), antibiotics (sulfonamides, penicillins, cephalosporins) and nonsteroidal anti-inflammatory drugs (NSAIDs), have been found to be associated with an increased risk of developing TEN. Other triggers may include viral infections, especially herpes simplex virus and Epstein-Barr virus, as well as other bacterial and fungal infections.

In terms of mortality, toxic epidermal necrolysis is a potentially lethal disease, with a reported mortality rate between 25% and 35%. Mortality is higher in older age groups and in those with extensive body surface area affected. In addition, complications associated with NET, such as sepsis, multiple organ failure and secondary infections, can also increase the risk of death.

Importantly, the epidemiology of toxic epidermal necrolysis may be influenced by genetic and ethnic factors. Certain histocompatibility antigen alleles, such as HLA-B*1502 in people of Asian descent, have been shown to be associated with an increased risk of developing NET induced by certain drugs, such as carbamazepine. In addition, differences in disease prevalence have been observed in different ethnic groups and geographic regions.

CLINIC

Stevens-Johnson syndrome (SJS) is characterized by a unique and distinctive clinical presentation involving multiple body systems. This disease is classified within the spectrum of blistering skin and mucosal diseases, and its clinical presentation is the result of a severe and generalized inflammatory immune response.

JSS typically begins with nonspecific, systemic symptoms, such as fever, malaise, sore throat, joint pain and weakness. These symptoms may precede skin manifestations by several days. As the disease progresses, characteristic skin lesions develop in the form of red or purple spots, known as bull's-eye or "flaming bull's-eye" lesions. These lesions are highly inflammatory and may present a burn-like appearance.

The skin lesions in JSS have a symmetrical pattern and usually affect the trunk, face, extremities, and mucous membranes. Over time, lesions may evolve into blisters or erosions that can rapidly coalesce and spread, leading to extensive epidermal detachment, known as toxic epidermal necrolysis. This detachment of the epidermis exposes the underlying dermis, which can result in significant loss of skin barrier function and the development of serious complications, such as secondary infections and fluid and protein loss.

In addition to cutaneous manifestations, JSS also affects the mucous membranes, especially those of the mouth, eyes and genitalia. This can result in the formation of blisters, erosions and ulcers in these areas, which is associated with symptoms such as painful swallowing, dry eyes, redness, tearing, blurred vision and painful urination.

At the systemic level, JSS can affect various organs and systems, such as the gastrointestinal tract, respiratory system and renal system. Patients may develop severe complications, such as difficulty swallowing due to ulcer formation in the esophagus, respiratory distress due to upper airway involvement, and kidney damage due to inflammation and tubular necrosis.

The severity of SJS is assessed using severity indices such as SCORTEN (Score of Toxic Epidermal Necrolysis), which takes into account variables such as age, extent of body surface area affected, presence of concomitant diseases and other clinical parameters. Mortality associated with JSS can vary, but is estimated to range from 10% to 30%.

However, toxic epidermal necrolysis (TEN) manifests clinically as an acute and severe dermatological disease characterized by extensive sloughing of the epidermis, the outermost layer of the skin, accompanied by severe and potentially life-threatening skin and mucosal lesions. This disease is considered a severe and extensive form of Stevens-Johnson syndrome (SJS).

The clinical presentation of NET is dramatic and may begin with nonspecific symptoms such as fever, malaise, sore throat and joint pain. These initial symptoms are followed by the appearance of characteristic skin lesions that manifest as extensive and progressive erythema (redness) in the form of patches or plaques that may be painful to the touch. These skin lesions usually rapidly progress to blistering and

982 Volume 03 Issue 05 May 2023 Corresponding Author: Néstor Daniel Rodriguez Trujillo
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erosions, which may coalesce and spread, resulting in large areas of epidermal detachment.

Loss of epidermal integrity exposes the underlying dermis, which can result in the appearance of burn-like lesions, ulcer formation and increased vulnerability to secondary infections. These skin lesions are widely distributed on the body, affecting areas such as the trunk, face, extremities and mucous membranes, including the mouth, eyes, respiratory tract and genitalia.

Mucosal complications in NET can be especially severe and debilitating. Blisters and erosions in the oral mucosa can cause severe pain, difficulty swallowing, loss of appetite and difficulty maintaining adequate food and fluid intake. The ocular mucous membranes may be affected, causing redness, tearing, eye pain and, in severe cases, may lead to corneal ulcers and loss of vision. The respiratory tract and genitalia may also show mucosal lesions, which may lead to respiratory symptoms, dysuria and difficulty in urination.

In addition to cutaneous and mucosal manifestations, NET may affect other body systems. There may be systemic manifestations, such as high fever, malaise, chills and alterations in laboratory values, such as the presence of leukocytosis and elevated liver enzyme levels. In severe cases, multiple organ dysfunction may occur, mainly affecting the respiratory, cardiovascular, renal and gastrointestinal systems, which may result in life-threatening complications.

**DIAGNOSIS**

The diagnosis of Stevens-Johnson syndrome (SJS) involves a thorough evaluation of the clinical findings, patient history and exclusion of other possible causes of the disease. Because SJS presents with a wide range of clinical manifestations and may be similar to other dermatologic conditions, accurate diagnosis requires careful evaluation and the involvement of an experienced medical team.

The diagnosis of JSS is based on established clinical criteria, such as the presence of severe cutaneous and mucosal lesions, blisters, erosions and extensive sloughing of the epidermis. The distribution and symmetry of the skin lesions, together with their rapid progression, are distinctive features. In addition, involvement of mucous membranes, such as the mouth, eyes, respiratory tract and genitalia, is a typical finding in JSS.

It is essential to obtain a detailed patient history, including a history of recent medications, infections, or environmental exposures that could be related to the onset of symptoms. JSS is strongly associated with the administration of certain drugs, especially antiepileptics, antibiotics, and nonsteroidal anti-inflammatory drugs. Identifying exposure to these drugs can provide important clues for diagnosis.

In addition, laboratory tests may be performed to assess the severity and possible complications of JSS. These may include complete blood tests to assess organ function, such as white blood cell count, liver enzyme levels, and inflammatory markers. In addition, skin and mucosal samples may be taken for biopsy and histopathological analysis, which may reveal characteristic changes of necrosis and epidermal detachment.

It is important to note that the diagnosis of JSS should be differentiated from other diseases with similar clinical manifestations, such as pemphigus vulgaris, exfoliative dermatitis and severe allergic reactions. This may require careful evaluation and the involvement of dermatology and allergic disease specialists.

It should be noted that the diagnosis of toxic epidermal necrolysis (TEN) involves a thorough clinical evaluation based on a combination of clinical findings, patient history, laboratory tests and histopathological analysis. Since NET shares clinical features with other serious dermatologic conditions, an accurate differential diagnosis is crucial.

The diagnosis of NET is established mainly by identifying the following characteristic clinical criteria: extensive and progressive epidermal detachment, severe skin lesions and blistering affecting a large body surface. These skin lesions are usually accompanied by erythema (redness) and may rapidly progress to blistering and erosions that coalesce and spread, leading to massive epidermal detachment. Symmetrical distribution of skin lesions and involvement of mucous membranes, such as oral, ocular, genital and respiratory, are also hallmark findings of NET.

Evaluation of the patient’s medical history is essential for the diagnosis of NET. A history of drug exposure should be investigated, especially drugs known to trigger NET, such as certain antiepileptics, antibiotics, and nonsteroidal anti-inflammatory drugs. The timing between drug exposure and symptom onset is an important factor to consider.

Laboratory tests play a complementary role in the diagnosis of NET. Blood tests can reveal findings such as leukocytosis (increased white blood cell count), elevated liver enzymes, and inflammatory markers, which can indicate the severity of the disease and help rule out other conditions. In addition, testing for concomitant infections, such as reactivity to human herpes virus or the presence of other pathogens, may be helpful in guiding appropriate patient management.

Definitive confirmation of the diagnosis of NET is made by histopathological analysis of skin and mucosal samples. These biopsies will reveal distinctive features, such as necrosis and epidermal detachment, as well as inflammation and destruction of the superficial layers of the skin.

It is important to emphasize that the diagnosis of NET must be differentiated from other conditions with similar clinical manifestations, such as Stevens-Johnson syndrome and
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exfoliative dermatitis. This requires careful analysis of the clinical findings and the involvement of dermatology and pathology specialists.

TREATMENT

The treatment of Stevens-Johnson syndrome (SJS) is a complex, multidisciplinary process that requires specialized medical care in a hospital setting. The main goal of treatment is to minimize the damage and complications associated with this life-threatening disease. The therapeutic approach focuses on aggressive disease, supportive care and specific treatment measures.

First, it is essential to immediately identify and discontinue any medications suspected of triggering SJS. This involves reviewing the patient's medication list and consulting with specialists in pharmacology and dermatology to determine the causal relationship and establish a safe alternative medication plan.

Management of the underlying disease includes control and treatment of secondary infections. Broad-spectrum antibiotics may be administered to prevent and treat concomitant bacterial infections, while cultures and sensitivity testing are performed to direct specific antimicrobial therapy. If an associated viral infection is identified, specific antiviral medications may be considered.

Supportive care is essential to ensure patient stability and comfort. General measures such as controlling body temperature, maintaining adequate hydration and providing adequate nutrition through alternative routes, such as enteral or parenteral feeding, can be used if oral intake is difficult or impossible due to mucosal lesions. In addition, meticulous skin and mucosal care should be provided to prevent secondary infections and promote healing.

In terms of specific treatment, administration of intravenous immunoglobulin (IVIG) has been shown to be beneficial in SJS. IVIG helps modulate the immune response and reduce inflammation, which may speed recovery and improve long-term outcomes. High doses of IVIG are administered over several days, depending on clinical judgment and severity of illness.

In severe cases of SSJ, the use of skin replacement therapy, such as skin grafting, may be considered. This involves transferring layers of healthy skin from donors or the patient's own skin to the affected areas to promote healing and regeneration of the epidermis.

In addition, measures to prevent complications should be implemented, such as close monitoring of organ function, especially of the respiratory, cardiovascular, renal and gastrointestinal systems. If organ dysfunction develops, intensive management in intensive care units may be necessary to provide life support and specialized treatment.

It is important to emphasize that the treatment of JSS must be individualized and tailored to the needs and characteristics of each patient. The medical team must work closely together to adequately assess and manage complications such as sepsis, respiratory failure, renal failure and coagulation disturbances.

And on the other hand, the treatment of toxic epidermal necrolysis (TEN) is a complex and challenging process that requires specialized medical care in a hospital setting. The therapeutic approach focuses on aggressive disease management, supportive care and prevention of serious complications.

Treatment of NET begins with the identification and immediate discontinuation of the triggering drug, if known. This involves a thorough review of the patient's medical history, including recent medications, and consultation with specialists in pharmacology and dermatology to determine the causal relationship and avoid future exposures to the triggering substance.

Aggressive medical management of NET involves hospitalization of the patient in a specialized unit, such as a burn unit or intensive care unit. Frequent and thorough monitoring of vital signs, organ function and hematologic parameters is essential to assess disease progression and adjust treatment accordingly.

Pharmacologic treatment focuses on control of inflammation and suppression of the dysregulated immune response. High-dose systemic corticosteroids may be used to reduce inflammation and stabilize the skin and mucous membranes. However, there is debate in the medical community about the use of corticosteroids in NET, and their benefit and risk must be evaluated individually in each patient.

In addition to corticosteroids, other immunomodulators, such as intravenous immunoglobulin (IVIG) and tumor necrosis factor (TNF) inhibitors, can be used to modulate the immune response and reduce the severity of the disease. These treatments can be administered in combination with corticosteroids or as alternative therapy in cases where corticosteroids are contraindicated.

Management of skin and mucosal lesions is essential to prevent secondary infections and promote healing. Meticulous care of the affected areas should be performed, including gentle cleansing, application of sterile dressings and use of specialized dressings to promote skin regeneration and prevent blister and ulcer formation.

Adequate hydration is essential in the treatment of NET. Intravenous solutions can be used to maintain optimal water and electrolyte balance, as fluid loss through skin lesions and mucous membranes can be significant.

Supportive care is an integral part of NET treatment. This involves providing the patient with a comfortable and calm
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environment, the use of analgesics for pain control, and the care of ophthalmology and dental specialists for the management of ocular and oral complications, respectively.

In severe cases of NET, transfer to an intensive care unit may be considered for intensive monitoring and treatment of systemic complications, such as respiratory failure, renal or hepatic dysfunction, and hemodynamic disturbances.

CONCLUSIONS
In conclusion, the comparison between toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SSJ) reveals that both are severe skin and mucosal disorders with overlapping clinical features and a similar pathogenetic basis. Both conditions are characterized by the presence of extensive epidermal sloughing, blistering and cutaneous erosions, as well as involvement of the mucous membranes.

Although they share similarities in terms of clinical presentation, NET and JSS differ in the severity and extent of epidermal detachment. NET is considered a more severe and extensive form of the disease, with epidermal detachment involving more than 30% of the body surface, whereas JSS is characterized by epidermal detachment involving less than 10% of the body surface.

From the etiological point of view, both NET and SSJ can be triggered by exposure to certain drugs, although they can also be associated with viral infections and autoimmune diseases. In both cases, the dysregulated immune response plays a crucial role in the pathogenesis of the disease, resulting in destruction and sloughing of the epidermis.

In terms of diagnosis and treatment, the general guidelines are similar for both conditions. Diagnosis is based on clinical criteria, patient history, laboratory tests, and histopathologic analysis. Management includes identification and discontinuation of the triggering drug, management of the underlying disease, supportive care and specific treatment to control inflammation and prevent complications.

However, it is important to note that NET is considered a more severe and potentially life-threatening form compared to SSJ, due to the extent and severity of epidermal detachment. Therefore, treatment of NET may require more intensive and specialized measures, such as intravenous immunoglobulin administration and management in intensive care units.

In summary, although toxic epidermal necrolysis and Stevens-Johnson syndrome share similar clinical features and pathogenetic basis, there are differences in the severity and extent of epidermal detachment. Early recognition, accurate diagnosis and an appropriate therapeutic approach are crucial to improve outcomes and minimize complications in both disorders. Multidisciplinary and specialized medical care plays a key role in the optimal management of these patients.

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