Stevens-Johnson syndrome and toxic epidermal necrolysis in childhood-onset systemic lupus erythematosus patients: a multicenter study

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ABSTRACT

Objective: To assess Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in a large population of childhood-onset systemic lupus erythematosus (cSLE) patients.

Methods: Multicenter study including 852 cSLE patients followed in Pediatric Rheumatology centers in São Paulo, Brazil. SJS was defined as epidermal detachment below 10% of body surface area (BSA), overlap SJS-TEN 10-30% and TEN greater than 30% of BSA.

Results: SJS and TEN were observed in 5/852 (0.6%) cSLE female patients, three patients were classified as SJS and two patients were classified as overlap SJS-TEN; TEN was not observed. The mean duration of SJS and overlap SJS-TEN was 15 days (range 7-22) and antibiotics induced four cases. Regarding extra-cutaneous manifestations, hepatomegaly was observed in two cSLE patients, nephritis in two and neuropsychiatric involvement and conjunctivitis were observed respectively in one patient. Hematological involvement included lymphopenia in four, leucopenia in three and thrombocytopenia in two patients. The mean SLEDAI-2K score was 14.8 (range 6-30). Laboratory analysis showed low C3, C4 and/or CH50 in two patients and the presence of anti-dsDNA autoantibody in two patients. One patient had lupus anticoagulant and another one had anticardiolipin IgG. All patients were treated with steroids and four needed additional treatment such as intravenous immunoglobulin in two patients, hydroxychloroquine and azathioprine in two and intravenous cyclophosphamide in one patient. Sepsis was observed in three cSLE patients. Two patients required intensive care and death was observed in one patient.

Conclusion: Our study identified SJS and overlap SJS-TEN as rare manifestations of active cSLE associated with severe multisystemic disease, with potentially lethal outcome.

Keywords: Stevens-Johnson syndrome; Toxic epidermal necrolysis; Childhood-onset systemic lupus erythematosus; Systemic lupus erythematosus; Childhood

INTRODUCTION

Systemic lupus erythematosus (SLE) is a rare multisystem autoimmune disease more common in adults (aSLE) with 10% to 20% of cases beginning in children and adolescents1. Childhood-onset SLE (cSLE) is characterized by the involvement of various organs and systems, such as mucocutaneous, which has been reported in 50 to 85% at the time of diagnosis or during the course of the disease2,3.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions with high morbidity and mortality, usually induced by medications or infections4,5. They result in acute onset of target lesions followed by detachment of the epidermis and epithelia resulting in extensive areas of denuded skin, necrosis and mucosal erosions, generally with the presence of Nikolski’s sign6,7. Both diseases are part of a single spectrum of severe epidermolytic reactions, differing mainly by the extent of skin detachment and type of cutaneous lesions.
The initial lesions are characterized by atypical targets and/or purpuric macules commonly in upper torso, proximal limbs, and face, spreading to the trunk and distal limbs. Palms and soles are often involved. Mucosal membranes of the eyes, mouth, nose and genitalia can initially appear, leading to an erosive and hemorrhagic mucositis.

Other clinical features such as fever, malaise and upper respiratory tract symptoms and ocular inflammation can precede the eruption by several days. Necrosis can occur in the epithelia of the respiratory tract, causing bronchial and tracheal obstruction and ventilatory compromise; in gastrointestinal tract, leading to exuberant diarrhea; and in kidneys, causing hypoperfusion, acute tubular necrosis and acute kidney injury. Mild elevation of liver enzymes is usual, although significant hepatitis or hepatic impairment are rare.

Of note, SJS and TEN can occur simultaneously with SLE and particularly in cSLE patients. There are, however, no reports characterizing their prevalence and describing SJS and TEN in a large population of cSLE patients.

METHODS

STUDY DESIGN AND PATIENTS
A retrospective multicenter cohort study was performed including 1,017 consecutive cSLE patients followed in ten Pediatric Rheumatology tertiary referral centers in São Paulo state, Brazil. The charts were revised from 2012-2014. One hundred and sixty five patients were excluded due to: incomplete medical charts (n=96), undifferentiated connective tissue disorder with 3 or fewer American College of Rheumatology (ACR) criteria for SLE (n=43), isolated cutaneous lupus erythematosus (n=11), neonatal lupus erythematosus (n=8), drug-induced lupus (n=5) and other autoimmune diseases (n=2). All the remaining 852 cSLE patients fulfilled the ACR criteria for SLE, with disease onset before 18 years of age and current age up to 25 years old. In all the participant centers the Committee for Research Ethics approved the study.

An investigator meeting was held in the beginning of the study in the city of São Paulo to define the protocol, including definitions of clinical, laboratory and treatment parameters, disease activity, SJS and TEN characteristics and outcomes (intensive care unit stay and death). All investigators used the same specific database. All patient's medical charts were reviewed according to this standardized protocol.

SJS was defined as epidermal detachment below 10% of body surface area (BSA) with purpuric macules or flat typical targets, overlap SJS-TEN with detachment of 10-30% of BSA with purpuric macules or flat typical targets and TEN with detachment of greater than 30% of BSA with or without purpuric macules or flat typical targets, also known as spots.

All cSLE patients with the suspicion of SJS, overlap SJS-TEN or TEN were evaluated by a local dermatologist.

DEMOGRAPHIC DATA, CLINICAL EVALUATION, DISEASE ACTIVITY AND DRUG THERAPY
Demographic data analysis included: gender, age at SJS/TEN onset, duration of cSLE before SJS/TEN in months and duration of SJS/TEN in days. Descriptors and definitions of SLE clinical manifestations were based on SLE Disease Activity Index 2000 (SLEDAI-2K) score of disease activity, and were evaluated at the manifestation of SJS/TEN. Other SJS/TEN characteristics included the identification of the triggering agent, presence of blisters/vesicles and mucosal involvement, percentage of body surface area with epidermal detachment and extra-cutaneous involvement. Other cumulative SLE clinical manifestations included hepatomegaly [based on physical exam with liver edge ≥ 2 cm below the right costal margin or imaging (ultrasound or computer tomography when available)] and splenomegaly [based on physical exam with palpable spleen or imaging (ultrasound or computer tomography when available)]. Neuropsychiatric lupus included 19 syndromes according to ACR classification criteria.

Complement levels (CH50, C3 and C4) were assessed by immunodiffusion, turbidimetric immunoassay or immunonephelometry. Anti-double-stranded DNA (anti-dsDNA) was assessed by indirect immunofluorescence or Enzyme Linked Immuno Sorbent Assay (ELISA); anti-cardiolipin (aCL) IgG and IgM autoantibodies by ELISA. All the autoantibodies profile were carried out at each center. The cutoff values from the kit manufacturer were used to define abnormal. Lupus anticoagulant was detected according to the guidelines of the International Society on Thrombosis and Hemostasis.

Drug treatment data (prednisone, intravenous methylprednisolone, chloroquine diphosphate, hydroxychloroquine sulfate, azathioprine, cyclosporine,
micofenolate, intravenous cyclophosphamide, intravenous immunoglobulin) were also recorded.

RESULTS

SJS and TEN were observed in 5/852 (0.6%) cSLE patients, all girls, with age ranging between 2 to 18 years old. Three patients were classified as SJS and two patients were classified as overlap SJS-TEN; TEN was not observed. In one patient these manifestations occurred at SLE diagnosis and in four patients during the follow-up. The mean duration of SJS and overlap SJS-TEN was 15 days (range 7-22) and four cases were induced by antibiotics. Demographical and clinical characteristics as well as disease activity (SLEDAI-2K) of the five cSLE patients were shown in Table I. Presence of autoantibodies, treatment and outcome were shown in Table II.

All patients had blisters, vesicles and mucosal involvement. Regarding extra-cutaneous manifestations, sepsis was observed in three patients, hepatomegaly in two, nephritis in two, conjunctivitis in two and neuropsychiatric involvement in one. Four patients had hematological involvement, such as lymphopenia <1,500/mm³ in four, leucopenia <4,000/mm³ in three, and thrombocytopenia <100,000/mm³ in two cSLE patients.

The mean SLEDAI-2K score was 14.8 (range 6-30). The laboratory tests analysis showed low C3, C4 and/or CH50 in two patients and the presence of anti-dsDNA antibodies in two patients. One patient had lupus anticoagulant positive and another one had anticardiolipin IgG.

Therapy in cSLE patients with SJS and TEN comprised of steroid use either in intravenous methylprednisolone or prednisone. Four patients needed additional treatment, such as intravenous immunoglobulin in two patients, combined hydroxychloroquine and azathioprine in two and intravenous cyclophosphamide in one patient. Regarding outcome, two patients required intensive care unit and death was observed in one patient.

DISCUSSION

Our multicenter study characterized SJS and overlap

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**TABLE I. DEMOGRAPHICAL, CLINICAL CHARACTERISTICS AND DISEASE ACTIVITY OF THE FIVE SJS/TEN cSLE PATIENTS**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) / gender</td>
<td>11 / Female</td>
<td>18 / Female</td>
<td>2 / Female</td>
<td>13 / Female</td>
<td>10 / Female</td>
</tr>
<tr>
<td>Duration of cSLE before SJS/TEN (months)</td>
<td>0</td>
<td>43</td>
<td>2</td>
<td>48</td>
<td>11</td>
</tr>
<tr>
<td>Duration of SJS/TEN (days)</td>
<td>14</td>
<td>7</td>
<td>22</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Identification of the triggering agent</td>
<td>Antibiotics</td>
<td>No</td>
<td>Antibiotics</td>
<td>Antibiotics</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Blisters-vesicles and mucosal involvement</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Epidermal detachment, % of body surface area</td>
<td>5</td>
<td>20</td>
<td>11</td>
<td>Less than 10</td>
<td>Less than 10</td>
</tr>
<tr>
<td>Extra-cutaneous involvement</td>
<td>Conjunctivitis Sepsis Hepatomegaly Lymphopenia Sepsis Nephritis Neutrophilic Leucopenia Lymphopenia Thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLEDAI-2K at SJS/TEN</td>
<td>10</td>
<td>15</td>
<td>13</td>
<td>6</td>
<td>30</td>
</tr>
</tbody>
</table>

SJS-TEN as rare manifestations in a large cSLE population. The advantage of including a large cSLE population selected in tertiary referral centers allowed a better evaluation of these rare and potentially lethal manifestations. The use of a standardized combined database, with proper SJS, overlap SJS-TEN and TEN definitions minimized possible bias. In addition, in two large prospective European studies characterizing SJS and TEN, association with SLE and other autoimmune rheumatologic diseases was found in approximately 0.6 to 5% of all patients with these severe manifestations8,9. We found five (0.6%) cSLE patients with SJS and overlap SJS-TEN in our cohort population, and one of them was previously reported (patient 1)11. TEN seemed to be rarer since we did not find any patient in our cohort study.

However, the main limitation of this study was the retrospective design and possible missing data. In addition, skin biopsies were not a routine procedure in all participant Pediatric Rheumatology centers. Only one patient had SJS features confirmed by autopsy (case 2). However, all other patients had a close drug causality and were evaluated by a local experienced dermatologist.

These skin vesiculobullous diseases are severe and life-threatening cutaneous adverse reactions mainly caused by drugs, infections or sometimes, unidentified causes7-9,21. Antibiotics are the most frequent cause followed by anti-inflammatories and analgesics, as observed herein4. Other organs are described to be involved as we found in most cases.

Classification of SJS and TEN is based on three clinical criteria: the pattern of individual skin lesions, their distribution and the maximum extent of epidermal detachment7-9. Importantly, due to the large detachment of the skin, TEN patients have higher mortality rates4,7.

The alternative diagnosis to SJS and TEN such as erythema multiforme and drug induced lesions, pemphigus, pemphigoid, acute graft versus host disease and other immunobullous diseases as well as infectious diseases like Mycoplasma, Herpes virus and HIV must be ruled out7.

In some cases, the diagnosis of lupus-induced TEN and classical TEN is intriguing. In both cases the classical clinical and histopathological features will be present, with epidermolytic reactions and skin detachment due to inflammatory dermatoses with keratinocyte apoptosis and the same molecular mediators involved13. Lupus-induced TEN tend to have a subacute presentation of weeks with the absence of systemic involvement and no history of drug ingestion, while classical TEN has an acute evolution within 3 to 4 days or sometimes within hours, with a close drug-related causality and negative immunofluorescence4,21. In contrast to SJS-TEN, cutaneous lupus demonstrates the prototypic interface dermatitis with deposition of immunoglobulins (IgG, IgM and/or IgA, C3) in direct immunofluorescence13,22,23.

In both manifestations, renal involvement is common. It is known that in cSLE renal disease has been reported in almost two thirds of the patients and more frequent than the adult population24,25. Due to systemic drug-induced hypersensitivity, SJS and TEN can also

<table>
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<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low C3, C4 and/or CH50</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>No</td>
<td>LA</td>
<td>ACL IgG</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Use of steroids</td>
<td>Prednisone 2mg/kg</td>
<td>Prednisone 1mg/kg</td>
<td>Prednisone 1mg/kg Intravenous methylprednisolone</td>
<td>Prednisone 0.8mg/kg</td>
<td>Prednisone 1mg/kg Intravenous methylprednisolone</td>
</tr>
<tr>
<td>Other treatment for SJS/TEN</td>
<td>IVIG</td>
<td>Cyclophosphamide IVIG</td>
<td>Hydroxychloroquine Azathioprine</td>
<td>None</td>
<td>Hydroxychloroquine Azathioprine</td>
</tr>
<tr>
<td>ICU stay</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Death</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

lead to drug-induced acute interstitial nephritis in almost 20% of the cases. In our cohort, 2 patients had lupus nephritis prior to cutaneous involvement (cases 2 and 5). One of them had worsening of the renal disease with hypertension and acute renal failure at SJS manifestation (case 2).

We also observed that all patients presented a SLEDAI-2K score higher or equal to 6. We hypothesized that SJS-TEN occurs in the exacerbation of lupus, concomitantly with the disease presentation or during flares. This finding should be further analyzed in order to establish a possible association and has not been described yet in the literature. There is no optimal treatment for this condition but glucocorticoids are frequently beneficial and intravenous immunoglobulin (IVIG) can be administered as an additional treatment. The exclusion of any triggering agent is required and antibiotics should be promptly discontinued, as occurred in four of our cSLE patients.

In conclusion, we have presented five patients with cSLE who presented SJS and overlap SJS-TEN at the time of cSLE diagnosis or during the course of the disease. Most patients had a clear drug causality mainly related to antibiotics and required an intensive care unit treatment, showing how rare and lethal these manifestations can occur in our population. Further efforts may be needed for the search of risk factors and treatment in the pediatric lupus patients.

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