Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Ear, Nose, and Throat Description at Acute Stage and After Remission

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IMPORTANCE Ear, nose, and throat (ENT) lesions are frequently involved in Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), although a detailed description is lacking in the literature.

OBJECTIVES To describe ENT lesions at the acute stage and follow-up in a large series of patients with SJS/TEN and identify factors associated with the severe ENT form.

DESIGN, SETTING, AND PARTICIPANTS Retrospective study of 49 patients with SJS/TEN hospitalized in a referral care center from 2005 to 2010. Patients who underwent a full ENT workup including examination and a nasal fiberoptic endoscopy by an otorhinolaryngologist in the acute phase and during follow-up at 2 and 12 months were included in the study.

MAIN OUTCOMES AND MEASURES Recorded variables included maximal body surface area (BSA) detachment, SCORTEN (Score of Toxic Epidermal Necrosis [a severity of illness score]), sites and type of ENT mucosal lesions, intensive care unit transfer, pulmonary infection, and mortality. “Severe ENT form” was defined by the occurrence of laryngeal lesions with the risk of airways obstruction. Clinical characteristics associated with severe ENT form were analyzed in univariate and multivariable analysis.

RESULTS Of the 49 patients who underwent a full ENT workup (female to male ratio, 1.1:1), ENT symptoms (eg, odynophagia, dysphagia, dysphonia, dyspnea, earache, nasal obstruction) occurred in 48 (98%). Dyspnea or dysphonia were significantly associated with severe ENT form (21% [P = .03] and 50% [P < .001], respectively). Topographic frequencies of lesions were as followed: lips and oral cavity (n = 46 [93%]) and pharynx and vestibule of the nose (n = 26 [53%]). Fourteen patients (29%) had severe ENT form. Findings for other recorded variables for those with vs without ENT examination are as follows: maximal BSA detachment (20% [0%–95%] vs 5.5% [0%–95%]; P = .004), SCORTEN (1 [0–5] vs 1 [0–5]; P = .54), intensive care unit transfer (10 [20%] vs 9 [19%]; P = .80), pulmonary infection (9 [18%] vs 6 [13%]; P = .10), and mortality (3 [6%] vs 5 [10%]; P = .70). In multivariable analysis, pulmonary infection was significantly associated with severe ENT form (odds ratio, 5.9 [95% CI, 1.1–32.8] [P = .04]). After remission of SJS/TEN, a complete ENT mucosal healing occurred in 36 patients (74%) at 2 months and in nearly all patients (n = 48 [98%]) at 1 year of follow-up.

CONCLUSIONS AND RELEVANCE Severe ENT form is associated with pulmonary infection and is easily detected by nasal fiberoptic endoscopy. ENT evaluation should be suggested when dysphonia or dyspnea is observed at the acute stage of SJS/TEN.

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Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are life-threatening severe cutaneous adverse reactions, with associated blistering, detachment of large epidermal sheets, and the involvement of at least 2 mucous membranes (eg, ocular, nasal, oral, genital, anal). Their annual incidence is estimated to be 1 to 2 persons per 1 million, and mortality at the acute stage reaches up to 22% (10% for SJS to 39% for TEN). The onset of SJS/TEN occurs 4 to 28 days after drug exposure, and no causative drug is yet identified in 30% of the patients. General symptoms such as influenza-like syndrome and fever, ocular pain, and ear, nose, and throat (ENT) pain often precede skin lesions. Mucous membrane lesions (ie, erythema, blisters, and/or erosions) precede skin detachment in 80% of the patients. Oral mucosa and ENT are frequently involved in small series in the literature. The aim of this study was to precisely describe ENT symptoms and lesions in a large series of patients with SJS/TEN.

Methods

Population
This retrospective study was approved by the CPP Paris IX local ethics committee. The study population included 49 patients with SJS/TEN who had a full ENT workup (ie, examination and nasal fiberoptic endoscopy by an otorhinolaryngologist). These patients were consecutively admitted in a national referral center from January 2005 to January 2010. The diagnosis of SJS/TEN was established according to the European Registry of Severe Cutaneous Reactions (RegiSCAR) criterion and confirmed by a skin biopsy result showing epidermal necrosis with a negative finding for immunoglobulin deposit along the dermoepidermal junction on direct immunofluorescence.

During this period, the characteristics of all patients admitted in the referral center were collected. Only patients who underwent ENT examination under routine care in the acute phase and during follow-up at 2 and 12 months were retrospectively considered.

Data Collection
Patients were classified as having SJS, TEN, or overlap syndrome according to their maximal body surface area (BSA) detachment (ie, SJS, <10%; TEN, ≥30%; and overlap syndrome, 10%-29%). For each patient the following variables were recorded: demographic data (age and sex), delay between disease onset and admission, duration of hospital stay, causative drug, associated immunosuppression factors (eg, cancer, human immunodeficiency virus seropositivity), initial and maximal BSA detachment, SCORTEN (Score of Toxic Epidermal Necrosis [a prognosis score including 7 independent clinical and biological variables]) at the day of admission, pulmonary infection, intensive care unit (ICU) transfer, tracheal intubation, and death. When assessed by bronchoscopy, bronchial detachment was described.

Standardized ENT Evaluation
The ENT workup was performed by 3 senior investigators (V.C., A.C., and J.F.P.) in the acute phase and during follow-up at 2 and 12 months. The ENT workup included the following at each consultation: ENT clinical data collection; examination of the oral cavity and ears; and a nasal fiberoptic endoscopy to evaluate nasal cavities and pharyngolarynx. Data were retrospectively collected and analyzed by 1 investigator (E.B.). The clinical ENT data recorded included symptoms (ie, odynophagia, dysphagia, dyspnea, dysphonia, nasal obstruction, epistaxis, earache, conductive deafness, otitis media) initial type of lesions (ie, enanthema, erosions, ulcerations, edema, scabs, pseudomembranes), topography of mucosal involvement (ie, oral cavity, pharynx, larynx, external ear, nose), and natural course of lesions.

Classification of Patients
Considering the prior literature about SJS/TEN, otolaryngologic manifestation, and the potential risk of upper airway obstruction, supraglottic and laryngeal lesions were considered to define a “severe ENT form.” Patients were subgrouped as “with severe ENT form” or “without severe ENT form.”

Statistical Analysis
Quantitative variables were expressed as mean (SD) or median (range) when appropriate and qualitative variables as number (percentage). All tests were 2 tailed, and \( P < .05 \) was considered statistically significant. The characteristics of the patients who were not included (without a standardized ENT physician examination) were compared with those included in the study sample. Table 1 gives the characteristics of the study population. Then, the characteristics of patients with and without severe ENT form were compared in univariate analyses. Odds ratios (ORs) were estimated with their 95% CIs using logistic regression models. Potential interactions were assessed by pairwise analyses, and confounding by fitting multiplicative models. Variables yielding \( P \) values smaller than 0.15 in the univariate analyses were entered into a multiple logistic regression model. The final model included the variables independently associated with severe ENT form. We conducted all statistical analysis using STATA Statistical Software (version 11.0, StataCorp LP).

Results

Study Population
During the study period, 49 of the 97 patients in the SJS/TEN cohort who were admitted consecutively in our department underwent a complete ENT workup (ie, examination and nasal fiberoptic endoscopy) and were considered the study population. The mean (SD) delay between disease onset and admission was 5 (3.8) (range, 1-20) days. The mean (SD) length of hospital stay was 21.5 (12.5) (range, 2-62) days. Causative drugs were identified in 41 patients (84%) and listed in Table 2. The initial onset presentation of SJS/TEN was cutaneous exanthema in 22 patients (45%), exclusively mucosal in 13 patients (26%), and concomitant cutaneous and mucosal in 14 patients (29%). The mean (SD) time interval between cutaneous and mucosal exanthema was 1.8 (3.0) (range, 0-18) days. ENT examination was...
performed with a mean (SD) delay of 6 (7.5) (range, 0-34) days after admission and 9 (9.8) (range, 1-50) days after disease onset. Because of secondary transfer of patients to our referral care center, there was a delayed ENT examination for 8 patients. Death was reported for 3 patients (6%) during hospital stay (cardiogenic shock, septic shock, and renal failure). Because of an open ongoing clinical trial, 38 patients (78%) were treated with cyclosporin during this period.† The characteristics of patients with a full ENT workup were compared with those of patients with SJS/TEN without ENT workup (Table 1). Patients with SJS/TEN and a full ENT workup did not significantly differ from the cohort without an ENT workup for age, sex, immunosuppression factor, SCORTEN, pulmonary infection, ICU transfer, and death (Table 1). However, the study population had significantly higher median (range) BSA detachment (20% [0%-95%] vs 5.5% [0%-95%]) (P = .004), and was significantly more treated by cyclosporin (78% vs 46%) or mechanical ventilation (16% vs 6%) (P < .001) (Table 1).

## Table 1. Demographic Data of 49 Patients With SJS/TEN

<table>
<thead>
<tr>
<th>Variable</th>
<th>With ENT Examination (n = 49)</th>
<th>Without ENT Examination (n = 48)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>37 (17-89)</td>
<td>45.5 (17-91)</td>
<td>.86</td>
</tr>
<tr>
<td>Female sex</td>
<td>26 (53)</td>
<td>22 (46)</td>
<td>.51</td>
</tr>
<tr>
<td>Immunosuppression factor</td>
<td>15 (30)</td>
<td>15 (31)</td>
<td>NA</td>
</tr>
<tr>
<td>Cancer</td>
<td>4 (8)</td>
<td>10 (21)</td>
<td>NA</td>
</tr>
<tr>
<td>HIV</td>
<td>14 (7)</td>
<td>6 (3)</td>
<td>.80</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>8 (4)</td>
<td>10 (5)</td>
<td>NA</td>
</tr>
<tr>
<td>BSA detachment, %</td>
<td>NA</td>
<td>20 (0-95)</td>
<td>NA</td>
</tr>
<tr>
<td>SCORTEN</td>
<td>NA</td>
<td>1 (0-5)</td>
<td>.54</td>
</tr>
<tr>
<td>Pulmonary Infection</td>
<td>9 (18)</td>
<td>6 (13)</td>
<td>.10</td>
</tr>
<tr>
<td>ICU transfer</td>
<td>10 (20)</td>
<td>9 (19)</td>
<td>.80</td>
</tr>
<tr>
<td>Tracheal intubation</td>
<td>8 (16)</td>
<td>3 (6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Death</td>
<td>3 (6)</td>
<td>5 (10)</td>
<td>.70</td>
</tr>
<tr>
<td>Treatment with cyclosporin</td>
<td>38 (78)</td>
<td>22 (46)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Abbreviations: BSA, maximal body surface area; ENT, ear, nose, and throat; HIV, human immunodeficiency virus; ICU, intensive care unit; NA, not applicable; SCORTEN, Score of Toxic Epidermal Necrosis; SJS/TEN, Stevens-Johnson syndrome and toxic epidermal necrolysis.*

## Table 2. Causal Drug Identified in 41 Patients*

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>7 (17)</td>
</tr>
<tr>
<td>Amifostine</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Antibacterial sulfonamides</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Others antibiotics</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Others</td>
<td>14 (34)</td>
</tr>
</tbody>
</table>

*Drug causality assessment was determined using the 6 ALDEN (Algorithm of Drug Causality for Epidermal Necrolysis) scoring criteria, which included the following: time to toxic epidermal necrolysis onset; drug present in the body at the time of the reaction onset; drug prechallenge or rechallenge; dechallenge, drug discontinued, or continued without harm; drug role, known for causality; other causes possible.*

## Table 3. ENT Symptoms in 49 Patients With SJS/TEN

<table>
<thead>
<tr>
<th>ENT Clinical Symptoms</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odynophagia</td>
<td>48 (98)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>45 (92)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Nasal obstruction</td>
<td>23 (47)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Ear ache</td>
<td>16 (32)</td>
</tr>
<tr>
<td>Conductive deafness</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Otorrhea</td>
<td>10 (20)</td>
</tr>
</tbody>
</table>

*Abbreviations: ENT, ear, nose, and throat; SJS/TEN, Stevens-Johnson syndrome and toxic epidermal necrolysis.*

## ENT Presentation

ENT symptoms (ie, odynophagia, dysphagia, breathing difficulties, dysphonia, nasal obstruction, earache) were found in 48 patients (98%), with odynophagia being the most frequent symptom (n = 48 [98%]), and their frequencies are listed in Table 3. ENT lesions were mostly located in the oral cavity (n = 46 [94%]), mainly the lips, the buccal mucosa, and the gum. Lesions included erythematous maculae (n = 45 [92%]), superficial erosions (n = 39 [80%]), oral ulcerations (n = 7 [14%]), and bullous (n = 5 [10%]). Most of the severe lesions were hemorrhagic bullous (n = 5 [10%]) on the palate (Figure). Nasal lesions were observed in 26 patients (53%), mainly in the vestibule. The nasal pits and the cavum were mostly intact. For 1 patient, the head of the middle turbinates was involved. Nasal lesions were scabs (n = 20 [41%]), enanthema (n = 19 [39%]), and erosions (n = 8 [16%]). Pharyngeal lesions were observed in 26 patients (53%) and consisted in enanthema (n = 26 [53%]), erosion (n = 15 [31%]), and edema of the epiglottis (n = 8 [16%]). Ulceration was reported for 1 patient. Laryngeal lesions that defined severe ENT form were found in 14 patients (29%) including enanthema (n = 14 [29%]), erosions (n = 2 [14%]), edema (n = 8 [16%]), and pseudomembranes (n = 3 [6%]) (Video). Diffuse pharyngolaryngeal lesions were found in
79% of the patients (11 of 14). Ear lesions were epidermolysis of the ear canal (n = 22 [45%]) and major chondritis (n = 2 [2%]). The ENT symptoms dysphonia or dyspnea were significantly more frequent in patients with severe ENT form vs those without severe ENT form (50% [P < .001] and 21% [P = .03], respectively).

Characteristics Associated With Severe ENT Form

The clinical characteristics of the patients with and without severe ENT are compared in Table 4. By univariate analysis, pulmonary infection was significantly associated with severe ENT form (OR, 7.3; 95% CI, 1.5-35.8) (P = .008). By multivariable analysis, pulmonary infection remained significantly associated with severe ENT form (OR, 5.9; 95% CI, 1.1-32.8) (P = .04).

Natural Course of ENT Disease

Twenty-nine patients (59%) required nasogastric feeding tube with a mean (SD) length of 11 (10.2) (range, 2-34) days. Placement of a nasogastric feeding tube over 10 days was necessary for 13 patients (27%). Twelve otitis externa (n = 12 [24%]) (ie, otorrhea and erythema in the ear canal) were secondarily reported at a mean (SD) delay of 17 (9.7) (range, 10-30) days after admission. At 2 months of follow-up, most patients (n = 36 [74%]) had a complete mucosal healing without sequelae. Persistent lesions were mostly located on the tongue (n = 10 [20%]). At the first year of follow-up, complete ENT mucosal healing without sequelae was confirmed in 48 patients (98%). For 1 patient, a persistent bullous lesion was located on the palate 7 months after disease onset, which displayed a congestive mucosa without alteration of the epithelium on histopathological examination (Figure).

Discussion

To our knowledge, this is the largest series to first describe acute-stage ENT manifestations in patients with SJS/TEN. All
patients included in this study underwent an otolaryngologist examination and a nasal fiberoptic endoscopy. Comparison of the characteristics of the study population with those of the nonincluded patients admitted in the referral center (without a standardized ENT physician examination) did not display any significant difference for sex, age, immunosuppression factor, disease severity criteria (SCORTEN), pulmonary infection, ICU transfer, or death. However, the management of the study population might have differed from the rest of cohort without a full ENT workup because they had higher BSA detachment or were notably receiving more mechanical ventilation or cyclosporin treatment. These factors might explain why these patients had received a full ENT workup under routine care.

Interestingly, despite potential selection bias, our main results are as follows: (1) Almost all patients (n = 48 [98%]) had ENT symptoms from disease onset. (2) The oral cavity had the highest topographic frequency (94%). (3) Fourteen patients with SJS/TEN (29%) had severe ENT form defined by the occurrence of laryngeal lesions with the risk of airway obstruction. (4) Patients with severe ENT form had significantly more dysphonia or dyspnea. (5) Complete ENT mucosal healing at 2 months was observed in 36 of 49 patients with SJS/TEN (74%) and in 48 (98%) at 1 year. (6) In multivariable analysis, severe ENT form was only significantly associated with pulmonary infection.

Our patients demographic and clinical characteristics are consistent with previously described series.11-15 Causal drugs used by patients included high-risk drugs identified in a prior case-control study (ie, allopurinol, antibacterial sulfonamides, lamotrigine, carbamazepine, nevirapine, and piroxicam).16 Our series mortality rate at the acute stage was 6%, which is lower than previously described in the literature (22%-35%); however, median (range) maximal BSA detachment was 20% (0%-95%) and most of the patients were managed in the department of dermatology and not the ICU, potentially minimizing the disease severity.

To our knowledge, ENT manifestations and follow-up in patients with SJS/TEN have not been described in detail in the literature. In prior studies, head and neck manifestations occurred in up to 95% of patients27,28 and in 93% in a pediatric series of 28 cases.29 In accordance with our study, the oral cavity was reported as the first topographic site of ENT manifestations and oral cavity or lip blisters as the first SJS/TEN sign.14 The lesions could also be located to gingiva, tongue, pharynx, nasal cavity, and larynx.6 Interestingly, laryngeal involvement was common in our series and more frequent than previously reported in the pediatric population (1 of 28 cases in the series reported by Stewart et al30). With the support of our results in comparing the study population characteristics with that of the entire cohort with SJS/TEN, particularly the lack of a significant difference in pulmonary infection, we suggest that laryngeal lesions are underreported. To add, our results possibly highlight that pulmonary infection associated with severe ENT form is more severe, requiring oral intubation.

After acute stage, SJS/TEN is significantly associated with long-term sequelae such as pigmentation or skin disorders, ocular synechia, symblepharon, blindness, chronic sialadenitis, dental abnormalities, or psychiatric disorders.17,20,21 Complete ENT mucous healing was observed in nearly in 74% of the patients after 2 months of follow-up and in 98% of the patients after 1 year of follow-up. In the literature, oral lesions usually heal without scarring complications4; in accordance with our series, their kinetic mechanism of healing is unknown.

In our series, severe ENT form was significantly associated with pulmonary infections. Dysphonia or dyspnea were also significantly associated with severe ENT form. Respiratory tract infection may be linked to bacterial colonization of pharyngolaryngeal mucosal lesions. Sepsis is described as the main cause of death at the acute stage of SJS/TEN. In a 5-year retrospective study, septicemia and pulmonary infections were associated with higher mortality.22 In a prospective series assessing pulmonary complications in 41 patients with SJS/TEN, all patients had oral cavity involvement, even those without pulmonary symptoms. Patients with pulmonary complications were classified into 2 groups with early (<48 hours) pulmonary manifestations or delayed pulmonary manifestations (pulmonary edema, atelectasis, and bacterial pneumonia).23 Specific bronchial necrosis was found in 10 patients (27%), but unfortunately laryngeal tracts was not described. More recently, in a study of 221 patients with SJS/TEN pulmonary infiltrate was significantly associated with mechanical ventilation, while oral lesion was not significantly associated with either specific bronchial erosion or mechanical ventilation.18 Because of our small sample of patients, a significant association between severe ENT manifestation and specific bronchial lesions was not displayed (P = .10); this may be linked to a lack of power.

Treatment for SJS/TEN mainly relies on early drug withdrawal; compared with supportive care, no specific treatment seems beneficial.2,22,24 Most of the patients in this series received cyclosporin because its use and effectiveness were evaluated in an open phase 2 trial from March 2005 to September 2007.25 In this trial, death rate and the progression of skin detachment were lower than expected, but its effect on severe ENT form was not evaluated. ENT manifestations largely respond to local care, and the routine use of prophylactic antibiotics or systemic steroids is not recommended.29 Our patients received mucosal supportive care including hygienic mouthwashes and oral topical anesthetics.36 At the acute stage, half of the patients were fed using a nasogastric tube because of oral mucosa pain or swallowing disorders or to limit aspirations. Scabs were softened by regular isotonic saline irrigation. Preventive aspiration of desquamating epidermis could also be suggested to limit external otitis.

Conclusions

Despite some bias linked to their management, patients with ENT workup did not differ from the rest of the population with SJS/TEN, especially regarding their severity factors. Complete ENT workup with nasal fiberoptic endoscopy led us to identify severe ENT form, which was associated to pulmonary infection. Nasal fiberoptic endoscopy at a patient’s bedside is simple, noninvasive, and helpful to detect severe ENT,
especially in the case of dysphonia or dyspnea. Because infection is the main cause of death in SJS/TEN, monitoring ENT symptoms or detecting laryngeal lesions may be relevant. Clinical perspectives include complete ENT examination when pulmonary infections are present to detect a potential relationship between bronchial detachment and severe ENT form or to determine the role of ENT standardized therapeutic protocols to limit pulmonary infections.

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REFERENCES


