Clinical, Etiologic, and Histopathologic Features of Stevens-Johnson Syndrome During an 8-Year Period at Mayo Clinic

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OBJECTIVE: **To examine clinical, etiologic, and histologic features of Stevens-Johnson syndrome and to identify possible correlates of clinical disease severity related to etiologic and histopathologic findings.**

PATIENTS AND METHODS: **This is a retrospective review of patients seen at Mayo Clinic between January 1, 2000, and December 31, 2007.**

RESULTS: **Of 27 patients (mean age, 28.1 years), 22 (81%) had involvement of 2 or more mucous membranes, and 19 (70%) had ocular involvement. Medications, most commonly antibiotics and anticonvulsants, were causative in 20 patients. *Mycoplasma pneumoniae* infection caused 6 of the 27 cases. Corticosteroids were the most common systemic therapy. No patients with mycoplasma-induced Stevens-Johnson syndrome had internal organ involvement or required treatment in the intensive care unit, in contrast to 4 patients each in the drug-induced group. Three patients had chronic ocular sequelae, and 1 died of complications. Biopsy specimens from 13 patients (48%) showed epidermal necrosis (8 patients), basal vacuolar change (10 patients), and subepidermal bullae (10 patients). Biopsy specimens from 11 patients displayed moderate or dense dermal infiltrate. Histologic features in drug-induced cases included individual necrotic keratinocytes, dense dermal infiltrate, red blood cell extravasation, pigment incontinence, parakeratosis, and substantial eosinophils or neutrophils.**

CONCLUSION: **Our clinical and etiologic findings corroborate those in previous reports. *M pneumoniae*–induced Stevens-Johnson syndrome manifested less severely than its drug-induced counterpart. The limited number of biopsies precludes unequivocal demonstration of histopathologic differences between drug-induced and *M pneumoniae*–induced Stevens-Johnson syndrome.**

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EM = erythema multiforme; EuroSCAR = European Study of Severe Cutaneous Adverse Reactions; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis

Stevens-Johnson syndrome (SJS) is a rare, severe, immune-mediated cutaneous reaction usually secondary to an idiosyncratic reaction to medication, although infection with *Mycoplasma pneumoniae* is also a well-documented cause.[1] In 1922, Stevens and Johnson[2] described a strikingly distinct disease in 2 children as an "extraordinary, generalized eruption with continued fever, inflamed buccal mucosa and severe purulent conjunctivitis." In ensuing years, controversy existed as to whether SJS indeed was a separate entity or merely a severe form of erythema multiforme (EM).[3] More recent evidence suggests that EM with mucous membrane involvement and SJS are 2 different diseases with distinct causes.[4] Although various classification systems exist, the most widely accepted consensus definition was proposed by Bastuji-Garin et al[5] in 1993: SJS consists of epidermal "detachment below 10% of the body surface area plus widespread macules or flat atypical targets." Other studies have described histopathologic correlates in patients with EM, SJS, and toxic epidermal necrolysis (TEN).[6-9] The aim of the current study was to retrospectively examine clinical, etiologic, and histopathologic data from patients with SJS to identify possible correlates of clinical disease severity related to specific etiologic and histopathologic findings.

PATIENTS AND METHODS

Patients with a new diagnosis of SJS who were treated at Mayo Clinic, Rochester, MN, between January 1, 2000, and December 31, 2007, were identified from the institutional medical index and text retrieval system. Patients who had refused research authorization were excluded from analysis. This study was approved by the Mayo Clinic Institutional Review Board.

Medical records were examined to abstract the following information: demographics, clinical features including extent of mucous membrane and skin involvement, identifiable etiologic classes of SJS, specific causative drugs, laboratory tests, treatment, follow-up data including chronic sequelae secondary to SJS, and histopathologic data.

All study patients met the consensus definition for SJS proposed by Bastuji-Garin et al[5] in 1993. The extent and severity of mucous membrane erosions were not used to classify a disease as SJS.[5] Patients identified with a clinical diagnosis of SJS who did not meet the aforementioned consensus criteria were excluded from analysis.

Cases were designated secondary to *M pneumoniae* in patients who had clinical features (eg, cough, fever, or constitutional symptoms) compatible with infection and positive IgM and IgG serologic findings of *M pneumoniae.* Cases were considered to be medication related when patients had negative laboratory test results for infectious etiologies and were known to have been exposed to the offending drug or drugs within the preceding few weeks.

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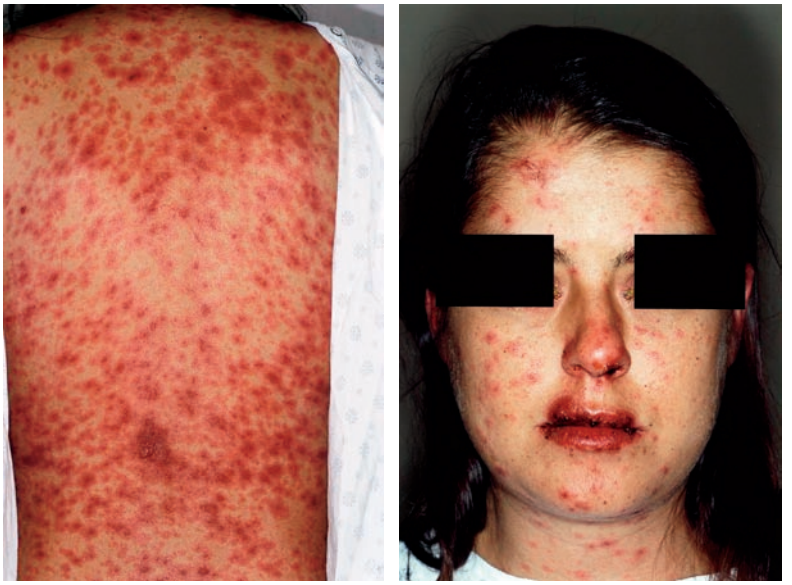

FIGURE 1. 29-year-old woman (patient 13 in Table 4) with Stevens-Johnson syndrome secondary to *Mycoplasma pneumoniae* infection. Left, Widespread macules ranging from erythematous to purpuric and flat atypical target lesions on the back. Right, Prominent hemorrhagic crust on the lips, eyes, and nasal mucosa.

Biopsy specimen slides were reviewed by a single dermatopathologist (M.J.C.) and examined for the presence of epidermal necrosis, basal vacuolar change, subepidermal bullae, intraepidermal bullae, epidermal infiltrate (qualitatively graded as poor, mild, moderate, or dense), epidermal infiltrate cell type, dermal infiltrate (qualitatively graded as poor, mild, moderate, or dense), dermal infiltrate cell type, and dermal infiltrate pattern (described as superficial perivascular, superficial perivascular and interstitial, periadnexal, or all 3). Cell types present in the dermal infiltrate other than lymphocytes (ie, eosinophils, neutrophils, and plasma cells) were qualitatively measured as few, moderate, or many. Other less common findings (eg, red blood cell extravasation, pigment incontinence, parakeratosis, regenerating epidermis, and hair follicle necrosis) were also recorded.

RESULTS

All 27 patients met published clinical criteria for SJS[5] and had widespread macules or flat atypical target lesions and limited areas of epidermal detachment on less than 10% of the body surface area (Figure 1). All patients also had oral mucous membrane involvement, with 22 (81%) experiencing involvement of 2 or more mucous membranes (Figure 1). Nineteen patients (70%) manifested ocular involvement, with the most common signs and symptoms being conjunctivitis, exudate, photophobia, "grittiness," and cicatrizing changes. Other affected mucous membranes were genitourinary (9 patients), nasopharyngeal (6 patients), rectal (2 patients), and respiratory (1 patient). Internal organ involvement was uncommon, with 4 patients experiencing cardiovascular, respiratory, or hepatic abnormalities. No patient experienced sepsis during the clinical course, although 1 patient died of complications related to SJS (ie, dyspnea, hypotension, and anemia). Clinical features of the patients are summarized in Table 1.

Drugs were the causative factors in 20 (74%) of the 27 patients (Table 2) (mean age, 31.4 years; range, 1-72 years). The mean interval between drug administration and SJS was 15.3 days (range, 2-42 days). Infection with *M pneumoniae* (confirmed with positive IgM and IgG serologic tests) led to 6 cases of SJS (mean age, 19 years; range, 10-36 years). Stevens-Johnson syndrome developed in 1 patient 20 days after immunization for smallpox, anthrax, and tetanus.

Serologic tests for *M pneumoniae* were performed in 11 (41%) of the 27 patients, 6 of whom had positive IgM and IgG antibodies demonstrating recent infection (Table 1). Twenty patients (74%) were tested for herpes simplex virus infection (swab cultures with or without serologic studies were obtained for 19 patients; serologic findings without a culture swab were obtained in 1 patient), and results were negative in all these patients. Various laboratory abnormalities were noted in several patients (Table 1), the most common of which were chest radiographic findings (eg, infiltrate, edema, bronchial inflammation), elevated liver function test results, and increased markers

TABLE 1. **Clinical Features, Laboratory Testing, and Treatment of Patients With Stevens-Johnson Syndrome**

Variable	No. (%) of patients[a]
Characteristic	
Age (y) at diagnosis	
Mean ± SD	28.1±22.3
Median (range)	18 (1.5-72)
<18	12 (44)
Sex	
Male	16 (59)
Female	11 (41)
Mucous membrane involvement	
1 site	27 (100)
≥2 sites	22 (81)
Fever	19 (70)
Painful skin	7 (26)
Ocular involvement	19 (70)
Internal organ involvement	4 (15)
Death due to Stevens-Johnson syndrome	1 (3.7)
Test	
Positive *Mycoplasma pneumoniae* serology (n=11)[b]	6 (22)
Positive herpes simplex virus (swab, serologic tests, or both) (n=20)	0 (0)
Abnormal chest radiographic findings	11 (41)
Elevated liver function test results[c]	10 (37)
Elevated markers of acute inflammation	9 (33)
Leukocytosis	6 (22)
Anemia	6 (22)
Elevated renal function test results[d]	3 (11)
Neutropenia	1 (4)
Treatment	
Hospitalization	26 (96)
Duration of hospital stay (d), mean ± SD (n=23[e])	8.0[f]±9.8 or 6.1±3.5
Duration of hospital stay (d), median (range) (n=23[e])	6[f] (1-50) or 6 (1-14)
Treatment in intensive care unit (n=26)	4 (15)
Corticosteroids	
Oral or intravenous	15 (56)
Topical with wet dressings	9 (33)
Intravenous immunoglobulin	6 (22)
Intravenous immunoglobulin plus corticosteroids	3 (11)
Immunosuppressants	1[g] (4)
Oral antibiotics	8 (30)

[a] All 27 study patients unless indicated otherwise.
[b] Positive serologic findings were defined as positive IgM and IgG antibodies demonstrating recent infection.
[c] Denotes elevated levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, or bilirubin.
[d] Creatinine and blood urea nitrogen.
[e] Of 26 hospitalized patients.
[f] Includes 1 patient hospitalized for 50 d for complications (eg, deep venous thrombosis, mediastinitis, and methicillin-resistant *Staphylococcus aureus* tracheitis).
[g] Received mycophenolate mofetil and dapsone for chronic ocular inflammation.

TABLE 2. **Etiology of Stevens-Johnson Syndrome in the 27 Study Patients[a]**

Causative factor	No. (%)	Reason for treatment
Medication	20 (74)	
Antibiotics	7 (35)	
Trimethoprim-sulfamethoxazole	3	UTI (2 patients); otitis media
Amoxicillin	1	URI
Azithromycin	1	Bronchitis
Cefdinir	1	Pneumonia
Ciprofloxacin	1	UTI
Anticonvulsants	7 (35)	
Phenytoin	4	Idiopathic seizure disorder; seizure disorder due to sagittal sinus thrombosis; seizure disorder due to cerebral palsy; seizure prophylaxis for brain abscess
Lamotrigine	2	Depression; seizure disorder due to hydrocephalus
Carbamazepine	1	Idiopathic seizure disorder
NSAIDs	2 (10)	
Nabumetone	1	Muscle pain
Rofecoxib	1	Leg cramps
Other	4 (20)	
Allopurinol	1	Gout
Probable anticonvulsant (phenytoin or carbamazepine)	1	Seizure disorder after cerebrovascular accident
Sertraline	1	Depression
Thalidomide or allopurinol	1	Multiple myeloma
Mycoplasma pneumoniae	6 (22)	
Immunization[b]	1 (4)	

[a] NSAIDs = nonsteroidal anti-inflammatory drugs; URI = upper respiratory infection; UTI = urinary tract infection.
[b] For smallpox, anthrax, and tetanus.

of acute inflammation (eg, erythrocyte sedimentation rate and C-reactive protein).

Of 26 patients (96%) hospitalized for treatment, 4 received treatment in the intensive care unit; it was unclear from our retrospective review of the records why 1 patient was not hospitalized (Table 1). For patients in whom data on the total length of the hospital stay were available (23/26), the mean duration of hospital stay was 8.0 days (range, 1-50 days); for the other 3 patients, our retrospective review of medical records showed that they had been hospitalized before evaluation at Mayo Clinic, resulting in a lack of complete information about the exact duration of their total hospital stay. One patient experienced complications, including deep venous thrombosis, mediastinitis, and methicillin-resistant *Staphylococcus aureus* tracheitis, that necessitated a prolonged hospitalization (50 days); when this outlier was excluded, the mean hospital stay for the other 22 patients was 6.1 days. Systemic therapies used in the cohort of 27 patients included corticosteroids (15 patients) and intravenous immunoglobulin (6 patients). One patient with drug-induced SJS received mycophenolate mofetil and dapsone for chronic cicatrizing ocular inflammation.

The clinical characteristics of the 20 patients with drug-induced SJS compared with those of the 6 patients with mycoplasma-induced SJS are shown in Table 3.

The mean follow-up after diagnosis was 16.6 months (range, 0-80 months). One patient with preexisting atrial

TABLE 3. **Clinical Comparison of Medication-Induced vs Mycoplasma-Induced Stevens-Johnson Syndrome (SJS) in 26 Patients**[a]

Characteristic	Precipitating factor	
	Medication (n=20)	*Mycoplasma pneumoniae* (n=6)
Age (y), mean ± SD	31.4±24.7	19±10.8
Age (y), median (range)	23 (1.5-72)	14 (10-36)
Mucous membrane sites involved, mean No.	2.25	2.83
Ocular involvement	12 (60)	6 (100)
Internal organ involvement	4 (20)	0 (0)
Treatment in ICU	4 (20)	0 (0)
Intravenous immunoglobulin treatment	5 (25)	1 (17)
Duration of hospital stay (d), mean ± SD	8.97[b]±11.2 or 6.4±3.9	5.2±2.6
Duration of hospital stay (d), median (range)	6[b] (1-50) or 5.5 (1-14)	6 (2-8)
Chronic sequelae	3 (15)	1[c] (17)
Death due to SJS	1 (5)	0 (0)

[a] Values are number (percentage) unless indicated otherwise. ICU = intensive care unit.
[b] Includes 1 patient hospitalized for 50 d for complications, including deep venous thrombosis, mediastinitis, and methicillin-resistant *Staphylococcus aureus* tracheitis.
[c] Ocular.

fibrillation and chronic obstructive pulmonary disease died during hospitalization of complications related to SJS (ie, dyspnea, hypotension, and anemia), and 5 patients were lost to follow-up after hospital discharge. Three patients had chronic ocular complications; the vision was affected in 2 of these 3 patients. One of the 3 patients with clinically important ocular involvement also experienced multiple oral mucoceles and painful defecation as a result of oral and rectal involvement, respectively. One patient with urethral involvement from SJS reported gradually improving urinary retention. At follow-up, 2 patients had died of causes unrelated to SJS (1 due to multiple myeloma and 1 due to cerebrovascular disease).

Biopsy specimens were available to review for 13 (48%) of the 27 patients; 2 patients each underwent 2 biopsies, and thus 15 biopsies were reviewed. Of the 15 biopsy specimens, 11 were from patients with drug-induced SJS; the other 4 were from 2 mycoplasma-induced cases (1 biopsy each) and 1 immunization-induced case (2 biopsies). Detailed information about the specific histopathologic findings of each biopsy specimen is provided in Table 4. Histologic features of drug-induced and mycoplasma-induced cases of SJS are illustrated in Figure 2.

Epidermal necrosis was present in 1 or more biopsy specimens for 8 (62%) of 13 patients; full-thickness necrosis was present in 6 patients (46%). Basal vacuolar change was observed in 10 (77%) of 13 patients, with 5 (38%) of the 13 patients demonstrating moderate to severe change. Biopsy specimens from 10 (77%) of the 13 patients contained subepidermal bullae, and 11 patients (85%) displayed either a moderate or dense dermal infiltrate (8, moderate; 3, dense), with lymphocytes representing the predominant cell type. Eosinophils were observed in 1 or more biopsy specimens from 8 patients, and neutrophils were present in 4 patients. Other less common findings included red blood cell extravasation (5/13 patients), pigment incontinence, regenerating epidermis, parakeratosis, and necrosis of the hair follicle.

Histologic features found only in drug-induced cases included individual necrotic keratinocytes, dense dermal infiltrate, red blood cell extravasation, pigment incontinence, and parakeratosis. Biopsy specimens that demonstrated a substantial number of eosinophils or neutrophils were also found to be drug related. Three biopsy specimens were reviewed from patients with SJS sequelae (eg, ocular, urinary, or death), and all 3 showed moderate or dense dermal inflammation; the biopsy specimen from the patient with ocular sequelae (ie, cicatrizing conjunctivitis) revealed dense dermal inflammation.

DISCUSSION

Much confusion exists regarding the nosology of SJS, which poses particular challenges for researchers conducting studies of SJS and reviewing previously reported cases. The distinction between SJS and EM major is controversial for some researchers, and they suggest instead that the 2 entities are synonymous; others contend that more extensive mucous membrane involvement in SJS differentiates it from EM major. To most accurately review the 27 cases of SJS in the current study and compare them with those reported in the medical literature, we used an accepted consensus definition of SJS that relies on the pattern and distribution of skin lesions, rather than on the extent and severity of mucous membrane involvement.[5,10] Although the degree of mucous membrane involvement is not an absolute criterion for SJS according to the consensus definition, mucosal erosions were reported to be present in more than 90% of patients by this classification scheme[5]; another study of 33 patients with SJS demonstrated mucous membrane involvement in all the patients, with 23 having 2 or more affected membranes.[4] Our findings are in keeping with these data because all 27 of our study patients had mucous membrane involvement, and 22 (81%) had involvement of 2 or more mucous membranes.

The mean age of our patients was 28.1 years, with nearly half younger than 18 years. This finding is concordant with the emphasis in the medical literature on SJS as a disease that occurs predominantly in younger patients.[1,11]

In addition to delineating SJS as a distinct entity from EM major by the clinical pattern of cutaneous lesions,

TABLE 4. **Histopathologic Findings on 15 Biopsy Specimens From 13 Patients With Stevens-Johnson Syndrome (SJS)**[a]

Patient No.	Sequelae of SJS	Time of biopsy after development of SJS (d)	Epi necrosis	BVac	Epidermal bullae[b] (sub, intra, or both)	Epidermal infiltrate		Dermal infiltrate		Other findings
						Extent	Cell	Extent (pattern)	Cell	
Drug-related etiology										
1	Death	3	FTN	Mild	Yes	Mild	Lymph	Mod (SPV)	Lymph, eos (few)	RBC ext[c]
2	None	3	INK	Mild	No	None	None	Dense (SPVI)	Lymph, eos (many)	None[d]
3	None	5	INK	Mild	Yes	Mild	Lymph	Mod (SPVI)	Lymph, neut (many)	RBC ext[d]
4	None	3	PTN	Mild	Yes	Mild	Lymph	Mod (SPVI)	Lymph	None[e]
5	None	10	FTN	None	Yes	None	None	Mild (SPV)	Lymph	RE[d]
6A[f,g]	None	39	None	None	No	None	None	Mild (SPV)	Lymph	PI[d]
6B[f,g]	None	23	None	None	No	None	None	Mild (SPV)	Lymph	None[d]
7	None	3	INK	Severe	Yes	Poor	Lymph	Dense (SPVI)	Lymph, eos (mod)	RBC ext, PK[e]
8[g]	Ocular, oral, rectal	28	None	Mild	No	Poor	Lymph	Dense (SPVI)	Lymph, eos (few), neut (few), plasma (few)	None[c]
9	None	4	FTN	Severe	Yes	Mod	Lymph	Mod (SPVI)	Lymph, eos (mod)	PI, RBC ext[d]
10	Urinary	4	PTN, INK	Severe	Yes	Mod	Lymph	Mod (SPVI)	Lymph, eos (few), neut (few)	PK, RBC ext[d]
Vaccination-related etiology										
11A[h]	None	5	FTN	Mod	Yes	Mild[c]	Lymph	Mod (SPV)	Lymph	None[d]
11B[h]	None	5	FTN	Mod	Yes	Mild	Lymph	Mod (SPV, PA)	Lymph, eos (few), neut (few)	HFN[d]
Mycoplasma pneumoniae–related etiology										
12	None	2	FTN	Severe	Yes	Mild	Lymph	Mod (SPV)	Lymph	None[e]
13	None	2	FTN	None	Yes	Mild	Lymph	Mod (SPVI)	Lymph, eos (few)	RE[d]

[a] BVac = basal vacuolar change; eos = eosinophils; epi = epidermis; FTN = full-thickness necrosis; HFN = hair follicle necrosis; INK = individual necrotic keratinocytes; intra = intraepidermal; lymph = lymphocytes; neut = neutrophils; mod = moderate; PA = periadnexal; PI = pigment incontinence; PK = parakeratosis; plasma = plasma cells; PTN = partial-thickness necrosis; RBC ext = red blood cell extravasation; RE = regenerating epidermis; SPV = superficial perivascular; SPVI = superficial perivascular and interstitial; sub = subepidermal.

[b] Subepidermal bullae were found in 11 of 15 biopsy specimens; 3 of these 11 specimens also had intraepidermal bullae.

[c] Direct immunofluorescence findings indicated lichenoid reaction (2 patients; 2/15 biopsies).

[d] Direct immunofluorescence findings were negative or nondiagnostic (8 patients; 10/15 biopsies).

[e] Direct immunofluorescence testing was not performed (3 patients; 3/15 biopsies).

[f] Biopsy specimens 6A and 6B were both from patient 6.

[g] Earlier biopsy specimens obtained from patients 6 and 8 before evaluation at Mayo Clinic were unavailable for review.

[h] Biopsy specimens 11A and 11B were both from patient 11, an 18-year-old armed services member whose SJS developed as a result of immunization for smallpox, anthrax, and tetanus.

several authors have further distinguished these 2 entities by their respective etiologies.[4,12] They found that SJS is usually related to drugs, whereas EM major is most commonly secondary to herpes simplex virus infection.[4,12] Our data support these findings, with 20 cases secondary to the use of medications, whereas no patient had a documented herpes simplex virus infection.

In our patients with drug-induced SJS, the mean interval between drug administration and onset of cutaneous findings was 15.3 days. Previous reports in the medical literature describe similar intervals, with the greatest risk of development of SJS occurring in the first 2 months of drug treatment[1] and an interval of 4 to 28 days being the most suggestive of drug causality in SJS.[13]

We found that antibiotics and anticonvulsants were the most common medications causing SJS, with trimethoprim-sulfamethoxazole and phenytoin the most common culprits in each drug class, respectively. Previous studies enumerating medications specifically associated with SJS have identified antibiotics, anticonvulsants, and nonsteroidal anti-inflammatory drugs.[10,11,13-16] A recent multinational case-control study in Europe called EuroSCAR (European Study of Severe Cutaneous Adverse Reactions) showed a high risk of SJS with the following medications: trimethoprim-sulfamethoxazole and other anti-infective sulfonamides, lamotrigine, carbamazepine, phenytoin, phenobarbital, allopurinol, nevirapine, and oxicam nonsteroidal anti-inflammatory drugs.[13] Among recently marketed drugs, nevirapine and lamotrigine were strongly associated with SJS, with sertraline showing a lower but still significant risk as well.[13] Our study reflects these findings, with 2 cases secondary to lamotrigine therapy and 1 case secondary to sertraline therapy. Moreover, recently reported data from the EuroSCAR study indicated that al-

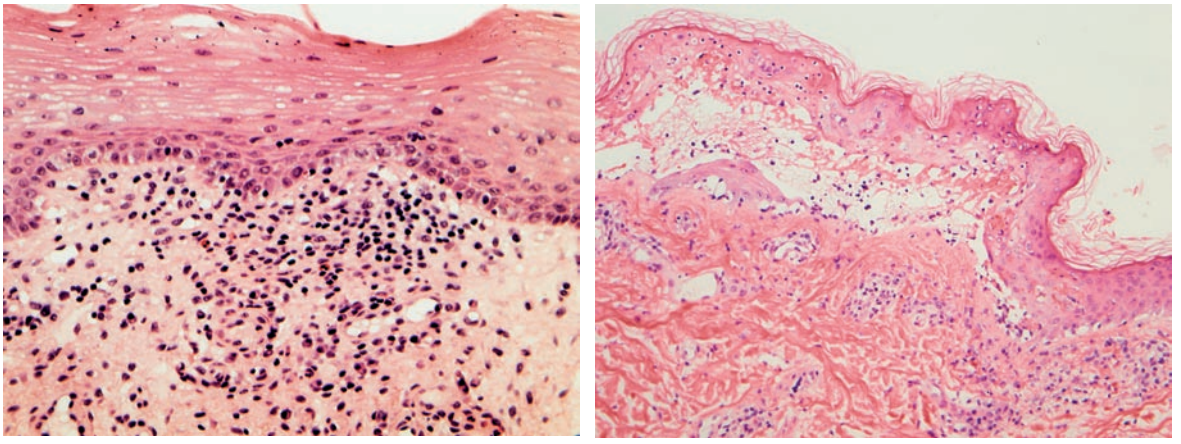

FIGURE 2. Histopathology of Stevens-Johnson syndrome. Left, Focal basal cell vacuolar change with dense superficial dermal lymphocytic inflammation and occasional eosinophils in patient with Stevens-Johnson syndrome secondary to lamotrigine therapy (hematoxylin-eosin, original magnification ×40). Right, Full-thickness necrosis, basal vacuolar change, and subepidermal bullae in patient with Stevens-Johnson syndrome secondary to *Mycoplasma pneumoniae* infection (hematoxylin-eosin, original magnification ×20).

lopurinol was the most common cause of SJS and TEN in Europe and Israel[17]; our study found 1 case of allopurinol-induced SJS, with another case possibly due to allopurinol or thalidomide (of note, thalidomide has been reported to induce TEN[18]).

M pneumoniae is also a well-known cause of SJS.[19,20] It usually affects children and young adults and has been reported as the most common infectious agent associated with SJS.[19] Nearly all patients manifest oral involvement, and approximately two-thirds of patients have ocular involvement.[19,20] Previous studies suggest that mycoplasma-induced SJS is associated with less frequent and less severe complications than those resulting from other causes.[20] In our study, 6 cases were due to *M pneumoniae* as confirmed by positive serologic findings; previous studies have documented 10%[15] to 29%[21] of SJS cases as secondary to *M pneumoniae* infection. In our series, the mean age of patients with mycoplasma-induced SJS (19 years) was younger than that of patients with drug-induced SJS (31.4 years). No patient with mycoplasma-induced SJS manifested internal organ involvement or required treatment in the intensive care unit, and the mean hospital stay was shorter than that observed in patients with drug-induced SJS, which augments previous assertions that mycoplasma-induced SJS may manifest less severely than its drug-induced counterpart.[20]

Numerous reports have described patients with "atypical SJS" who were infected with *M pneumoniae* and presented with severe mucositis without skin lesions.[22] Given that the pattern and distribution of cutaneous lesions, rather than mucous membrane involvement, are the hallmarks of the revised classification of SJS,[5] some authors argue that these cases do not represent SJS and are better termed *M pneumoniae*–associated mucositis.[23] All 6 of our patients with mycoplasma-induced SJS had both skin and mucous membrane involvement. The strong association between *M pneumoniae* and mucositis is further evident in our study when considering that the mean number of mucous membranes involved and the percentage of patients presenting with ocular involvement were higher in the mycoplasma-induced group than in the drug-induced SJS group.

Patients with *M pneumoniae*–associated SJS frequently receive antibiotics during the early stages of their respiratory illness before the onset of a mucocutaneous eruption, which at times can make it difficult to determine the precise etiology of SJS. Of the 6 cases in our study attributed to *M pneumoniae*, 4 were treated with antibiotics before the development of mucocutaneous lesions (median, 2 days; range, 0.5-4 days).

Interestingly, vaccinations have been associated with the development of SJS.[24,25] In our study, SJS developed in an 18-year-old man in the armed forces 20 days after he underwent immunization for smallpox, anthrax, and tetanus.

The role of corticosteroids in the treatment of SJS is controversial.[1] Some investigators say that corticosteroids may promote infectious complications and lead to a poorer prognosis.[1] However, recently published data from the EuroSCAR study do not reflect an increased mortality in patients treated with corticosteroids but rather a possible beneficial effect that deserves further exploration.[26] Of note, sepsis developed in none of the 15 of our 27 patients who received treatment with corticosteroids for SJS, although 1 patient treated with corticosteroids and intravenous immunoglobulin had a prolonged hospital stay and experienced

multiple complications, including methicillin-resistant *S aureus* tracheitis. The patient who died of complications related to SJS also received corticosteroids (without concurrent intravenous immunoglobulin). Although the small number of patients treated with systemic agents precluded conclusions about survival benefits from therapy, patients overall generally did well with supportive care with or without systemic treatment. General diagnostic and treatment recommendations for patients with SJS are summarized in Table 5.

Three patients in our study had chronic ocular complications due to SJS. However, SJS-related ocular disease is not only the sequelae of the acute disease process but also can occur with a variable course several years after onset of SJS and is not always the direct result of conjunctival scarring.[27]

In addition to developing clinical classification schemes based on the patterns and distribution of skin lesions, some authors have sought to differentiate EM from SJS and TEN by their histopathologic features. Rzany et al[6] examined biopsy specimens from patients with EM major, SJS, and TEN and found no differences in histologic features (eg, eosinophils) by etiology (ie, drug vs infection). In our study, histologic features such as epidermal necrosis, basal vacuolar change, subepidermal bullae, and dermal infiltrate were common, regardless of the underlying cause. In contrast to the findings by Rzany et al,[6] we identified several histologic features that were observed only in drug-induced cases; these included individual necrotic keratinocytes, dense dermal infiltrate, red blood cell extravasation, pigment incontinence, and parakeratosis. Moreover, biopsy specimens that demonstrated a substantial number of eosinophils or neutrophils were also found to be drug related. The importance of these findings is unclear, given that only 4 of the 15 biopsy specimens indicated that SJS was due to causes other than drugs (2 from *M pneumoniae* and 2 from immunization-induced SJS). In addition, differences in histologic findings could be related to the evolution of individual lesions because biopsies were not strictly matched between groups due to the timing of the biopsy in relation to the onset of mucocutaneous findings.

In a more recent study that focused on identifying histologic criteria with prognostic importance in patients with TEN, a dense dermal mononuclear infiltrate was found to portend a worse prognosis.[7] Dense dermal inflammation was observed in the biopsy specimen from the patient who experienced ocular sequelae (ie, cicatrizing conjunctivitis) that required therapy with mycophenolate mofetil and dapsone, but only moderate dermal inflammation was found in the patient who died of SJS-related complications. The limited histologic data in our study prevent any firm conclusions about clinical and etiologic correlates based on histologic patterns.

TABLE 5. **Recommendations for Diagnosis and Treatment of Stevens-Johnson Syndrome**

Diagnosis
Identify and discontinue potential causative drug(s); common offending agents include antibiotics, anticonvulsants, NSAIDs, and allopurinol
Perform skin biopsy (eg, lesional biopsy for routine microscopy with hematoxylin-eosin staining and perilesional biopsy for direct immunofluorescence microscopy) to confirm diagnosis and rule out other conditions, including pemphigus vulgaris, bullous pemphigoid, paraneoplastic pemphigus, linear IgA bullous dermatosis, staphylococcal scalded skin syndrome, acute graft-vs-host disease, acute generalized exanthematous pustulosis, and virus infection
In patients with cough, fever, and constitutional symptoms, perform chest radiography and serologic studies (eg, IgM and IgG) for *Mycoplasma pneumoniae* infection
In patients with mucosal erosions and crust, consider swab culture for herpes simplex virus infection
If concerned about internal organ involvement and/or sepsis, perform laboratory studies (eg, complete blood cell count, electrolytes, glucose, creatinine, and liver function tests) and obtain cultures (eg, skin, urine, blood, and intravascular lines), as appropriate
Treatment
Providing supportive care is the most important measure
Monitor fluids, electrolytes, and body temperature and watch for signs of infection/sepsis
Obtain ophthalmology consultation for recommendations (eg, antiseptic eyedrops) and measures to decrease long-term sequelae (eg, scarring and vision loss)
Provide saline to involved mucosal surfaces and orifices (eg, oral and nasal)
Suggest analgesia (eg, oral "swish-and-spit" solutions containing lidocaine, diphenhydramine, and Maalox)
Apply white petrolatum jelly (Vaseline) to denuded skin
Consider tap water wet dressings with topical corticosteroids for areas of active inflammation (eg, red and itchy)
Give antibiotics (eg, azithromycin) in cases due to *M pneumoniae* infection; otherwise, antibiotic therapy should be initiated only if sepsis or other infection occurs and should not be used for prophylaxis
Avoid skin trauma
Provide management in the intensive care unit if the following are needed/noted: extensive wound care, clinically important medical comorbid conditions (eg, cardiac, pulmonary, or renal), internal organ involvement, sepsis, and hemodynamic or electrolyte instability
Consider IVIG (total dose of 3 g/kg in divided doses over 3 d) in severe cases (need to check IgA level because anaphylaxis can occur in IgA-deficient patients)
Giving systemic corticosteroid therapy is controversial and should be considered only in severe cases early in the disease course (ie, before clinically important epithelial sloughing has occurred) because it could promote infectious complications and sepsis; if used, intravenous methylprednisolone 2 to 2.5 mg/kg/d in divided doses for a few days can be considered
At hospital discharge, perform close ophthalmology follow-up and monitor other mucosal surfaces (eg, genitourinary and gastrointestinal) for chronic sequelae such as strictures, with referrals to specialists as appropriate

IVIG = intravenous immunoglobulin; NSAIDs = nonsteroidal anti-inflammatory drugs.

We recognize and acknowledge the shortcomings of the current study: it is retrospective, the cohort is small, and biopsy specimens were not obtained from all patients.

Given the small number of biopsy specimens obtained from patients with SJS due to causes other than drugs, it is unclear whether specific etiologic correlates (ie, drug vs *M pneumoniae*) can be garnered from our histologic data. Because we used a recently devised (1993) consensus definition of SJS, limitations exist when comparing our data to those of earlier studies that used alternative classification schemes.

CONCLUSION

Our findings corroborate previously reported clinical and etiologic associations with SJS. *M pneumoniae*–induced SJS clinically manifested less severely than its drug-induced counterpart. Confirmation of possible histopathologic differences between drug-induced and *M pneumoniae*–induced SJS requires further studies with larger patient cohorts.

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