Characterization of Children With Recurrent Episodes of Stevens Johnson Syndrome

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We performed a retrospective chart review for all cases of recurrent Stevens Johnson Syndrome (SJS) from March 2013 to March 2016. Nine children had 29 episodes of SJS or incomplete SJS; all children were male and 8 (88%) were white. Episodes affected mucus membranes with minimal skin involvement. Mycoplasma infections and HLA-B27/-B51 were common.

METHODS

All children in this case series were identified at CHCO by International Classification of Diseases, Ninth Revision code 101.00. We performed a retrospective chart review for all cases of recurrent Stevens Johnson Syndrome (SJS) from March 2013 to March 2016. Nine children had 29 episodes of SJS or incomplete SJS; all children were male and 8 (88%) were white. Episodes affected mucus membranes with minimal skin involvement. Mycoplasma infections and HLA-B27/-B51 were common.

RESULTS

Nine children had a combined 29 episodes (median 3 episodes/child, range 3–4 episodes per child) (Table 1). Eighteen (62%) episodes met our case definition for SJS, and 11 (38%) were classified as incomplete SJS. There were 19 mucositis only episodes among 4 children in our cohort (range 1–9 per child) that did not meet inclusion criteria. Median age of first documented episode was 10 years, (range 4–16 years), and the median interval between SJS episodes was 15 months (range 2–69 months). A total of 20 episodes (69%) resulted in hospitalization (median hospital duration 7 days, range 1–47 days) (Table 1).

All 9 children were male, and 8 (89%) self-identified as white. The study children had previous diagnoses for their recurrent disease that included zinc deficiency, stomatitis, scarlet fever, and periodic fever, aphthous stomatitis, pharyngitis and adenitis.

Clinically, the oral mucosa was affected in all episodes, with less frequent involvement of the conjunctivae (79%), urethra...
| Patient | Age, Years | Gender | Ethnicity | Evaluation Site | Hospital | SJS Category | First Symptom(s) | Cough | Fever | Rash | Number of | Conjunctivitis | Urethral Lesions | Pseudocysts | Positive M. | HSV PCR or Culture | PCR or Culture | PCR | Mpg IgM | HSV PCR or Culture | ESR on Admission | CRP on Admission | ICU | Amniotic Membranes | Mucus | Duration, Days | Membranes | AEDs or Abx* | IFA | Admission | Graft | Abbreviations: Abx, antibiotics; AED, antiepileptic drug; AI/AN, American Indian/Alaskan Native; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HSV, herpes simplex virus; ICU, intensive care unit; IFA, immunofluorescent assay; Ig, immunoglobulin; Mpg, Mycoplasma pneumoniae; ND, not done; PCR, polymerase chain reaction; SJS, Stevens-Johnson Syndrome; +, positive or present; -, negative or not present. *Includes any antibiotic or antiepileptic within the 3 months before onset of mucosal or skin lesions, excluding azithromycin, as reported in the medical record. |
were negative. All 15 samples tested for HSV by PCR or culture metapneumovirus, parainfluenza virus type 2, and rhinovirus/s were consistent with SJS by dermatopathology and not consistent with areas of hypergranulosis. Both biopsies were believed to be consistent with SJS by dermatopathology and not consistent with Behçet’s disease.

Of the 21 episodes with diagnostic testing obtained, 6 (29%) had a positive Mp PCR or IgM IFA (Table 1). Additional pathogens identified include Chlamydia pneumoniae, human metapneumovirus, parainfluenza virus type 2, and rhinovirus/enterovirus. All 15 samples tested for HSV by PCR or culture were negative.

Two children underwent immunologic evaluation during an active episode, and 6 children were evaluated between 1 and 10 months after an episode. Human leukocyte antigen testing performed on 7 children revealed diverse genotypes, although HLA-B27 and HLA-B51 were seen in 2 (29%) and 3 (43%) children, respectively; 2 children had both HLA-B27 and HLA-B51. One child (Patient 1) who was heterozygous for HLA-B27/HLA-B51 had a skin biopsy that was not consistent with Behçet’s disease.

Outcomes were often severe with 1 child requiring 2 admissions to the intensive care unit for airway management and 4 children (6 episodes) requiring amniotic membrane grafts (Table 1). Two children subsequently developed urethral strictures requiring surgical intervention, and 5 children had signs or symptoms concerning for chronic lung disease after episodes. Treatment, which included intravenous Ig (4 episodes), systemic steroids (7 episodes), and antibiotics active against Mp (16 episodes) had no measurable impact on outcome. Prophylaxis with colchicine (n = 1) and azithromycin (n = 4) did not prevent subsequent episodes.

**DISCUSSION**

We present the first comprehensive clinical description and basic immunologic evaluation of a cohort of children diagnosed with a recurrent Stevens-Johnson-like syndrome. We found a wide spectrum of disease severity, even among episodes in the same child, ranging from oral mucositis-only episodes treated as an outpatient to episodes requiring admission to the intensive care unit and amniotic membrane grafting. Other children had prolonged hospitalizations of up to 6 weeks and suffered significant morbidity such as urethral strictures and chronic lung disease. Our cohort had several interesting findings. All children were male, and 8 of 9 self-identified as white, which has been previously reported [6]. Our patients each had multiple episodes meeting our predefined case definitions, and many had additional mucositis-only episodes. The mucosal-predominant presentation we observed has frequently been observed in Mp-associated SJS [2, 5].

The clinical histories and diagnostic testing often suggested an infectious etiology. Mycoplasma pneumoniae was identified in 29% of the tested episodes, although 2 episodes were by Mp IgM IFA only. Most episodes included cough and fever before the development of any mucosal or skin lesions. It is interesting to note that HSV was not detected during any episodes. In previous studies, specific HLA types have been associated with SJS disease and recurrent erythema multiforme [7–9]. HLA-B51 was found in 3 (43%) and HLA-B27 in 2 (29%) of our small samples, which are more frequent than that seen in the overall population [10]. HLA-B27 and -B51 are both associated with Behçet’s disease, and HLA-B51-associated Behçet’s is male predominant [11]. However, none of these children met the 1990 International Study Group nor the 2015 Paediatric Behçet’s Disease consensus classification criteria for pediatric Behçet’s disease [12]. Dermatopathology obtained in 2 patients from active skin lesions, including 1 heterozygous for HLA-B27/-B51, was not consistent with Behçet’s. These findings support a genetic susceptibility and antigenic trigger, such as Mp.

There is controversy surrounding the nomenclature of SJS and similar diseases. Historically, SJS has been referred to as erythema multiforme major or exudativum. Mycoplasma pneumoniae-associated SJS has been called Mp-associated mucositis (MPAM), atypical SJS, incomplete SJS, Fuch’s syndrome, and Mp-induced rash and mucositis (MIRM). A diagnosis of SJS requires an episode of acute illness with inflammation of 2 or more mucus membranes and consistent skin lesions [3]. In our case series, 18 episodes met the SJS case definition, but 11 had incomplete SJS and another 19 documented episodes only involved a single mucus membrane. In all cases, the disease phenotype was strongly mucus membrane-predominant with minimal skin disease. Although several episodes had positive Mp PCR and/or IgM testing, many episodes had negative Mp testing, distinguishing them from a diagnosis of MIRM or MPAM, although it is possible these were false negatives or taken after clearance of the organism. Favoring a more descriptive name that encompasses the spectrum of disease in these patients, with minimal skin disease extent and severity as well as the lack of a consistent trigger, we propose the nomenclature “recurrent multifocal mucositis.”

Our study was a retrospective chart review with its inherent limitations. We sought to avoid some of the inherent biases by creating predefined case definitions. Ideally, immunologic studies would also include samples during active disease on all children.
CONCLUSIONS

In summary, we report a case series of children with recurrent SJS-like disease. Many episodes did not meet the traditional case definition of SJS and might be more accurately described as recurrent multifocal mucositis. These children did not meet classification criteria for Behçet’s. Diagnostic testing identified *M. pneumoniae* infection associated with several episodes, but many episodes had negative *M. pneumoniae* testing. Unfortunately, the episodes can be associated with significant morbidity. The recurrent nature of the disease process, with multiple episodes of varying severity, a mucous membrane predominance, and evidence of respiratory infection, suggests a genetic predisposition with a possible infectious trigger. Further cohort studies are needed with improved surveillance, genetic, immunologic, and diagnostic evaluations.

Notes

Author contributions. D. O., J. A., and S. D. conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript submitted. C. L. and L. P. contributed significantly to the acquisition and analysis of data, drafting and revising the manuscript, and approved the final manuscript to be submitted.

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