Stevens-Johnson Syndrome without Skin Lesions: A Rare and Clinically Challenging Disease in the Urgent Setting

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ABSTRACT

Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme are life threatening diseases causing mucocutaneous eruptions and can be difficult to manage medically. When oral tissues are involved, airway management can be of critical importance. Fluid and electrolyte imbalance are common and protocols to prevent secondary infection are initiated. All three conditions are rapidly evolving. Stevens-Johnson syndrome is more commonly associated with Mycoplasma pneumoniae in the pediatric population and drug hypersensitivity in adults, whereas erythema multiforme is mostly associated with herpes simplex virus in the adult population. These diseases are T-cell-mediated immune reactions, thought to represent a spectrum of the same disease. Clinical and immunohistochemical techniques are capable of differentiating Stevens-Johnson syndrome from erythema multiforme and provide insight into the possible underlying pathology creating the disease. Rare cases of Stevens-Johnson syndrome without skin manifestations have been associated with Mycoplasma pneumoniae and predominantly occur in males. In-hospital management is recommended to provide airway support, maintain fluid intake, electrolyte balance, obtain multi-speciality consultation, and to perform diagnostic testing. We describe a case of a 14 year old male with atypical Stevens-Johnson syndrome and a review of the literature.

KEYWORDS: Stevens-Johnson syndrome; Toxic epidermal necrolysis; Erythema multiforme; Immunohistochemical; Episcleritis; Ulcerative stomatitis; Mycoplasma pneumoniae associated mucositis (MPAM); Fuchs syndrome; Major histocompatibility class; Non-MPAM atypical Stevens-Johnson syndrome.

ABBREVIATIONS: MPAM: Mycoplasma pneumonia-associated mucositis; SJS: Stevens-Johnson syndrome; TEN: Toxic Epidermal Necrolysis; EM: Erythema Multiforme; HSV: Herpes Simplex Virus; MP: Mycoplasma Pneumonia; IVIg: Intravenous immunoglobulins; HLA: Human Leukocyte Antigen; TNF-alpha: Tumor Necrosis Factor-alpha.

INTRODUCTION

Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Erythema Multiforme (EM) are immune hypersensitivity disorders associated with drug or infectious exposure, which can be life threatening. SJS and TEN are believed to be the same disease, with TEN representing the more severe form of the disease spectrum. Historical information such as exposure to specific drugs or infections, and clinical information such as the characteristics of skin lesions and their distribution have been useful in differentiating between and SJS, TEN, or
EM. Histologic and histochemical analyses remain the optimal methods of differentiating these diseases.\textsuperscript{1-4} SJS, TEN, and EM are felt to be cytotoxic-mediated, and various strategies are used for management with newer treatment protocols being devised. Recent case reports describe rare variants of SJS without skin manifestations.

**CASE REPORT**

A 14 year old previously healthy male with mild fever and malaise was seen by his primary care doctor for bilateral conjunctivitis and cough, for which he was prescribed azithromycin. After two doses he developed painful mouth swelling and the azithromycin was discontinued. This was similar to a previous reaction he had with penicillin three years earlier which resolved spontaneously after discontinuation. His symptoms worsened despite being off the azithromycin and he was prescribed oral prednisone, which was ineffective and discontinued after three days. He was referred to an ophthalmologist who felt his conjunctivitis represented a herpetic infection, and was started on ganciclovir ophthalmic gel and prednisolone acetate drops which he used for three days. He was subsequently seen by ENT who noted a new development of bleeding oral lesions and multiple blisters of the lips and oral mucosa (Figure 1). Magic mouthwash was prescribed. The patient experienced increasing difficulty with sustaining oral fluid intake and breathing due to his throat swelling, and was admitted to the hospital. On admission, the patient presented with dehydration, a non-productive cough, sensitivity to light, and blurred vision. A chest X-ray was performed and showed no abnormalities. On ophthalmologic examination, visual acuity was 20/20 in the right eye and 20/40 in the left eye. Pupils were equal, round and reactive to light. There was extensive ulceration of the conjunctiva of both eyes and diffuse fluorescein staining across the conjunctiva and cornea, with the left eye worse than the right. Focal episcleral injection in the right eye was noted (Figure 2). No adhesions or symblepharon were appreciated although inferior conjunctiva pseudomembrane formation was noted, right eye greater than the left. Funduscopic examination disclosed no abnormalities of the optic nerve, macula, or retinal vasculature.

Blood serology disclosed a C-reactive protein of 1.61 mg/dL, white blood cell count of 8.6 K/UL, and was negative for mononucleosis, Herpes Simplex Virus (HSV) 1 and 2, human immunodeficiency virus, influenzae, and *Mycoplasma Pneumoniae* (MP) IgM antibody. MP IgG was mildly elevated at 0.65 U/L (0.09-0.33 U/L) and decreased to 0.35 U/L after one day. *Mycoplasma* PCR was negative in oral cavity lavage. Epstein Barr virus nuclear and capsid antigen IgG were positive with values of >8.0 (<0.91). Coxsackie B Virus Titors were negative with values <1:10 for Types 1,2,3,4, and 6. Coxsackie B Type 5 had a value of 1:20 (<1:10). Coxsackie A Type 9 titer was negative with a value of <1:8 (<1:8). The presumed diagnosis was SJS without skin lesions due to azithromycin hypersensitivity with concurrent Epstein-Barr infection.

The patient was discharged within four days of admission in stable condition. Ophthalmological follow-up disclosed healing of his episcleritis and conjunctival and corneal lesions after continued use of lubricant eye drops. Subsequent clinical follow ups showed complete resolution after one month.

**METHODS**

We performed a systematic electronic literature search using the PubMed and Ovid MEDLINE databases. The last search was performed on April 7, 2015. The keywords used were: atypical Stevens Johnson syndrome, incomplete Stevens-Johnson syndrome, Stevens-Johnson syndrome without skin lesions, *Mycoplasma pneumoniae* associated mucositis, and Fuchs syndrome. All literature was limited to the English language.

Titles and abstracts were read to determine eligibility. Patients were included if they met the criteria for atypical SJS which included: lesions involving at least two mucous membranes (mouth, ocular, or genital), no skin involvement, and positive infection or suspected drug reaction.

**RESULTS**

Our search yielded 1,192 publications that included the keywords listed in our methods section. 24 articles met the criteria for atypical SJS. In total, there were 32 patients described.
including our reported patient. Patients were separated into two categories: children ages 3 to 16 years of age (17 patients, Table 1) and adults 18 to 44 years of age (15 patients, Table 2). Information for each case includes age, sex, chest involvement, genital involvement, etiology, diagnosis, diagnostic testing, and treatment. No patients under the age of 3 or over the age of 44 were reported in the literature.

Of the pediatric cases (Table 1), fifteen patients were male (88%), ten patients had chest involvement (59%), ten patients had genital involvement (59%), and fourteen patients had positive MP infection (82%). One was treated with immunosuppressants, all were treated with antibiotics (mainly macrolides), and one was treated with intravenous immunoglobulins (IVIg). All patients had a favorable outcome and all had complete resolution to their baseline health.

A prior review of atypical SJS by Vujic, et al. in 2014 yielded 818 search results, of which only 11 articles (13 patients) met their criteria.26 The review was limited to adult patients between the ages of 18 to 38 years of age. Ten patients were male (77%), six patients had chest involvement (46%), nine patients had genital involvement (69%), and all patients had positive MP infection (100%). Nine were treated with immunosuppressants and ten were treated with antibiotics, which were mainly macrolides and fluoroquinolones.

For the adult cases, one case was excluded from Vujic, et al. for minimal skin involvement, and three more were included. Of those three additional cases, 2 were male, 2 had chest involvement, none had genital involvement, and two had positive MP infection. All were treated with immunosuppressants, two were treated with antibiotics, and one was treated with IVIg. All patients had a favorable outcome.

Four cases were not associated with MP (Table 1-2). Of the pediatric cases, one cause was unknown and two were from a suspected drug reaction. The presumed cause in the adult case was from MP despite having negative serological testing, although she did test positive for influenza type B.

DISCUSSION

Erythema Multiforme

EM, SJS, and TEN are acute, immune-mediated, hypersensitivity reactions to certain medications or infections, which are believed to trigger a cytotoxic response. EM was previously thought to be part of the spectrum of SJS and TEN, but today it is recognized as a distinct entity with different clinical and epidemiological characteristics.29,30 EM is manifested by characteristic raised, bullous skin lesions that are palpable. Epidermal detachment occurs in less than 10% of the body surface area and there is minimal mucous membrane involvement. Oral lesions are described as polymorphic, erosive, ampullary, and erythematous.28 EM occurs mostly in adults between 20 to 40 years old31 and is most often caused by HSV.2,28,30

Stevens-Johnson Syndrome

SJS was first described in 1922 by Albert Mason Stevens and Frank Chambliss Johnson.32 It is considered to be a single disease entity with TEN, with less severity. The process begins with fever and flu-like symptoms, followed by a break-out of severe mucosal erosions and diffuse, flat atypical skin lesions that are non-palpable. SJS has a prevalence of 1.2-6 /million cases per year, with a mortality rate of 5-10%.3,28 The most commonly identified cause of SJS in children is infection and drug sensitivity for adults.28,16,19,35 Viral associated with SJS include coxsackie virus, HSV, AIDS, influenza, hepatitis, mumps, and Epstein-Barr. Associated bacterial agents include group A beta-hemolytic streptococci, diphtheria, brucellosis, lymphogranuloma venereum, mycobacteria, MP, rickettsia, tularemia, and typhoid.

Atypical Stevens-Johnson Syndrome/Mycoplasma Pneumoniae-Associated Mucositis

The first case of atypical SJS was described by Maj Otto F. Sieber in 1967.11,19,23 Most cases of this disorder have a better prognosis and recovery time than typical SJS, and to date there have been no mortalities from this condition. It is difficult to determine at the onset of this disorder if it will proceed to complete SJS or TEN. Ocular involvement occurs in every case and can include diffuse bullous conjunctival edema, pseudomembranes of the conjunctiva, corneal epithelial defects and episcleritis.14 In 2005, Schalock and Dinulos proposed that the diagnosis of atypical SJS be classified as Mycoplasma pneumoniae-associated mucositis (MPAM) due to the striking feature that atypical cases of SJS are associated with MP.11 MP is the most common cause of childhood pneumonia and is a self-limiting disease managed without antibiotics, which can explain why there is a better prognosis for MPAM.

In our review of the literature, four atypical cases were not associated with MP, therefore not fitting the criteria for MPAM (Tables 1 and 2). Of the pediatric cases, one cause was unknown and two were from a suspected drug reaction. The adult case was more complicated because the presumed cause was from MP despite having negative serological testing, only because the more likely cause of atypical SJS is from MP. The patient tested positive for influenza type B, which we suspect was the actual triggering factor. This suggests there may be other variant forms of atypical SJS, which we feel is the case for our patient. We suspect our patient developed a reaction to the azithromycin, which similarly occurred after a dose of penicillin three years prior with the exception of the mucosal necrosis. A similar case is described by Lamireau et al., of a 7-year-old boy that initially presented with non-MPAM atypical SJS, which recurred and resulted in a complete SJS.8
EBV: Epstein Barr Virus; RSV: Respiratory Syncytial Virus.
Age, sex, chest involvement, genital involvement, etiology, diagnosis, diagnostic methods, and treatment for 17 pediatric cases of atypical Stevens-Johnson syndrome. *The literature shows a variability in initial treatment, with the ultimate treatment being focused on treating Mycoplasma pneumonia or inflammation which is shown in this table.

Table 1: Pediatric cases of atypical Stevens-Johnson syndrome.

| Author et al. | Age | Sex | Chest Involved | Genital Involved | Etiology | Diagnosis | Diagnostic Testing | Treatment* |
|---------------|-----|-----|----------------|------------------|----------|-----------|---------------------|------------|
| Alter*        | 13  | M   | N              | N                | MP       | MPAM      | Complement fixation titer | Erythromycin |
|              | 10  | M   | Y              | Y                | MP       | MPAM      | Complement fixation titer | Erythromycin |
|              | 12  | M   | Y              | Y                | MP       | MPAM      | Complement fixation titer | Erythromycin |
| Bressan²      | 9   | F   | N/A            | Y                | MP       | MPAM      | IgM, agglutination assays | IVIg        |
| Fearon³       | 8   | M   | Y              | N                | MP       | MPAM w/ RSV | Agglutination assays | Roxithromycin |
| Lamireau⁴     | 6   | M   | Y              | N                | MP       | SJS       | Mouth culture, oral PCR, IgG, - cold agglutinin | Erythromycin, thalidomide |
|              | 7   | M   | N              | N                | Not Stated | SJS       | Serology, - PCR | Rovamycin, prednisone |
| Latsch⁴       | 13  | F   | Y              | Y                | MP       | SJS w/o skin lesions | Throat swab PCR, microparticle agglutination assay, IgM, -IgA, -IgG | Clarithromycin |
|              | 11  | M   | N              | N                | MP       | SJS w/o skin lesions | Sputum specimen, microparticle agglutination assay, IgM, IgA, IgG | Clarithromycin |
| Meyer Sauteur⁵| 7   | M   | Y              | Y                | MP       | Fuchs     | Throat swab PCR, complement fixation titer | Azithromycin |
| Ravin⁶        | 14  | M   | Y              | Y                | MP       | Atypical SJS | Throat swab PCR | Cefuroxime, azithromycin |
|              | 16  | M   | Y              | Y                | MP       | Atypical SJS | Throat swab PCR | Ceftriaxone, azithromycin |
| Schalock⁷     | 17  | M   | N/A            | N                | MP       | MPAM      | IgG | Azithromycin |
| Strawn⁸       | 15  | M   | Y              | Y                | Drug     | Atypical SJS | N/A | Cefdinir, azithromycin |
| Trapp¹¹       | 13  | M   | N/A            | Y                | MP       | MPAM      | IgM, - cold agglutinin | Azithromycin |
| Vanfleteren¹⁴ | 14  | M   | Y              | Y                | MP       | SJS w/o skin lesions | IgG, IgM | Clarithromycin, amoxicillin-clavulanic acid, acyclovir |
| Ours          | 14  | M   | N              | N                | Drug     | SJS w/o skin lesions w/ EBV | IgG, -IgM, - oral PCR, EBV NA IgG and CA IgG | Doxycycline |
Age, sex, chest involvement, genital involvement, etiology, diagnosis, diagnostic methods, and treatment for 15 adult cases of atypical Stevens-Johnson syndrome. *The literature shows a variability in initial treatment, with the ultimate treatment being focused on treating Mycoplasma pneumonia or inflammation which is shown in this table.

**Table 2:** Adult cases of atypical Stevens-Johnson syndrome.

| Author et al. | Age  | Sex | Chest Involved | Genital Involved | Etiology | Diagnosis | Diagnostic Testing | Treatment* |
|---------------|------|-----|----------------|------------------|----------|-----------|-------------------|------------|
| Birch         | 21   | F   | N/A            | Y                | MP       | Atypical SJS | Esophageal biopsy, - PCR, IgM | IV Ig, levofloxacin |
| Havilza       | 32   | F   | N/A            | N                | MP       | Fuchs      | Antibody titers       | Prenisolone, acyclovir, cefuroxime, levofloxacin |
| Negaga        | 38   | F   | N/A            | N                | MP       | Fuchs      | Antibody titers       | Prenisolone, acyclovir, cefuroxime, levofloxacin |
| Hillebrand    | 23   | M   | Y              | Y                | MP       | Incomplete SJS | Throat swab PCR, agglutination IgM IgG titer | Amoxicillin-clavulanic acid, azithromycin |
| Kirke         | 18   | M   | N              | Y                | MP       | SJS        | Oral biopsy, - immunofluorescence, IgM, complement fixation titer, cold agglutinin | Prednisolone |
| Li            | 26   | M   | N              | Y                | MP       | Fuchs      | Oral biopsy, IgM, -cold agglutinin | Amoxicillin, oseltamivir, methylprednisolone, clarithromycin |
| Majima        | 44   | F   | Y              | N                | MP       | Presumed   | SJS-like mucositis w/o skin lesions | IgM + influenza B from nasal swab | Methylprednisolone, prednisolone, ampicillin, azithromycin |
| McGouran      | 18   | M   | N              | Y                | MP       | Atypical SJS | Complement fixation titer, agglutination assays, convalescent serum sample | Methylprednisolone |
| Ramasamy      | 19   | M   | Y              | N                | MP       | Incomplete SJS | Oral biopsy, - immunofluorescence, IgM, complement fixation titer | Co-amoxiclav, erythromycin |
| Sieber        | 22   | M   | Y              | Y                | MP       | SJS        | Throat swab, MP hemagglutination-inhibition, complement fixation titer | Prednisone, sodium cephalothin, tetracycline |
| Sternbersky   | 22   | M   | N/A            | Y                | MP       | Fuchs      | IgG, IgM               | Clarithromycin |
| Varghese      | 20   | M   | Y              | N                | MP       | MPAM       | IgG, IgM, immunofluorescence | Levofoxacin, clindamycin, IV Ig, methylprednisolone |
| Vujic         | 23   | M   | Y              | N                | MP       | MPAM       | Oral mucosa biopsy, IgA, IgG, IgM, -immunofluorescence | Doxycycline, prednisolone |
| Walicka       | 27   | M   | Y              | Y                | MP       | SJS        | Immunoenzymatic examination | Ceftriaxone, fluconazole, ciprofloxacin, cyclosporine A, fenoterol and ipratropium bromide (nebulizer), doxycycline, ambroxol, fenoterol |
| Yachoui       | 29   | M   | N/A            | Y                | MP       | Atypical SJS | IgM               | Solumedrol |
To our knowledge, there are only four reports of SJS associated with azithromycin, with our case being the first described for atypical SJS. The first reported case describes a 5-year-old boy who developed oral pain and skin eruptions three days after taking azithromycin. Initial HSV testing was unremarkable, but showed an increase in IgM antibody after retesting. They suspected the HSV was reactivated after the use of steroids, which may explain the positivity for Epstein-Barr in our case.

Genetic Predisposition

The underlying root for the spectrum of disease presentation and treatment responses between atypical SJS, MPAM, SJS, TEN and EM may have some underlying genetic influences. A strong genetic association can be formed by examining Human Leukocyte Antigen (HLA) typing, occurrences in family members, and recurrence. HLA-B*5701, HLA-B*5801, HLA-B*1502, HLA-A*3101, HLA-A*0206, HLA-B*4403, HLA-A29, HLA-B12, HLA-DR7, and HLA-A2 are linked to SJS drug hypersensitivity reactions. Differences can also be distinguished in their early stages. The number of granulysin- and perforin-expressing CD8+ cells are greater in SJS than EM, while the number of Foxp3 and CD4+ cells are lower. However, this technique is unavailable in atypical cases where there are no skin lesions present. Oral biopsies have been performed for atypical SJS/MPAM, which show highly necrotic mucosa with extensive inflammatory infiltrate consistent with SJS.

Management and Treatment

There is a complexity of the treatment for a condition which may in the long run be self-limiting, however may evolve due to its complexity. Treatment with antibiotics and immunosuppressive agents remains the mainstay of management for patients with a suspected infectious cause. There are questions about efficacy and safety regarding the use of corticosteroids, however, an improvement in the disease indicates that there is an inflammatory component that needs to be treated. It is common for patients to be treated with an antiviral when there is a suspected viral infection or when being treated with corticosteroids. Patients with suspected adverse reactions to medication must be withdrawn from it. The use of plasmapheresis and hemodialysis to remove these agents is debatable.

Other treatments such as IVIg in patients with SJS, TEN, or EM are sometimes used to target Fas/Fasl interactions, and are shown to have reduced mortality rates. IVIg was used in only one case of atypical SJS which produced a good outcome (Table 2). Additional treatments include Tumor Necrosis Factor-alpha pathway antagonizers (TNF inhibitors, pentoxyfilline, thalidomide, infliximab) and immunomodulators (cyclophosphamide, cyclosorpin, N-acetylcysteine, and pentoxyfilline) to reduce the amount of steroids. Maintaining airway support and balancing nutritional and fluid intake is also crucial in improving the condition of these patients.

CONCLUSION

EM, atypical SJS, MPAM, SJS, and TEN are all disorders which change rapidly and may pose life threatening consequences. Despite all therapeutic efforts, the mortality rate is increased with the severity of the disease, age of the patient, and sensitivity of PCR ranges from 78-100%, while serology ranges from 50-66%.

Skin biopsies are a definitive way to differentiate SJS/TEN from EM. Histopathological analyses typically show subepidermal blistering, widespread keratinocyte apoptosis, and full-thickness epidermal necrosis and detachment with a sparse dermal mononuclear infiltrate. Differences can also be distinguished in their early stages. The number of granulysin- and perforin-expressing CD8+ cells are greater in SJS than EM, while the number of Foxp3 and CD4+ cells are lower. However, this technique is unavailable in atypical cases where there are no skin lesions present. Oral biopsies have been performed for atypical SJS/MPAM, which show highly necrotic mucosa with extensive inflammatory infiltrate consistent with SJS.
with any underlying medical condition. Chronic ocular complications and mucosal scarring may persist after treatment. We recommend that all patients with ocular, buccal and genital mucosa erosions have ophthalmologic, ENT and dermatologic consultation. Patients should be admitted in the acute setting, particularly when there are issues of airway integrity. This allows for greater patient stabilization, improved diagnosis, and better multi-specialty team approach to the complex and often unusual patient presentation.

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CONSENT STATEMENT

Consent was obtained by the patients father as patient was a minor.

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