

CASE REPORT

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Immunodeficiency and post-operative antibiotic use leading to development of toxic epidermal necrolysis

Patrina Agosta, Sophia Halassy, Sharon Miller, Sayeh Nabati

ABSTRACT

Introduction: The rarity of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) often lead to a missed diagnosis of a severe, life-threatening disease spectrum. Major risk factors include immunodeficiency and use of certain medications. Patients often present with fever and mucositis which can quickly lead to skin sloughing rash. Rapid diagnosis, treatment, and transfer to the Intensive Care or Burn Unit are essential preventing morbidity and mortality.

Case Report: Our case presents a patient whose initial complaint consisted of poorly controlled pain from a primary herpetic outbreak. Her hospital course eventually led to an unrelenting fever, oral lesions, and rash along her neck and chest rash which encompassed her entire body within 12 hours and led to sloughing of her areola and labia, and even labial agglutination. Rapid transfer to a Burn Unit, aggressive fluid hydration, and close monitoring were critical in her care.

Conclusion: The rapid progression and high morbidity and mortality rates make it important for healthcare personnel to recognize SJS quickly. Obstetricians and Gynecologists especially should have heightened awareness as the failure to provide a gynecologic exam can have devastating effects. Every patient with signs or symptoms of SJS, especially those with risk factors such

as immunocompromise or use of specific medications, should undergo a prompt and thorough workup.

Keywords: Herpes simplex virus, Nitrofurantoin, Steven–Johnson syndrome, Toxic epidermal necrolysis

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INTRODUCTION

Steven–Johnson syndrome (SJS), albeit rare, is a condition that if not recognized early can have detrimental effects. The field of Obstetrics and Gynecology involves a number of ulcerative cutaneous lesions involving the mucous membranes. A wide differential diagnosis should be formulated when these conditions are encountered. We present a case in which a woman was diagnosed with a primary herpes outbreak based on clinical presentation and serology. Whether it was actually a primary outbreak leading to an immunocompromised status and then SJS or SJS which was mistaken for a primary herpes simplex virus (HSV) outbreak, the signs and symptoms of SJS should be familiar to every Obstetrician and Gynecologist.

CASE REPORT

A 40-year-old G7 P6-0-1-7 female initially presented to the office with a primary complaint of painful

Patrina Agosta^{1,2}, MD, Sophia Halassy^{1,2}, MD, MS, Sharon Miller¹, MD, FACOG, Sayeh Nabati¹, MS3

Affiliation: ¹Ascension Providence Hospital, Department of Obstetrics & Gynecology, Southfield, Michigan, USA; ²Michigan State University, School of Human Medicine, East Lansing, Michigan, USA.

Corresponding Author: Sayeh Nabati, Ascension Providence Hospital, Department of Obstetrics & Gynecology, Southfield, Michigan 48075, USA; Email: sayeh.nabati@ascension-external.org

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urination, vaginal burning, and irritation. On examination, vesicular lesions were noted, a culture for herpes simplex virus (HSV) and other sexually transmitted infections (STIs) was collected. Given that this was the first of such occurrences for the patient, she had been given a diagnosis of primary HSV outbreak and was given prescriptions for topical lidocaine jelly and Valacyclovir. During the same office visit, the patient was noted to have slight erythema and induration at a laparoscopic port-site incision after having undergone a right-sided salpingectomy for ectopic pregnancy 15 days prior to this current office visit. She was given a prescription for Nitrofurantoin. Despite proper compliance, the vulvar pain persisted and the patient later developed chills and a febrile episode of 102 degrees Fahrenheit (°F) at home two days after her office visit, prompting her to present to the emergency department for further evaluation.

At the time of emergency department evaluation, her vital signs were stable, and her surgical incision was noted to be without signs of infection. External genitalia examination demonstrated extensive vulvar vesicular lesions consistent with herpetic outbreak. A minority of the vesicles was surrounded by erythema, and expressed purulent discharge. The patient did not have evidence of leukocytosis. Review of previous in-office culture results was negative for herpes or other STIs. Regardless, she was admitted to the hospital for pain management with Lidocaine jelly, Ketorolac, and Hydrocodone/Acetaminophen, as needed, and continued on Valacyclovir.

Other than her history as highlighted above, the patient had a history of five full-term vaginal deliveries and one full-term cesarean section due to twin gestation. Her last menstrual period was approximately one month before, and she had a pertinent gynecological history of chlamydia infection in the past, which was successfully treated. Her medical history was significant for asthma, and she had not undergone any other surgery other than previously described.

During in-hospital stay, the patient had complained of a sore throat and upper respiratory infection-like symptoms. She was given Chloraseptic spray, menthol lozenges, and Pseudoephedrine for relief. The patient was also prescribed moisturizing eyedrops for conjunctival irritation. She was noted to have decreasing leukopenia from 5.1 to 3.9 K/mcL. Herpes simplex virus serology was positive for both immunoglobulin (Ig) G and IgM. A rapid Streptococcus test was negative. On the evening of hospital day 3, the patient had a low-lying fever of 100.8 °F along with some tachycardia. An Internal Medicine consultation was placed for further evaluation. Physical examination findings were significant for mild papular skin rash in the upper trunk and neck area. A working diagnosis of viral syndrome was made. The patient was started on aggressive intravenous (IV) fluid hydration and Ceftriaxone until final upper respiratory cultures resulted. Due to her myriad and acute worsening of symptoms, a human immunodeficiency virus (HIV) and hepatitis panel was also obtained. Infectious disease was consulted.

The following day, there was rapid decompensation in the patient state. She was noted to have an accelerated progression of a bullous, erythematous rash, encompassing the patient's face and upper chest. The patient had severe conjunctival injection of both eyes with associated blurry vision. She was noted to have severe tachycardia, and persistent fever with max temperature of 103 °F, despite repeated Acetaminophen administration. With a working diagnosis of sepsis, the patient was placed in the Intensive Care Unit (ICU) with aggressive fluid management. She was started on Vancomycin, Piperacillin/Tazobactam and the Valacyclovir was discontinued due to fear of drug reaction. The patient was given Methylprednisolone and she was closely monitored. Workup included computerized tomography (CT) of the abdomen and pelvis, which were negative. All serum laboratory values and cultures were within normal limits, except for mild elevation in inflammatory markers (e.g., C-reactive protein and erythrocyte sedimentation rate).

The next day, the patient was noted to have significant mucositis progression. The rash spread quickly, and there was gross sloughing of the right labia minora and right areola. The patient had labial agglutination, diffuse maculopapular rash with sloughing, bilateral conjunctival injection with erythema and swelling of bilateral eyelids, encompassing more than 40% of her body in totality. A final diagnosis of toxic epidermal necrolysis (TEN) was made. Due to quick and rapid deterioration of the patient, the patient was transferred to a primary hospital site's specialized burn unit for further care.

DISCUSSION

Stevens–Johnson syndrome is a rare phenomenon, so rare that according to a global population-based study, the incidence is estimated to be only 1.0–6.0 per million [1]. The incidence appears to be greater in immunocompromised patients, especially those with HIV and cancer [2, 3]. It is more prevalent in the female population with a 2:1 ratio [4]. Our case involved an adult female who may have had an altered immunity after surgery, and have led to the development of her primary herpetic outbreak.

Stevens–Johnson syndrome is the result of a type IV hypersensitivity reaction [5] and its pathogenesis is not completely understood. In general, it is thought to be due to dysregulation of cellular immunity [6]. This dysregulation causes activation of cytotoxic T and natural killer cells [7] which release various cytotoxic signals including granulysin [8], perforin/granzyme B, and Fas/Fas ligand [9] which take effect on keratinocytes [10]. This leads to detachment of the epidermis due to extensive necrosis [11]. Stevens–Johnson syndrome is considered a disease continuum with increasing severity progressing to TEN. It involves skin detachment of <10% of the body surface and progression to TEN involves detachment of >30% of body surface area [12, 13], such as our patient, who also had

mucosal membrane involvement. Mucous membranes are affected in over 90% of patients [12, 13].

While over one-third of Stevens–Johnson cases have no identified cause [14], those that do are often found to be associated with medical drug use. The most common drugs include sulfa antibiotics, allopurinol, aromatic antiepileptics, and oxicam nonsteroidal anti-inflammatory drugs (NSAIDs) [15, 16]. Typical exposure time to onset of reaction is 4 days to 4 weeks. The risk of developing SJS is limited to the first 8 weeks of treatment [14, 17]. Our patient developed symptoms one week after completion of her sulfa antibiotic (Nitrofurantoin). It is thought that these medications bind directly to the major histocompatibility complex (MHC) class I and the T cell receptor and lead to clonal expansion of the drug-specific cytotoxic T cells that kill keratinocytes [18]. While several HLA haplotypes have been implicated in drug-specific susceptibility [19–21] there has been failure to identify any highly penetrant genetic factors associated with SJS [22].

Clinical presentations often mirror flu-like prodrome including malaise, myalgia, and arthralgia with a high fever which can exceed 102.0. These symptoms often present one to three days prior to mucocutaneous lesions [23]. In our case, mucositis lesions developed within 12 hours of her febrile illness. Cutaneous lesions often start as an erythematous rash that progresses to coalescing macules or targetoid lesions with purpuric centers [24, 25]. These lesions typically start on the face and spread down to the thorax, most often sparing the scalp, palms, and soles [26, 27], such as our case and slough off with a light touch known as the “nikolsky sign.” Our patient had sloughing of her areola and vulvar epithelium with only slight palpation. Mucosal lesions can involve the oral, ocular, urogenital, pharyngeal, or esophageal mucosa [23, 28–30]. Oral erosions present as mucositis and stomatitis [31, 32] and urogenital lesions can present as ulcerative vaginitis, vaginal adhesions, vulvar bullae, and urethritis which can all lead to urinary retention and cystitis [29, 33]. Symptoms of conjunctival irritation, photophobia, skin blistering, and pain on swallowing can also be seen [23, 34] and were all present in our female patient.

Stevens–Johnson syndrome is primarily a clinical diagnosis; however, workup can include a number of tests. Laboratory work includes complete blood count with differential, metabolic panel, erythrocyte sedimentation rate, and C-reactive protein. Blood and mucosal lesion cultures can be obtained as patients are at high risk of sepsis due to skin sloughing and exposed membranes. A chest radiograph should be obtained in all patients [35]. A skin biopsy for histopathologic examination and direct immunofluorescence can aid in confirming diagnosis. Apoptotic keratinocytes scattered throughout the basal layer of the epidermis; however, this should be noted that this is a finding that can be seen in other conditions as well. Direct immunofluorescence is always negative [11].

Severity and prognosis of SJS depends upon the percentage of body surface area involved in the amount of skin sloughing [35]. The severity and prognosis of a

patient with SJS can be determined using the SCORTEN scale [36]. Individual prognostic factors are given a point and the overall score is associated with a corresponding mortality rate. The score for our patient was 3 (notably serum bicarbonate=15 mEq/L, heart rate=140 beats per minute, involved body surface area >30%), indicating a 35% mortality rate and diagnosis of TEN.

A key aspect in the treatment of SJS is identification and withdrawal of the offending agent if one can be identified [37]. Patients should be treated in a hospital setting, particularly in an Intensive Care or Burn Unit if possible [38, 39]. Supportive care is the main goal and includes fluid and electrolyte replacement, pain control, and treatment of concomitant infections [40–42]. While sepsis and superinfections are prominent and remain one of the leading causes of death, systemic antibiotics are not advised or employed universally and should be used based on individual cultures [43]. Special attention should be placed to identifying ocular for immediate treatment as effects can be detrimental. Early gynecologic exam is important and one that can be easily missed. Steven–Johnson syndrome increases the risk of vulvovaginal adhesions as well as metaplastic changes of tissue. The use of intravaginal corticosteroids and soft vaginal dilators can aid in the prevention of adhesions [44].

CONCLUSION

It is important for all healthcare personnel to be aware of SJS as it is a disease that can easily be mistaken or missed in its early stages. Its rapid progression and associated morbidity and mortality should prompt early investigation and treatment. Obstetricians and Gynecologists should have a heightened awareness as the failure to provide a gynecologic exam can have devastating effects and could even lead to patient death. Any patient with important risk factors such as immunodeficiency and recent use of antibiotics presenting with rash and febrile episode should undergo a proper workup.

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Author Contributions

Patrina Agosta – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Sophia Halassy – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Sharon Miller – Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Sayeh Nabati – Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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