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Influenza B virus infection and Stevens–Johnson syndrome

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Abstract

A 2-year-old boy with influenza B infection and rapidly worsening targetoid skin lesions with mucosal involvement was diagnosed with Stevens–Johnson syndrome (SJS) and treated with oseltamivir and intravenous immunoglobulin, with resolution of illness. Subsequent quadrivalent inactivated influenza vaccine was well tolerated. This case highlights the rarity of SJS in the setting of influenza B infection and addresses the safety of administering subsequent influenza vaccines to such individuals.

Keywords

influenza vaccine; intravenous immunoglobulin; vaccine safety

1 | INTRODUCTION

A previously healthy 2-year-old Hispanic boy presented in the winter of 2013 with a 5-day history of fever, congestion, rhinorrhea, myalgia, and a progressive pruritic facial eruption. Two days before, his pediatrician had started dexamethasone, ibuprofen, famotidine, and diphenhydramine because of suspicion of an allergic skin eruption. There were no known medication exposures, including acetaminophen or ibuprofen, preceding the appearance of skin lesions. Over the next 2 days, skin lesions became widespread, prompting reevaluation. Immunizations were up to date, including a yearly seasonal trivalent inactivated influenza vaccine 3 months before presentation. He had been vaccinated for influenza at 9, 12, and 23 months of age without incident. A household contact had experienced "flu" symptoms before current symptom onset.

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Vital signs were significant for fever 101°F, tachycardia, and tachypnea with normal blood pressure. Skin examination revealed pink, annular, edematous papules and plaques on the face, trunk, buttocks, and extremities, many with dusky, violaceous centers (Figure 1). Multiple tense vesicles and targetoid erythematous papules were located perianally. Rare serous vesicles were noted centrally, with negative Nikolsky and Asboe-Hansen signs. There was no skin tenderness. Additional findings included cervical lymphadenopathy, mildly injected sclera, and dry crusted lips. There was no genital or palmoplantar involvement. The remainder of the physical examination was unremarkable.

Laboratory evaluation revealed leukocytosis (17×10^9/L) and high C-reactive protein (10 mg/L). Empiric therapy with azithromycin, acyclovir, and clindamycin was initiated while serologic titers and cultures (urine, skin, blood) were pending. Because of continued fever, piperacillin/tazobactam was added on hospital day 2. A nasopharyngeal swab was positive for influenza B and negative for mycoplasma and 18 other common respiratory pathogens according to a respiratory viral polymerase chain reaction (PCR) panel.[1] Oseltamivir therapy was initiated and supportive care provided. Skin biopsy (Figure 2) revealed necrotic keratinocytes within the epidermis and an interface dermatitis consistent with the erythema multiforme/Stevens–Johnson syndrome (EM/SJS) spectrum of inflammatory dermatoses. Immunofluorescence studies were negative for immunobullous disease. Antistreptolysin O (ASO), mycoplasma, parvovirus, herpes simplex virus (HSV), Epstein–Barr virus (EBV), and cytomegalovirus titers; surface bacterial and viral cultures; blood culture; and urine culture were negative, and acyclovir and antibiotics were subsequently discontinued.

Despite supportive therapy, the patient's eruption rapidly progressed to involve more than 10% of his body surface area, with skin fragility and denudation (Figure 3), requiring transfer to intensive care. Wound care and fluid management continued, and given the progression of cutaneous disease, intravenous immunoglobulin (IVIg) 1 g/kg/d was administered for 3 days, resulting in defervescence and skin stabilization. His lesions reepithelialized and he was discharged on hospital day 7. He was well with minimal postinflammatory hypopigmentation noted 3 months after hospital discharge.

During the following influenza season, after discussion with vaccine safety experts, the child received an inactivated quadrivalent influenza vaccine containing both influenza B lineages with close monitoring. He tolerated the vaccine well, without any reported adverse reaction after vaccination.

2 | DISCUSSION

EM, SJS, and toxic epidermal necrolysis (TEN) are thought to fall along a continuum of severe cutaneous reactions requiring prompt recognition and initiation of supportive care.[2] There are many classification systems used in diagnosis, most commonly based on the degree of mucosal and skin involvement or etiology of the illness.[2] Medications are the most common cause, with allopurinol, nevirapine, sulfa derivatives, amminopenicillins, cephalosporins, nonsteroidal antiinflammatory agents, quinolones, and antiepileptic medications found as frequent culprits.[2] Infectious pathogens have been associated with this disease spectrum, including viral (HSV, HIV, EBV, influenza, coxsackie) and bacterial

(Mycoplasma pneumoniae, typhoid, diphtheria, group A *streptococcus)* organisms.[3] Immunizations against measles, mumps, and rubella have also been temporally associated with the onset of SJS.[2,3] Reports of EM, SJS, and TEN in the setting of influenza virus infection are rare.

The classification of EM major and SJS is controversial, given their similar histologic features and mucosal findings. They are commonly differentiated based on disease etiology, with infection being more supportive of EM major and medication more suggestive of SJS/TEN.[2] Despite the viral association in our patient, the rapid progression, toxic appearance, and facial-truncal distribution led us to classify his eruption as SJS.

The mortality of this spectrum of disease can be quite high: 5–15% in SJS and up to 30% in TEN.[3,4] Treatment is supportive and includes adequate hydration, nutrition, wound care, and transfer to a burn or intensive care unit if warranted. Ocular care with lubricating ointments and ophthalmologic consultation is recommended.[4] Topical antibiotics are often used; use of systemic prophylactic antibiotics is controversial, typically initiated when signs and symptoms of sepsis are present.[4] The use of oral glucocorticoid therapy is contro- versial.[4] Additional reported therapies include etanercept, cyclosporine, IVIg, and plasmapheresis.[4] In our case, the clinical course stabilized rapidly with IVIg administration, consistent with previously published pediatric cases.[5] Our patient also received oseltamivir in light of the positive influenza B PCR. Oseltamivir is recommended for treating influenza A and B in children and may decrease the severity and length of illness, especially if given within the first 48 hours of symptoms.[6]

Although our patient had received three prior injections of trivalent inactivated influenza vaccines at ages 9, 12, and 23 months without incident, there was concern that reexposure to influenza B antigen in the form of vaccination during subsequent influenza seasons might increase the chance of disease recurrence. A review of the English-language literature (Ovid, Scopus, PubMed databases) for cases of EM, SJS, or TEN associated with influenza infection or vaccination revealed one case of SJS and one case of EM temporally associated with influenza virus infection.[7,8] One case of EM and two cases of SJS were temporally associated with inactivated influenza vaccination (one case of SJS with concomitant flucloxacillin and another with H1N1 vaccine).[9–11] None of these cases were in children.

The Centers for Disease Control and Prevention (CDC)-funded Clinical Immunization Safety Assessment (CISA) provides a consultation service for US health care providers with vaccine safety questions regarding their patients, which includes assessment of causality of adverse events after vaccination with licensed vaccines.[12,13] Advice from the CDC and CISA is meant to assist with decision making rather than to direct individual patient management. This group reviewed the case history, available literature, reports from the CDC and Food and Drug Administration, and the Vaccine Adverse Event Reporting System (VAERS), which is a spontaneous reporting system that accepts reports of vaccine adverse events as the reporter (e.g., patient, parent, health care provider, vaccine manufacturer) describes, with no attempt to determine causality.[14] At the time of this review, one published VAERS article described 35 cases of possible SJS/TEN after vaccination from 1990 to 1999.[15] Six had skin eruptions after vaccinations and before the use of other medications.

The onset of eruption ranged from 0 to 22 days (mean 5 days) after vaccination. One case was associated with inactivated influenza vaccine in a 24-year-old woman, with eruption occurring on the day of vaccination.

A multicenter Italian study quantifying the risk of SJS after medication and vaccination did not identify immunization as a risk for SJS.[16] After considering available information, experts in the CISA group concluded that our patient's clinical event was consistent with SJS and that influenza B infection was the most likely cause.

Given the absence of substantive data to verify a causal relationship between influenza vaccination and SJS and concern that the child would be at greater risk of recurrence with subsequent influenza B infection, experts in the CISA group recommended vaccination with the quadrivalent inactivated influenza vaccine containing two type B and two type A virus strains with close monitoring. Inactivated vaccine was recommended instead of live attenuated vaccine to eliminate the possibility of vaccine virus replication, which could potentially mimic the chain of events that occurred with his wildtype influenza B infection 1 year earlier. Our patient was subsequently vaccinated with quadrivalent inactivated influenza vaccine with observation. He tolerated vaccination without incident and remained asymptomatic at follow-up after vaccination. He subsequently received two additional annual intranasal live attenuated trivalent influenza vaccines without incident.

Although previously reported cases of influenza-related EM, SJS, and TEN are rare, we suspect that as sensitivity of testing improves with the use of PCR for diagnosis, more cases might be identified. In our case, IVIg may have stabilized disease progression. Controlled clinical trials are needed to better support routine use of IVIg in the treatment of these disorders. Annual vaccination against influenza is recommended for individuals 6 months of age and older.[17] A history of EM, SJS, or TEN after influenza virus infection is not a specified precaution or contraindication, but patients with a similar history should be monitored closely in the postvaccination period. The lack of recurrence of SJS after influenza vaccination in our case may be of interest to providers facing a similar clinical dilemma in the future.

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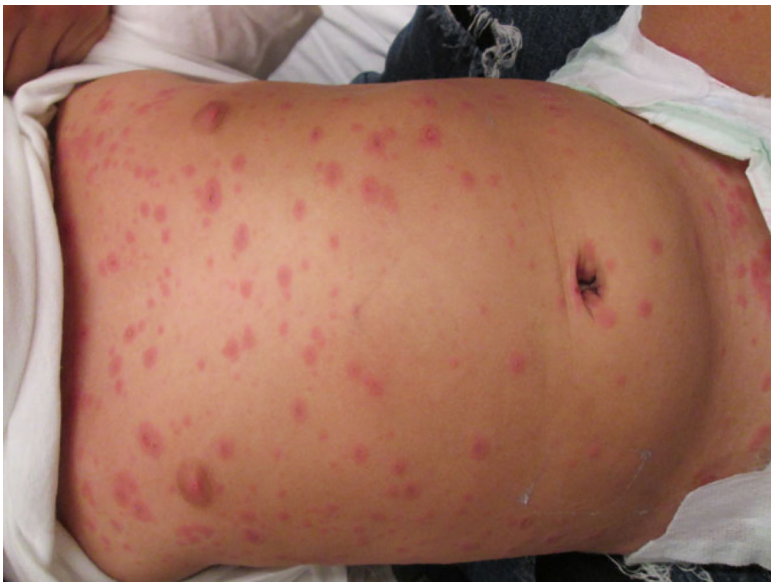

FIGURE 1.
Day of presentation: many circular pink edematous papules and small plaques with dusky violaceous centers

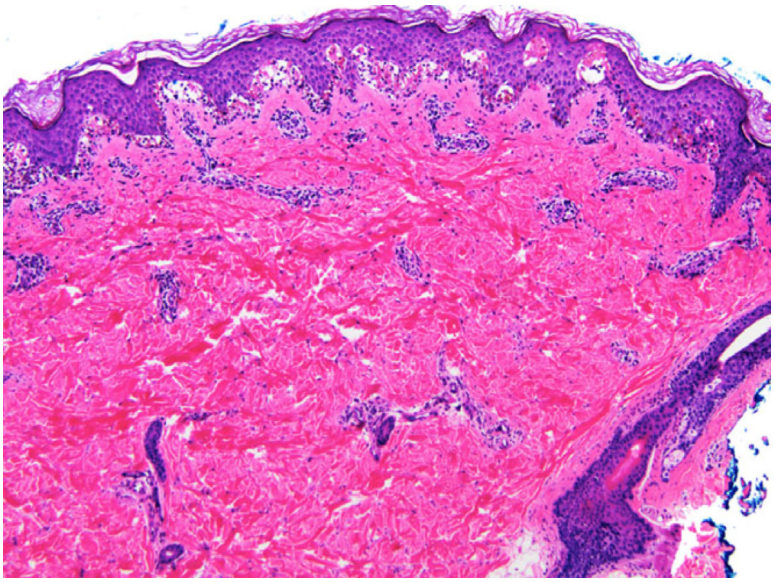

FIGURE 2.

Skin biopsy pathology revealed necrotic keratinocytes within the epidermis and an interface dermatitis consistent with the erythema multiforme/Stevens–Johnson syndrome/toxic epidermal necrosis spectrum of inflammatory dermatoses

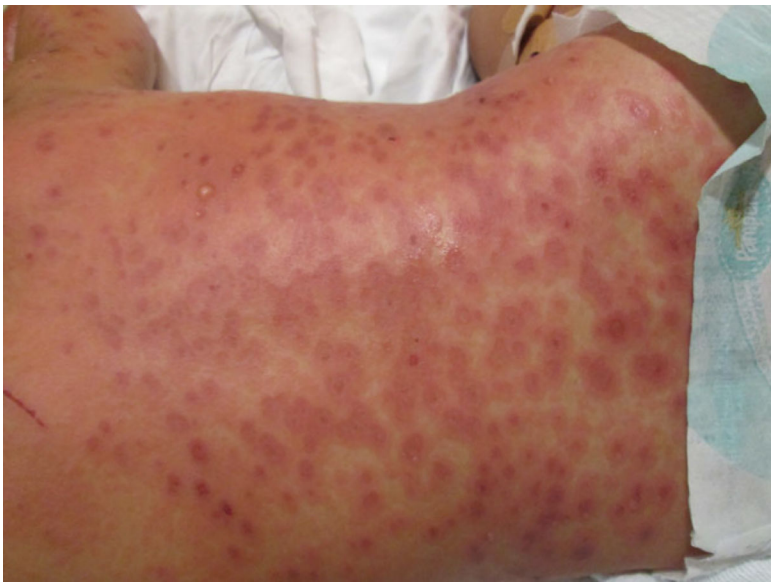

FIGURE 3.
Day 2 of hospital course: rapidly progressing rash with more than 10% skin fragility and denudation