Vaccine-induced toxic epidermal necrolysis: A case and systematic review

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Abstract

Background: Erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are cutaneous hypersensitivity reactions that develop in response to specific triggers such as medications and certain infections. Vaccines, which undergo rigorous safety testing prior to use in humans, are a rare cause of SJS/TEN and little is known about the frequency of such events and corresponding pathogenesis.

Objective: Herein, we discuss a case of suspected TEN in a 19-year-old woman who received the meningococcal B vaccine (the first report of such an association) and conduct a systematic review of the associated literature. We also discuss management of this patient with a single dose of etanercept.

Methods: Relevant literature was searched using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method.

Results: A total of 29 articles reporting EM, SJS, or TEN following vaccination were included from >5 countries. Of the 29, 22 articles reported EM, 6/29 reported SJS, and 4/29 reported TEN (3 articles reported cases of both EM and SJS/TEN).

Conclusions: We suggest consideration of vaccines as an etiology for cases of SJS or TEN that begin with an EM-like presentation, and provide further evidence for the use of etanercept as a viable treatment for TEN.

Keywords: Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, vaccines

Introduction

Erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) are all cutaneous hypersensitivity reactions to specific antigens. EM is further divided into major and minor subtypes, depending on whether or not there is mucosal involvement. SJS and TEN were once classified as distinct entities, but are now widely accepted as having the similar etiologies and pathogenesis; they differ only in severity as measured by percent body surface involvement (BSA), [1]. EM major, owing to the presence of mucosal erosions and similar histopathologic features, partially overlaps with SJS/TEN, but is generally regarded as a separate disorder, with its own etiology and unique target lesions on clinical examination [1, 2]. The identification of EM is crucial, however, as re-exposure to the offending antigens is thought to potentially allow for progression to more severe hypersensitivity reactions such as SJS or TEN [3, 4].

The most common inciting agents of SJS/TEN are medications including sulfonamides, certain antibiotics, anticonvulsants, non-steroidal anti-inflammatory drugs, and allopurinol, whereas EM tends to occur in response to infectious agents such as herpes simplex virus (HSV-1 and 2) or *Mycoplasma pneumonia* [5]. Vaccination has infrequently been linked to EM and even more infrequently to SJS and TEN [6]. Since the early 1900s, the number of cases of vaccination-induced EM appear to be in the

hundreds to low thousands in total [6-9]. Vaccination-induced SJS/TEN is much more rare, occurring in the published literature less than twenty times [6, 8, 10]. Herein, we report a case of suspected TEN following administration of the meningococcal vaccine (Trumenba) and present a review of the current literature surrounding vaccination-induced EM, SJS, and TEN.

Case Synopsis: A 19-year-old woman with no significant past medical history presented to dermatology clinic for evaluation of a 5-day history of a bullous rash and painful oral lesions. The rash started on her left upper arm 8 days after receiving a vaccine for meningococcus B (Trumenba) in her left deltoid, before spreading to her face, torso, legs, and neck. The patient denied fevers, malaise, or recent preceding illnesses. She was in the final days of completing a 3-week course of omeprazole for gastritis, but otherwise denied intake of any other medications, herbs, or supplements. On initial examination by the dermatology consultant (day 13 post-vaccination), the patient had evidence of tense bullae and violaceous targetoid plaques on her face, neck, trunk, and bilateral upper and lower extremities; she also exhibited erosions involving the mucosal lips. At that time, erythema multiforme major was favored over SJS or TEN given the targetoid nature of the majority of her lesions. The patient was started on empiric valacyclovir, doxycycline, and oral prednisone. A shave biopsy was performed on the left upper arm and showed marked interface dermatitis with numerous scattered necrotic keratinocytes and a superficial perivascular lymphocyte-predominant inflammatory infiltrate (**Figure 1**). IgM and PCR for HSV-1 and HSV-2 as well as IgM for *Mycoplasma pneumoniae* were negative.

Two days after outpatient evaluation the patient was admitted to the hospital owing to progression of the rash. The patient now had nearly 80% body surface area (BSA) involvement with dull erythematous targetoid macules, some with overlying intact annular bullae; she had epidermal detachment of 30% of her BSA (**Figure 2**). The patient also had superficial erosions and crusting noted on her lips, vaginal mucosa, and perianal area. Her corresponding SCORTEN score was 1, with an associated mortality risk of 3.2% (SCORTEN criteria = age>40, associated malignancy, heart rate>120, serum BUN>28 mg/dL, detached BSA>10%, serum bicarbonate<20 mEq/L, serum glucose>252 mg/dL). Infectious studies for HSV and *Mycoplasma* were repeated upon admission and again were negative. Chest X-ray did not reveal any abnormalities. Over the next two days, the patient developed conjunctival injection and the eruption became more confluent and dusky; desquamation was observed. Owing to concern for possible toxic epidermal necrolysis, a one-time dose of etanercept 50mg/mL was administered to the left upper arm. Within one day the rash had stabilized and was less symptomatic. By three days there was evidence of re-epithelialization. The patient was discharged 7 days after receiving etanercept.

Methods

In conducting a literature review examining cases of EM, SJS, and TEN after vaccination, we followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA), [11]. Articles were identified by searching PubMed and Google Scholar; the search terms are listed in **Table 1**. Articles were screened for eligibility. Inclusion criteria were broad; case reports, clinical trials, post-marketing surveillance studies, and systematic reviews were all included. Case reports, even if lacking important data such as patient age, sex, time to onset, and duration, were included to keep this review broad and obtain an overall estimate of the number of reported cases in the literature.

Results

The results from our literature search are shown in **Table 2**. To summarize, 29 articles reporting EM, SJS, or TEN following vaccination were included from >5 countries; 23 of these were case reports. 3 post-marketing surveillance studies, along with 3 United States national reporting agency reviews: the US Food and Drug Administration (FDA), the Vaccine Adverse Events Reporting System (VAERS), and the National Communicable Disease Center. Of the 29 articles included in this review, 5 were related to hepatitis B vaccination, 4 to measles-mumps-rubella (MMR), 4 to smallpox, 3 to varicella, 2 to human papillomavirus (HPV), 2 to diphtheria-pertussis-tetanus (DPT), 1 to meningococcus B, 1 to polio, 1 to influenza, and 1 to *Hemophilus influenza* type B (HiB). Combinations of vaccines were involved in three reports (i.e. oral

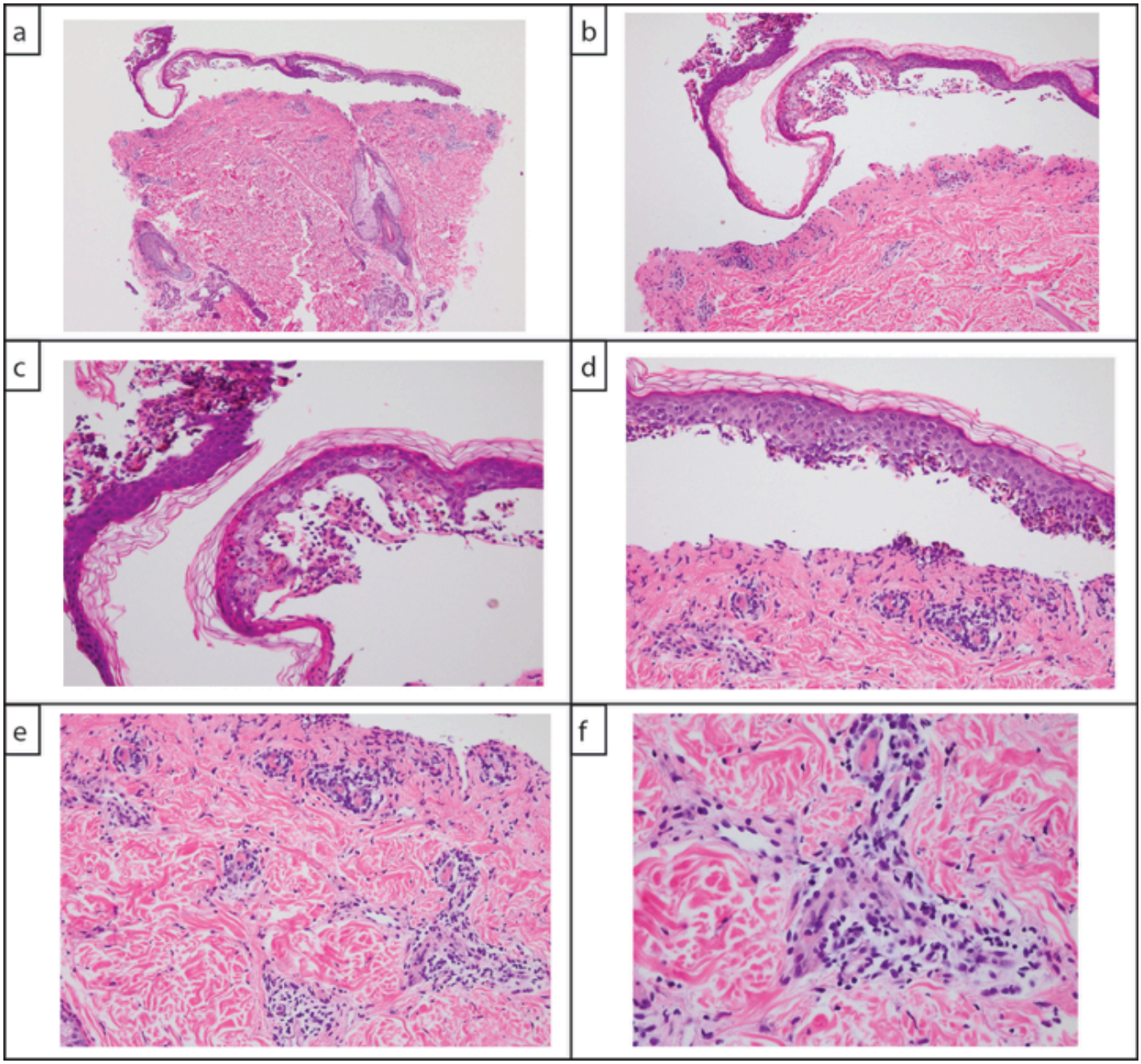

Figure 1. *Histopathology of lesions (shave biopsy, left upper arm). A) Epidermal detachment, superficial perivascular inflammation, H&E, 4%; B) Basket weave orthokeratosis, interface dermatitis, epidermal detachment, H&E, 10%; C) Interface dermatitis; necrotic keratinocytes, H&E, 20%; D) Interface dermatitis with subepidermal clefting and necrotic keratinocytes, H&E, 20%; E) Superficial perivascular lymphocyte-predominant inflammatory infiltrate; no eosinophils, H&E, 20%. (F) Perivascular lymphocyte-predominant inflammatory infiltrate, H&E, 40%.*

polio + DPT + Hep B, BCG, and pneumococcal), two reports involved non-standard vaccines (H1N1 and hantavirus), and one report did not specify which vaccines were used. Of the 29 articles, 22 reported EM, 6/29 reported SJS, and 4/29 reported TEN (three articles reported cases of both EM and SJS/TEN).

Case Discussion

Our patient presented with dusky erythema and violaceous, edematous targetoid lesions followed by desquamation and late re-epithelialization after meningococcus B vaccination. Early clinical presentation with target-like lesions and mucosal involvement suggested a diagnosis of EM major; however, later clinical features supported a diagnosis of TEN. In such cases, differentiating between EM major, SJS, and TEN is difficult and careful attention to the morphology of lesions, pattern, percentage of involved skin (BSA), histology, and possible inciting agents are essential for proper diagnosis.

EM, SJS, and TEN are all triggered by a delayed-type hypersensitivity reaction to an offending antigen. Morphologically, the lesions of EM are well-defined,

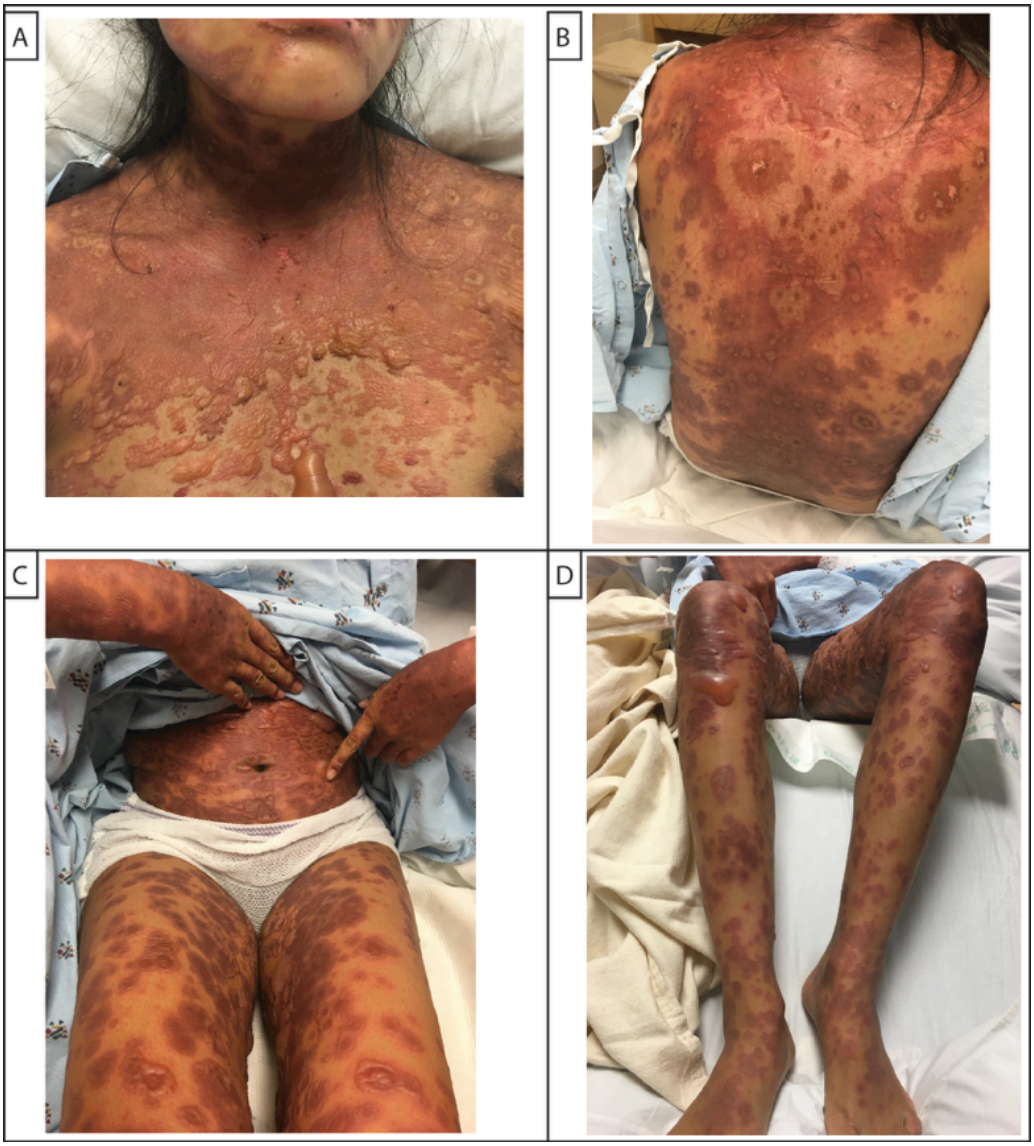

Figure 2. *Patient photographs, 2 weeks post-vaccination. (a) Patient with 80% body surface involvement (BSA) including mucosal regions (lips, vagina, perianal region). (b) Dull erythematous targetoid macules with overlying intact annular bullae. (c) Truncal involvement. (d) Lower extremity involvement.*

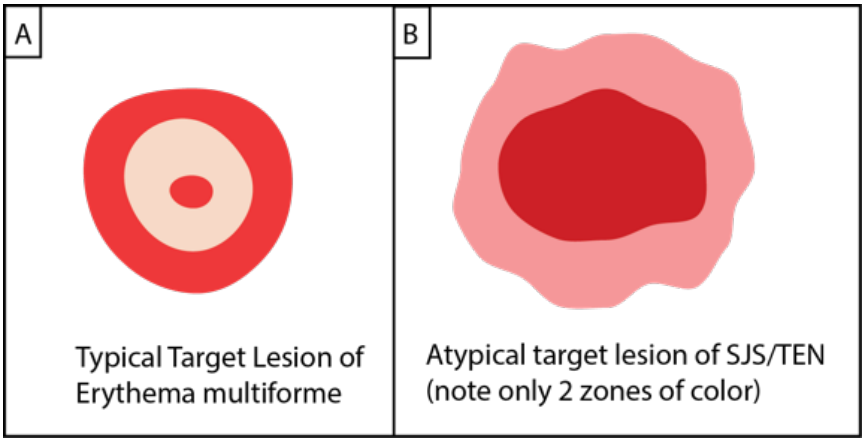

Figure 3. *Schematic representation of lesions in EM and SJS/TEN*

Table 1. *Search Terms.*

Database	Search Terms	Number of Results Reviewed
PubMed	Erythema multiforme after vaccination	31
	Stevens Johnson after vaccination	14
	Toxic epidermal necrolysis after vaccination	14
	Erythema multiforme and vaccine	99
Google Scholar	Erythema multiforme after vaccination	150
	Vaccination induced erythema multiforme	20
	Toxic epidermal necrolysis after vaccination	50

papular targets with central disks of erythema, raised edematous intermediate rings, and red outer rings (**Figure 3**), [12]. In SJS/TEN, the lesions are predominantly macular (often coalescing into larger, confluent patches), dusky red to purpuric in hue, and sometimes contain atypical targets with necrotic centers [2]. Clinically, EM occurs more frequently on the acral extremities and SJS/TEN more commonly on the trunk and mucosal surfaces. However, when there is widespread involvement this distinction becomes unclear. EM, SJS, and TEN share many histopathologic features including necrosis of keratinocytes, dermal lymphocyte infiltration, and detachment of the epidermis from the dermis. However, the presence of dermal lymphocytes is usually more pronounced in EM whereas the epidermal necrosis is more extensive in SJS/TEN [2]. Another important distinction is that exposure often triggers SJS or TEN, in particular sulfonamides, other antibiotics (β-lactams, tetracyclines, quinolones, etc.), anticonvulsants (phenytoin, phenobarbital, lamotrigine, and carbamazepine), anti-retrovirals (nevirapine, abacavir), non-steroidal anti-inflammatory drugs, and allopurinol [1]. In contrast, causality of EM is often attributed to infections with herpes simplex virus (HSV-1 and 2), or less commonly *Mycoplasma pneumonia*; *Mycoplasma* is somewhat unique in that it can also trigger a variant of SJS known as MIRM as well [1, 5, 13].

The immunologic theory behind vaccine-induced cutaneous hypersensitivity is relatively consistent in the literature. Most authors agree that antigens in the vaccine are expressed on the surface of keratinocytes, generating a CD8+ T lymphocyte immune response against epidermal cells (Type IV hypersensitivity). This leads to apoptosis of keratinocytes and detachment at the dermal-epidermal junction [10, 14]. This process is not immediate, explaining the typical 3 to 5 day latency period observed in most of the case reports included in this review. The vaccine antigens are thought to be preferentially expressed in skin cells for unknown reasons, perhaps owing to individual genetic susceptibility as seen in allopurinol and carbamazepine-induced SJS/TEN in the Han Chinese population (those possessing HLA-B*5801 and B*1502 alleles), [1].

Determining the antigen responsible for our patient's adverse reaction is difficult, especially given the different components present in vaccines. Most preservatives and fixatives, such as aluminum, thimerosal, and formaldehyde, can cause mild Type IV hypersensitivity reactions at the site of injection but are not known to induce widespread necrosis [6, 15]. Several cases from the literature do present compelling evidence that microbial-specific proteins from the vaccines drive hypersensitivity. Karincaoglu et al. observed EM major in a 3-month-old boy given his first dose of diphtheria-pertussis-tetanus and oral polio vaccine [9]. The child was given his second dose of the same vaccines a few months later, except that cellular pertussis was switched to acellular pertussis the second time; no reaction developed. Thus, the cellular pertussis vaccine was considered to be the primary triggering agent [9]. In the cases reported by Wakeel, the hepatitis B vaccine (Engerix B) caused EM in patients who had safely received other thimerosal-containing vaccines prior to Engerix B [16]. Since Engerix B is a relatively pure suspension of hepatitis

Table 2. *Characteristics of Reported Cases of Vaccine-induced EM, SJS, and TEN.*

Year	Vaccine	# of cases	Age (years)	Sex (M, F, or unspecified)	EM, EM+,† SJS, or TEN	Mucos-al involve-ment (m,o)††	Systemic symp-toms (+/-)	Time to onset (days)	Duration (days)	Treatment	Potential confounders (medications, illnesses)	Citation	Report type
1905	Smallpox	1	23	F	EM	-	+	3	17	-	-	[7]	Case report
1965	Smallpox	1	0 (8mo)	u	EM	-	-	25	5-15	IVIG and oral steroids	-	[26]	Case report
1968	Smallpox	107	-	u	EM	-	-	-	-	-	-	[27]	Survey of 10 US states
1974	Measles	1	1	F	TEN	m, o	-	6	11	IV steroids	None	[23]	Case report
1984	DPT	2	0 (2 mo), 1.5	M, M	EM	-	-	24h, 2h	-	-	None	[3]	Case report
1986	Hep B	8	24-61	u	EM	m in 1 pt	-	-	-	-	Unspecified medication	[28]	FDA report
1987	HiB	4	2+	M	EM	-	-	1-7	-	-	Cephalosporins (2 pts)	[29]	Post-mar-keting sur-veillance
1988	OPV, DT	1	0 (9 mo)	M	EM	-	-	0 (8 h)	7	Oral steroids, antihista-mines	None	[30]	Case report
1992	Hep B (En-gerix B)	1	27	F	EM	-	-	7	-	None	None	[16]	Case report
1994	Hep B (En-gerix-B)	1	11	F	EM	-	-	6	10	Oral steroids	None	[17]	Case report
1994	DT	1	-	u	EM	-	-	-	-	-	Not specified	[31"con-tainer-ti-tle":"JA-	Review of case reports
1997	Measles	1	0 (10mo)	M	SJS	m	+	1-2	28	Oral steroids	none	[24]	Case report
1999	MMR	1	13	F	TEN	m, o	+	7	20	antibiotics	None	[10]	Case report
1999	Polio	1	-	u	EM	-	-	-	-	-	-	[32]	Case report
2000	Hep B (HB VAX DNA 5")	1	11	M	EM	-	-	4	6	-	None	[33]	Case report
2000	Varicella (Varivax)	20	1-29	u	EM	-	-	1-40	-	-	-	[34]	Post-mar-keting sur-veillance

Year	Vaccine	# of cases	Age (years)	Sex (M, F, or unspecified)	EM, EM+,† SJS, or TEN	Mucos-al involve-ment (m,o)††	Systemic symp-toms (+/-)	Time to onset (days)	Duration (days)	Treatment	Potential confounders (medications, illnesses)	Citation	Report type
2000	Varicella (Varivax)	3	1-29	u	SJS	m	-	1-40	-	-	Sulfa drugs (1 pt)	[34]	Post-mar-keting sur-veillance
2000	Varicella	41	<9yrs	u	EM			7-35	-	-	-	[35]	Post-mar-keting sur-veillance
2000	Varicella	5	<9yrs	u	SJS	m	-	7-35	-	-	-	[35]	Post-mar-keting sur-veillance
2001	Not speci-fied	6	-	u	SJS/TEN	m	-	-	-	-	Not specified	[8]	National reporting system (VAERS)
2004	Smallpox, anthrax, tetanus	1	19	M	SJS	m	+	20	7	Abx and antivirals	none	[12]	Case report
2006	MMR	1	1.5	M	EM	-	-	8	21	Oral steroids	None	[36]	Case report
2006	Hep B (En-gerix B)	1	0 (1mo)	F	EM	o	-	1	4	-	None	[15]	Case report
2006 case	Menin-gococcal (Menactra)	1	20	M	EM	-	-	7-14		Antihist	None	[4]	Case report
2007	DPT and OPV	1		F	EM+	m	-	10	14-21	-	-	[9]	Case report
2008	OPV, DPT, hep B, influenza	1	0 (2 mo)		EM	-	-	14	-	-	None	[37]	Case report
2010	HPV (Gar-dasil)	1	19	F	EM	-	-	10	7	Topical steroids, antihist	None	[14]	Case report
2010	HPV	1	15	F	EM	-	-	7	2-3	oral steroids	None	[5]	Case report
2011	Influenza	1	65	F	SJS	m	-	1	7	Oral steroids	Flucloxacillin	[18]	Case report
2011	H1N1	1	49	F	EM	-	-	1	7	None	Other medica-tions, none new	[38]	Case report

Year	Vaccine	# of cases	Age (years)	Sex (M, F, or unspecified)	EM, EM+,† SJS, or TEN	Mucos-al involve-ment (m,o)††	Systemic symp-toms (+/-)	Time to onset (days)	Duration (days)	Treatment	Potential confounders (medications, illnesses)	Citation	Report type
2012	Varicella	1	12	M	SJS	o	+	14	12	IVIG, oral steroids	None	[25]	Case report
2012	Hantavirus (HFRS)	1	20	M	TEN	m, o	-	1	21	Oral steroids, abx	None	[22]	Case report

Vaccine Abbreviations: DPT = diphtheria, pertussis, and tetanus; HiB = Hemophilus influenza type B; OPV = oral polio vaccine; DT = diphtheria and tetanus; MMR = measles, mumps, and rubella; HPV = human papilloma virus; HFRS = hemorrhagic fever with renal syndrome

Other Abbreviations:

† EM+ *= erythema multiforme major*

†† Mucosal *involvement (m,o) à o = ocular, m = any mucosal surface besides ocular*

B surface antigen (HBSAg), containing only small amounts of thimerosal and yeast protein, the HBSAg was felt to be the most likely inciting agent of EM. This hypothesis is further supported by evidence of an EM-like rash in the prodromal period of active hepatitis B infection; a purified solution of HBSAg would be expected to cause a similar rash without the risk of lifelong infection [15-17].

We also hypothesize that a combination antigen could have resulted in TEN in our patient, since she was taking omeprazole at the same time she received the meningococcal vaccination. This combination antigen theory is classically used to explain the maculopapular eruption seen in patients who receive amoxicillin for EBV, presumably related to some offending EBV-amoxicillin combination molecule [18, 19]. The same reasoning was used in the case of a 65-year-old woman who developed SJS in response to the influenza vaccine administered concomitantly with flucloxacillin [18]. A theoretic "penicilloyl-influenza antigen" was hypothesized to be the inciting agent in this case. Omeprazole itself has been associated with TEN in the literature [20, 21proton pump inhibitors (PPI], although it is unlikely to have been the sole precipitant of TEN in our patient since her rash originated at the site of vaccination (upper left arm). Temporally, TEN development in our patient is more consistent with the timing of her vaccination (one week prior to symptom development) than her initiation of omeprazole (approximately one month prior to symptoms).

One of the aims of this review was to compare cases of vaccine-induced SJS/TEN and to see if, as in the case of our patient, an EM-like initial presentation was common. Interestingly, the initial morphologies of TEN following vaccination appear to fall into three general categories: macular, vesicular, and targetoid (EM-like). A macular rash, often dusky red in color, was by far the most common initial morphology of TEN post-vaccination, as would be expected for the majority of cases of TEN related to other etiologies [8, 22, 23]. Vesicles were the presenting morphology in 4 cases; notably, all occurred after administration of a measles-containing vaccine [10, 23-25]. EM-like targetoid lesions, similar to those seen in our patient, were the presenting morphology in 3 cases, occurring after smallpox, measles, and influenza vaccinations [8, 10, 12, 18]. In one particular case where a 19-year-old man developed SJS after receiving the smallpox vaccine, Chopra et al. described a disease course that initially resembled erythema multiforme but, over the course of several days, evolved into Stevens-Johnson syndrome [12]. Considering the similarities between these aforementioned cases and our patient's, it seems reasonable to hypothesize that TEN, especially in response to vaccines, may present initially as erythema multiforme in a subset of cases.

Treatment options for vaccine-induced TEN include plasmapheresis, IVIG, and perhaps most promisingly, TNF inhibitors such as etanercept. With our patient, one dose of etanercept (Enbrel) 50 mg/mL subcutaneously seemed to change the course of the disease; marked reduction in edema and cessation of progression of disease was seen in just 24 hours. Although our patient was initially treated with oral prednisone based on the EM-like appearance of her rash, we decided to switch to our hospital's TEN protocol when her lesions worsened after steroid therapy. Further studies evaluating the effectiveness of TNF inhibitors in the management of TEN are in progress.

Conclusion

Stevens Johnson syndrome and toxic epidermal necrolysis are rare complications of vaccination. We have described a case of TEN following meningococcal vaccine that initially presented with features of erythema multiforme major. This does not appear to be an isolated event, as other cases of vaccine-induced SJS/TEN are described in the literature with an initial EM-like presentation (although this is the first report of such a response following the meningococcal vaccine). Owing to the small number of reported cases, it is difficult to know if an EM-like presentation of TEN is a common variant of vaccination-induced TEN. However, if a patient has an initial EM-like presentation that progresses to TEN, consideration for vaccination as the cause of the eruption may be paramount.

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