

Pediatric Erythema Multiforme in the Emergency Department More Than “Just a Rash”

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Objectives: Erythema multiforme (EM) is characterized by symmetrical acrally distributed target lesions; however, other conditions can mimic the clinical features of EM. Although it is typically self-limiting, alternative diagnoses may be life-threatening and require immediate identification and treatment. This study aimed to investigate the clinical spectrum and accuracy of diagnosis of pediatric EM in the emergency department (ED).

Methods: A retrospective, descriptive study of all pediatric patients with an ED information system diagnosis of EM at 2 EDs in Southeast Queensland between January 2010 and July 2013. Cases were evaluated using previously established EM classification criteria.

Results: Seventy patients (34 males and 36 females) with a diagnosis of EM were identified. From 57 cases where a diagnosis could be established, 9 cases fulfilled the classification criteria for EM. No patients had mucosal involvement, and therefore, all 9 cases were classified as EM minor, with the majority (89%) attributed to viral infection. Of the 48 cases that did not fit the criteria, the most common condition misdiagnosed as EM was urticaria multiforme ($n = 20$).

Conclusions: In the ED setting, EM in children is frequently misdiagnosed. Greater awareness of diagnostic factors for EM may improve diagnostic accuracy. Teledermatology and incentives to include clinical pictures in the (electronic) medical record may be useful adjuncts for patients with suspected EM and other dermatological conditions.

Key Words: erythema multiforme, diagnosis, teledermatology, urticaria

(*Pediatr Emer Care* 2015;00: 00–00)

Erythema multiforme (EM) is an acute mucocutaneous condition and is an external manifestation of an immune-mediated reaction to triggers such as viral infections and medications.^{1–5} It is characterized by symmetrical acrally distributed target lesions, which appear as concentric rings of erythema and pale edema around a central macule or blister.^{6,7} However, target lesions are not pathognomonic for EM, and it has many clinical mimics.^{7–9} Conditions that present in a similar manner to EM include urticaria, fixed drug eruption, serum sickness-like reaction, and Kawasaki disease and are important to consider in the context of a pediatric patient presenting to the emergency department (ED) with a “rash.”^{10–16} Accurately diagnosing EM directs appropriate investigation and management, and although EM is typically self-limiting, alternative diagnoses may require immediate identification and treatment to prevent complications.

It is also essential to differentiate EM from life-threatening conditions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).^{17,18} Erythema multiforme has historically been linked with SJS and TEN as part of a continuous spectrum; however, this disease grouping was redefined in 1993 by

Bastuji-Garin et al⁶ in an effort to delineate clear definitions and diagnostic criteria for each condition. As a result of this proposed classification, EM has been separated from SJS and TEN, which are together considered to be variants in severity of the same disease.^{6,19} This classification has subsequently been confirmed by a number of studies, including the prospective case-control Severe Cutaneous Adverse Reactions (SCAR) study.²⁰ The majority of EM studies have involved an adult in-patient population, and previous research in a pediatric in-patient population suggests that EM is often misdiagnosed.²¹

Therefore, this study aimed to describe the diagnosis and management of pediatric EM in ED. We aimed to (1) classify pediatric EM according to the diagnostic criteria of Bastuji-Garin et al,⁶ (2) review the appropriateness of diagnosis and propose possible alternative diagnoses, (3) review the adequacy of clinical documentation, and (4) describe the assessment and management of pediatric EM in the ED.

METHODS

Study Design

This was a retrospective, descriptive study using medical record review. The study was approved by the local health district's human research ethics committee.

Study Setting and Population

We selected pediatric patients with a diagnosis of EM from 2 EDs in Southeast Queensland. The first hospital has a tertiary ED, servicing a 570-bed major metropolitan teaching hospital. The second hospital has an urban ED, servicing a 270-bed general hospital. Attendance in 2012 was 67,000 and 55,000 respectively, of which between 20% and 25% were children younger than 15 years. The tertiary hospital had a 24-bed general pediatric ward.

The study population composed of children younger than 15 years with an ED information system (EDIS) diagnosis of *International Classification of Diseases, Tenth Revision, Clinical Modification* L51.9—erythema multiforme at Gold Coast Hospital and Robina Hospital between January 1, 2010, and July 1, 2013.

Data Collection

We retrospectively reviewed the medical records of all eligible patients. Paper medical records were reviewed for cases identified between January 1, 2010, and November 2011, and electronic medical records were used for the period between November 2011 and July 1, 2013. Seventy cases were identified, and diagnosis of EM was adjudicated using the criteria of Bastuji-Garin et al (Table 1).⁶ In addition to demographic information and clinical characteristics, data were collected on investigations, treatment, and disposition—including re-presentation, admission, and further in-patient management. Other variables relating to the ED presentation included the Australasian Triage Scale (ATS—scale from 1 to 5, with 1 being most urgent and 5 least urgent), presenting complaint, and the seniority and specialty of the doctor who made the diagnosis of EM. The index presentation of EM was taken as the presentation where EM was first

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TABLE 1. Classification Criteria for EM, SJS, and TEN Proposed by Bastuji-Garin et al⁶

Classification	
EM minor	
Epidermal detachment < 10% BSA	
Acrally distributed typical target lesions (<3-cm diameter, symmetrical round shape, well-defined border, and 3 concentric color zones) and/or raised atypical target lesions (<3-cm diameter, round, only 2 concentric color zones, and/or poorly defined border)	
No mucosal involvement	
EM major	
As for EM minor, plus involvement of ≥1 mucosal surfaces (oral, ocular, or genital lesions)	
SJS	
Epidermal detachment < 10% BSA	
Flat atypical target lesions (round, nonpalpable lesions reminiscent of EM but with only 2 concentric color zones and/or a poorly defined border) or widespread macules	
SJS/TEN overlap:	
Epidermal detachment between 10% and 30% BSA	
Flat atypical target lesions or widespread macules	
TEN	
Epidermal detachment > 30% BSA	
Flat atypical target lesions or widespread macules	

diagnosed, and data were obtained from this presentation only. Information on patients who presented with a rash within 72 hours preceding the index presentation of EM was obtained, as well as re-presentation to ED within 72 hours.

Classification

Cases were categorized as “definite” EM minor or EM major when all of the criteria were well documented or visualized by photographs. Cases were considered as “likely” EM when “target lesions” or “typical target lesions” were described by an ED or pediatric registrar or consultant in conjunction with an EM diagnosis and acral localization with less than 10% body surface area (BSA)

epidermal detachment. The “likely” category accounted for the inclusion of cases that appeared to fit the criteria but did not have all aspects of the detailed lesion morphology documented. Erythema multiforme was considered “possible” when such target lesions or typical target lesions were documented but were asymmetrical or not localized to acral surfaces. “Unlikely” EM incorporated cases that either had no target lesions or had another lesion morphology pattern that supported a more likely alternative diagnosis. Information on rash morphology and characteristics were collected to determine possible alternative diagnoses, with criteria for a number of differential diagnoses included on the data collection sheet. Cases were considered to contain insufficient information when lesion morphology could not be determined from the ED documentation.

Causative Factors

Information was collected to determine possible herpes simplex virus (HSV) or mycoplasma pneumoniae (MP) infection. Herpes etiology was suspected for cases with documented herpes infection within 3 weeks before EM onset or history of recurrent herpes. *Mycoplasma pneumoniae* was attributed to cases with mycoplasma isolation on flocked swab samples or serology and suspected in the event of recent febrile pneumonia without a known causative organism. Information was collected on medication use in the week before EM onset, history of allergies or adverse drug reactions, and history of serum sickness-like reaction. Antecedent immunization was also recorded, as well as any illness or prodrome preceding EM symptom onset by 1 week or less.

RESULTS

Seventy patients with an EDIS diagnosis of EM were identified during the study period. There were 34 males and 36 females, ranging in age from 2 months to 12 years (mean age, 40 months). Four cases were excluded owing to a lack of documentation—2 cases did not have any clinical notes recorded in the patient's electronic medical record, and the paper-based medical records of 2 other patients were unable to be obtained. Nine cases had insufficient documentation to support either a diagnosis of EM or any other diagnosis. Of the 57 cases where a diagnosis could be established, 9 fulfilled the criteria proposed by Bastuji-Garin et al⁶ (Table 2).

TABLE 2. Patients With EM

Number	Age	Sex	ATS	Duration of EM Pre-ED, h	Preceding Symptoms	Preceding Illness	Preceding Medication Use Within 1 wk	Suspected Etiology
1	2 y	M	3	48	Fever, cough, coryza	URTI	—	Viral infection
2	21 mo	F	2	20	—	OM	Amoxicillin	Infection or drug related
3	16 mo	F	2	24	Malaise, diarrhea	OM	Amoxicillin	Infection or drug related
4	2 y	F	4	120	Fever, coryza, diarrhea, vomiting	URTI	—	Viral infection
5	2 mo	M	2	48	Immunization*	—	—	Immunization*
6	9 mo	F	3	72	Fever, diarrhea, vomiting	Likely viral illness	—	Viral infection
7	12 y	F	3	48	Fever, coryza, malaise, headache, myalgia	Likely viral illness	—	Viral infection
8	2 y	M	4	8	Coryza	OM	Unspecified antibiotics for OM	Infection or drug related
9	4 y	M	2	24	Cough	URTI	—	Viral infection

*Immunization against DTP, poliomyelitis, HiB, hepatitis B, pneumococcal, and rotavirus.

Em dashes indicate none.

Erythema Multiforme

Nine patients with an ED diagnosis of EM fit the classification criteria—4 males and 5 females with a median age of 24 months (range, 2 months to 12 years). One patient was brought in by ambulance, and 4 patients were assigned an ATS score of 2. There were no patients with mucosal involvement, and therefore, all 9 patients were classified as EM minor according to the criteria.

Erythema multiforme etiology was attributed to an upper respiratory tract infection (URTI) in 3 children, otitis media (OM) in 3 children, and nonspecific viral illness in 2 children. One case in a 2-month-old infant was attributed to preceding immunization. He received diphtheria-tetanus-pertussis (DTP), poliomyelitis, *Haemophilus influenzae* type B (HiB), hepatitis B, pneumococcal, and rotavirus as per the Australian immunization schedule.

The most frequent systemic symptoms were fever (4/9), cough (4/9), diarrhea (3/9), and malaise (2/9). None of the patients had any symptoms or positive laboratory test results indicative of HSV or MP infection. Only 1 patient had blood samples taken, and all values were within the reference range. Treatment in the ED was primarily supportive. Three patients received paracetamol, and 1 patient received an antihistamine (cetirizine). No patients received steroids.

Eight patients were discharged home from ED with advice on the anticipated self-limiting course of EM and appropriate supportive care. One patient was admitted to the ward and discharged the next day. Of the 8 patients who were discharged from ED, 3 re-presented within 72 hours. One of the patients who re-presented to ED on the evening of the index EM presentation was admitted to the ward overnight and then discharged the next day. No complications or sequelae were subsequently documented for any patient, and no cases were recurrent.

Differential Diagnosis

Of the 48 cases that did not fit the criteria for a definite or likely diagnosis of EM, 20 children had a clinical picture consistent with urticaria multiforme, and an additional 10 had urticaria. Fifteen children had a preceding viral illness and clinical signs indicating a viral exanthem rather than EM. One case each of serum sickness-like reaction, Henoch-Schönlein purpura (HSP), and varicella (chicken pox) was noted. Serum sickness-like reaction was noted in a 16-month-old girl who was treated with cefaclor for an ear infection 1 week before cutaneous symptom onset. One case of likely HSP was supported by lower limb purpura, symmetrical polyarthralgia, abdominal pain, and proteinuria. Henoch-Schönlein purpura was originally diagnosed the preceding day in the ED, and this patient received a diagnosis of EM after re-presenting with evolving purpuric lesions demonstrating central clearing.

DISCUSSION

In this study of pediatric EM in the ED setting, more than two thirds of children were misdiagnosed. Nine patients were confirmed as EM minor according to the proposed classification criteria, with the majority (89%) attributed to viral infection.⁶ In children and adults, infection is the most common underpinning of EM, with HSV and MP frequently implicated.^{3,20–22} This series did not identify HSV or MP for any cases of EM, which may reflect a lack of investigations and a limitation of retrospective analysis. Medications were also not identified as definitive etiological factors in this series, which is consistent with the findings in previous studies of pediatric EM.^{2,3,21} Although cefaclor has been linked with pediatric cutaneous adverse drug reactions including EM, medication use as a triggering factor has been more consistently documented for pediatric SJS and TEN.^{17,23} In contrast to pediatric EM, adult EM is often attributed to preceding

medication use.^{4,20} Erythema multiforme was associated with preceding immunization in one case in this study, a 2-month-old male infant. This patient developed cutaneous signs of EM 48 hours after receiving the recommended 2-month vaccinations as per the Australian National Immunisation Program Schedule. Immunization is recognized as a rare cause of EM and has been documented in children after DTP, hepatitis B, influenza, HiB, poliomyelitis, and measles-mumps-rubella vaccinations.^{24–27} A diverse etiology highlights the patient-specific immune response as the basis of cutaneous symptoms, and it is thought that alternating deposition of circulating toxin and blood flow in the epidermis gradually results in the typical target lesion.⁹

The hypersensitivity reaction leading to target lesions is not unique to EM, but consideration of clinical characteristics and morphology can help differentiate a number of possible diagnoses. The most common condition misdiagnosed as EM was urticaria multiforme in this series (20 of 48 misdiagnosed patients). Urticaria multiforme is a descriptive term for a morphologic appearance of acute urticaria, characterized by annular and polycyclic wheals with central clearing and ecchymotic centers, which are often mistaken for the true target lesions of EM.^{10,11,14,28,29} Compared with the fixed acrally distributed lesions of EM, urticaria multiforme involves evanescent lesions affecting the trunk, face, and extremities.¹¹ Lesions typically commence as small urticarial macules or papules, rapidly evolving to form variably sized annular and polymorphic wheals. Individual lesions fade within 24 hours, although the total duration of the rash may persist for more than a week.^{11,14} Pruritis, dermatographism, and facial/acral angioedema typical of urticaria may also be associated with urticaria multiforme, and it typically responds well to antihistamine treatment.^{11,14} In this study, no patients with urticaria multiforme had acrally localized lesions. In contrast to the EM group, which displayed target lesions but no urticaria or wheals, 85% of the urticaria multiforme group had urticarial plaques and 40% had annular/polycyclic wheals with central clearing. Three quarters of patients with urticaria multiforme had the term *target lesions* documented but were classified as urticaria multiforme owing to other factors including lesion distribution and other lesion morphology. Ten patients had urticaria, exhibiting a similar clinical picture to urticaria multiforme but without the annular and polycyclic wheal morphology (Figs. 1 and 2).³⁰

Serum sickness-like reaction is commonly mistaken for both EM and urticaria multiforme owing to the presence of polycyclic urticarial wheals with central clearing.^{11,23} The reaction most commonly occurs consequent to medication use, particularly the antibiotic cefaclor, and the presence of arthralgias and fever favor the diagnosis.²³ In contrast to true serum sickness, which is



FIGURE 1. Urticaria multiforme, originally misdiagnosed as erythema multiforme, affecting the arms and trunk. In this case, evanescent annular and polycyclic wheals with ecchymotic centers started on the face and were not localized to acral surfaces.



FIGURE 2. Urticaria multiforme that was originally misdiagnosed as erythema multiforme. In this case, lesions started on the trunk. A, Polycyclic wheals on the proximal thigh. B, Wheals on the lateral trunk, sparing the back. C, Urticaria multiforme affecting the anterior trunk and legs.

mediated by immune complex deposition and complement activation in response to animal serum or protein containing medications, serum sickness-like reaction occurs after nonprotein drug initiation. Serum sickness-like reaction displays a similar polycyclic urticarial rash but without the immune complexes and systemic manifestations of true serum sickness such as vasculitis and nephritis.¹¹ Other possible differential diagnoses in children that seem similar to EM include Rowell syndrome (lupus erythematosus with associated EM-like target lesions and a positive speckled antinuclear antibody pattern), erythema marginatum, and hemorrhagic edema of infancy.^{7,31–33}

In keeping with the varied cutaneous manifestations of immune-mediated hypersensitivity reactions, it is possible that a number of different cutaneous patterns of disease may evolve within the disease course of a single patient. Sequential erythema nodosum, EM, and HSP have been reported in a child with MP infection, and another recent case described EM as the first sign before progression to incomplete Kawasaki disease.^{16,34}

Although pediatric dermatological presentations to the ED are often not urgent, the diversity of rashes and spectrum of severity can lead to confusion in both diagnosis and treatment.^{35,36} A potential knowledge gap has been identified in the ED, where a lack of experience and a focus on more acute conditions may contribute to decreased accuracy in rash diagnosis.³⁷ A study investigating diagnostic agreement between pediatricians in the ED and dermatologists found that 42% of all skin conditions were misdiagnosed and that dermatologists modified the treatment in 30% of cases.³⁵ In this present study based in Southeast Queensland, Australia, no cases were consulted on or reviewed by a dermatologist. This lack of specialty input would only be amplified in more peripheral or rural hospital ED settings. Teledermatology

has been proposed as a viable option for integrating the multidisciplinary management of patients with skin complaints in the ED, and a recent pilot study in an Australian ED setting enabled rapid diagnostic and treatment advice.³⁷ Although it is likely that multiple alternative diagnoses were entertained, the misdiagnosis of EM in the present study could possibly represent an overall lack of confidence in rash diagnosis in the ED. Although many rashes such as EM have a self-limiting course, some dermatological presentations may be life threatening and pose a challenge for the direction of appropriate management. The potentially life-threatening conditions of SJS and TEN are differentiated from EM by lesion morphology and extent of epidermal detachment (Table 1) and are also more strongly associated with drug reactions.^{17,18} Identification and cessation of the causative drug are critical to disease resolution, and supportive treatment is essential owing to deficits in cutaneous barrier function. Potential complications are similar to those seen in burns, depending on the extent of skin loss, and include electrolyte imbalances, bacterial infection, and sepsis.^{17,18} Within the EM spectrum, the mucous membrane involvement of EM major may extend further than obvious oral mucosa, including multiple occult sites such as the respiratory and gastrointestinal tracts, and is consequently more than “just a rash.”

Teledermatology may therefore be a useful adjunct in the ED, particularly for dermatological emergencies.³⁷ Teledermatology emphasizes the visual nature of skin conditions, and the retrospective classification of EM on clinical grounds proved difficult when documentation was inadequate to convey lesion morphology and distribution. In 9 cases, documentation was insufficient to determine lesion morphology not only for EM but also for any other condition. One case that had insufficient documentation for the index presentation of EM increased to “likely” EM upon re-presentation, where both typical and atypical targets were well described in an acral distribution. It is also possible that a number of cases may have been EM but with insufficient description to fit the criteria when reviewed retrospectively. In addition to improving clinical documentation, incentives to add photographs to the (electronic) medical record will improve the clinical description of skin lesions for current and future presentations. For pediatric patients with EM, the majority of children are discharged from hospital with supportive care advice owing to the self-limiting nature of the illness. In this study, 3 (38%) of 8 patients discharged with EM minor re-presented within 72 hours, highlighting the importance of improving health literacy and providing structured discharge instructions to parents.

LIMITATIONS

The retrospective nature of this study is one limitation, as clinical records and documentation may have been incomplete, highlighted by the fact that documentation was insufficient in 9 cases to establish a diagnosis. It is also possible that descriptions in the medical records were not morphologically accurate. Another limitation was the use of a single adjudicator; however, a data collection sheet specifying mostly binary variables aimed to limit this potential bias. Data on a wide range of specific history and clinical presentation items were collected, and a uniform set of existing diagnostic criteria and criteria for alternative diagnoses were used. Furthermore, although this study included patients from both a tertiary and urban ED, the findings may not be directly generalizable outside Southeast Queensland, Australia. Lastly, clinicians making a diagnosis of EM would be unlikely to enter a different diagnosis in EDIS, but we are unable to comment on the number of potentially missed patients with EM that were

attributed an alternative *International Classification of Diseases, Tenth Revision*, code.

CONCLUSION

Erythema multiforme is a relatively uncommon pediatric presentation to the ED but is an important differential diagnosis for a number of other conditions that present with targetoid lesions. In this study, a substantial proportion of patients with suspected EM were misdiagnosed in the ED. Greater awareness of diagnostic factors for EM may improve diagnostic accuracy of “rash” in the ED, with resultant appropriate advice and treatment options. Teledermatology and incentives to include clinical pictures in the (electronic) medical record may be useful adjuncts for patients with suspected EM and other dermatological conditions.

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