Erythema multiforme in children

Ran D. Goldman MD FRCPC

Abstract

Question Children who present with rashes with "target" lesions are frequently diagnosed with erythema multiforme (EM). This is a self-limiting condition in most children; how should primary care providers differentiate between this and urticaria or Stevens-Johnson syndrome, and what is the recommended course of treatment?

Answer While EM is common in children, urticaria is also very common and tends to be more "waxing and waning" compared with EM's fixed lesions. Stevens-Johnson syndrome and toxic epidermal necrolysis are more severe and distinct conditions; they have much more substantial mucous membrane involvement and contain widespread erythematous or purpuric macules with blisters. Since EM is a self-limiting condition, treatment of EM in children is generally supportive, and rarely do children need hospital admission for rehydration. In more severe cases involving mucous membranes or substantial pain, some patients will benefit from topical steroids or antihistamines. When children present with signs of herpes infection, antiviral treatment (acyclovir) may be of benefit. Systemic steroids should be reserved for the most challenging cases.

L'érythème polymorphe chez l'enfant

Résumé

Question Un diagnostic d'érythème polymorphe (EP) est souvent posé chez les enfants qui présentent une éruption cutanée avec des lésions « en cibles ». Il s'agit d'un problème spontanément résolutif chez la plupart des enfants. Comment les professionnels de la santé peuvent-ils faire la distinction entre un EP et l'urticaire ou le syndrome de Stevens-Johnson, et quel est le traitement recommandé?

Réponse L'érythème polymorphe est commun chez les enfants, mais l'urticaire l'est tout autant et a tendance à être « en croissance et en décroissance » en comparaison des lésions fixes de l'EP. Le syndrome de Stevens-Johnson et la nécrolyse épidermique toxique sont des problèmes plus graves et distincts; ils comportent une atteinte des membranes muqueuses bien plus considérable, ainsi que des macules érythémateuses ou purpuriques avec des cloques. Puisque l'EP est un problème qui se résorbe de lui-même, le traitement chez l'enfant consiste en des soins de soutien; il est rare qu'une hospitalisation soit nécessaire pour une réhydratation. Dans les cas plus sévères impliquant les membranes muqueuses ou une douleur considérable, certains patients pourraient bénéficier de stéroïdes topiques ou d'antihistaminiques. Lorsqu'un enfant présente des signes d'infection au virus de l'herpès, un traitement antiviral (acyclovir) pourrait être bénéfique. Les stéroïdes systémiques devraient être réservés aux cas les plus problématiques.

Erythema multiforme (EM) is an immune-mediated, mucocutaneous condition frequently characterized by "target" lesions[1] mostly involving the skin but also, at times, involving the mucous membranes (oral, ocular, or genital mucosa). These are annular macules, which later become papules, not infrequently coalescing to plaques.

Early in EM's course the lesions are isolated, but over a few days they may become confluent and the "target" nature of these lesions may become more difficult to identify. In children, lesions are most frequently located on the extremities with no specific distribution between the arms and legs. Unlike other pediatric conditions with a rash, there is no anticipated progression, and distribution may be just a few new lesions a day or many developing at a rapid pace.

Findings of histologic studies suggest inflammatory perivascular areas and interface infiltration, hyperkeratosis, granulation tissue, mucinosis, and acanthosis.[2] The causes of EM are mostly viral (80% to 90%) or drug related.[1] Herpes simplex virus type 1 is the most commonly identified cause; other implicated viruses include herpes simplex virus type 2, cytomegalovirus, Epstein-Barr virus (infectious mononucleosis), influenza, and most recently COVID-19 (mostly in patients younger than 30 years or older than 55 years).[3] Vulvovaginal candidiasis and mycoplasma pneumonia are also associated with EM.

Medications that may trigger the appearance of EM include antibiotics (eg, erythromycin, nitrofurantoin, penicillins, sulfonamides, tetracyclines), antiepileptic medications, nonsteroidal anti-inflammatory drugs, and vaccines (which are the most common cause in young infants). Other conditions associated with EM are inflammatory bowel disease, hepatitis C, leukemia, lymphoma, and solid-organ cancer malignancy.

When encountering a child with possible EM, inquire about recent infections or symptoms that may represent such infections, as well as history of medications used. In most children the diagnosis can be made after history and examination, and no further testing is recommended.

For children with more severe cases, involving mucous membranes or with substantial pain, empiric therapy may be reasonable. Rarely, and in prolonged or undifferentiated cases, skin biopsy may be needed, but the decision is likely best made after consultation with a dermatologist.

Differential diagnosis

Urticaria is a frequent finding in children, and at times it is hard to differentiate from EM, especially early after presentation. History can help differentiate between these distinct conditions; EM involves fixed lesions for a few days, while urticaria (from allergic reaction or infection) will likely be transient (appear and disappear repeatedly) and will be self-limiting within a few days. However, at times the conditions are indistinguishable, and this has been coined *urticaria multiforme*.[4]

The most important differential diagnoses for EM that involve the mucous membranes are Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis. All 3 are immune-mediated epidermal conditions with variable clinical presentations; however, SJS and toxic epidermal necrolysis each have high mortality and lack an effective treatment.[5] While in the past these conditions were considered to be on a continuum, they are now recognized as having distinct features and diverse outcomes, resulting in the need for different management strategies. Erythema multiforme is mostly considered to be papular and generally has target-like lesions; SJS usually contains widespread erythematous or purpuric macules with blisters.[6]

Treatment

For children who present with EM, treatment is generally supportive, with observation. Some will benefit from topical steroids or antihistamines.[7] The use of systemic steroids among children has been a source of debate.[8] Since EM is a self-limiting condition in most children, systemic steroids should be reserved for the most severe cases—serving as an adjuvant therapy; aiming to suppress cytokine and chemokine response, as well as T cell function; and decreasing adhesion of inflammatory molecules to blood vessel endothelium.[9]

For children who present with signs of herpes infection, early after its onset primary care physicians should consider antiviral treatment (acyclovir), as it seems to reduce the severity and duration of EM eruptions in some children. One retrospective case series suggested that herpes-associated EM can be precipitated by sun exposure and may not respond to treatment with oral or topical acyclovir.[10] Prophylactic treatment with acyclovir can be considered, but evidence is limited.

When oral mucous membranes are involved or when children are systemically unwell, in pain, or experiencing considerable discomfort, admission to hospital for hydration should be considered.

Competing interests
None declared

Correspondence
Dr Ran D. Goldman; e-mail **rgoldman@cw.bc.ca**

References

1. Sokumbi O, Wetter DA. Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. *Int J Dermatol* 2012;51(8):889-902.
2. Khan P, Mudassar M, Baloch FA, Waqas M, Khan A. Spectrum of morphological changes in erythema multiforme. *J Med Sci* 2020;28(3):218-22.
3. Bennardo L, Nisticò SP, Dastoli S, Provenzano E, Napolitano M, Silvestri M, et al. Erythema multiforme and COVID-19: what do we know? *Medicina* (Kaunas) 2021;57(8):828.
4. Emer JJ, Bernardo SG, Kovalerchik O, Ahmad M. Urticaria multiforme. *J Clin Aesthet Dermatol* 2013;6(3):34-9.
5. Cheng L. Current pharmacogenetic perspective on Stevens-Johnson syndrome and toxic epidermal necrolysis. *Front Pharmacol* 2021;12:588063.
6. Auquier-Dunant A, Mockenhaupt M, Naldi L, Correia O, Schröder W, Roujeau JC; SCAR Study Group (Severe cutaneous adverse reactions). Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol* 2002;138(8):1019-24.
7. Riley M, Jenner R. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. Bet 2. Steroids in children with erythema multiforme. *Emerg Med J* 2008;25(9):594-5.
8. Chan M, Goldman RD. Erythema multiforme in children: the steroid debate. *Can Fam Physician* 2013;59:635-6.
9. Michaels B. The role of systemic corticosteroid therapy in erythema multiforme major and Stevens-Johnson syndrome: a review of past and current opinions. *J Clin Aesthet Dermatol* 2009;2(3):51-5.
10. Weston WL, Morelli JG. Herpes simplex virus–associated erythema multiforme in prepubertal children. *Arch Pediatr Adolesc Med* 1997;151(10):1014-6.

Can Fam Physician 2022;68:507-8. DOI: 10.46747/cfp.6807507