Recurrent erythema multiforme major in an 8-year-old patient with recurrence of herpetic gingivostomatitis and HLA-B*5801 haplotype: A causal or casual relationship?

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INTRODUCTION

Erythema multiforme (EM) is an immune-mediated reaction first described by von Hebra[1] in 1860, presenting typically as acrofacial target lesions. The rash may be confined to the skin (EM minor), or it may involve ocular, oral, or genital mucosa with systemic symptoms (EM major). In most cases, only 1 outbreak of EM occurs in a lifetime; however, very rarely, repeated episodes of EM may occur, known as *recurrent EM*.[2] Few cases of pediatric recurrent EM have been reported, with the etiology being identified in less than half of these cases.[3] We report a pediatric case of recurrent EM resistant to conventional treatments in which a peculiar human leukocyte antigen (HLA) haplotype has been identified.

Abbreviations used:

EM: erythema multiforme
HLA: human leukocyte antigen
HSV: herpes simplex virus
IVIG: intravenous immunoglobulins

CASE REPORT

An 8-year-old boy presented to the pediatric emergency room for the abrupt onset of erythematous patches with central vesicles localized to the upper and lower limbs, including the palmo-plantar regions. The lesions appeared a few days after the spontaneous resolution of a herpetic gingivostomatitis. The patient had no drug history and was otherwise healthy. His personal history included a previous EM minor episode after herpetic stomatitis, which occurred 1 year prior. He was discharged with the diagnosis of recurrent EM minor and treated with acyclovir therapy. Three days after discharge, the patient came back to the emergency room because of the onset of extensive de-epithelialization of the oral mucosa, tongue, and lips (Fig 1, *A*); ocular hyperemia associated with photophobia; genital erosions; and symmetrical blisters and ulcerations involving the upper and lower limbs (Fig 1 *B* and *C*) and the trunk. He had also fever, malaise, and myalgia. Herpes simplex virus (HSV) 1 serology found a positivity of IgM and IgG; cytomegalovirus, parvovirus B19, and *Rickettsia* and *Mycoplasma pneumoniae* serology (both IgM and IgG) were negative.

Two skin biopsies performed on his left leg found epidermal spongiosis, keratinocytes apoptosis with blistering at the dermoepidermal junction, and poor dermal inflammatory infiltrate (Fig 2, *A* and *B*); direct immunofluorescence was negative. The clinical history, cutaneous lesions, serologic results and

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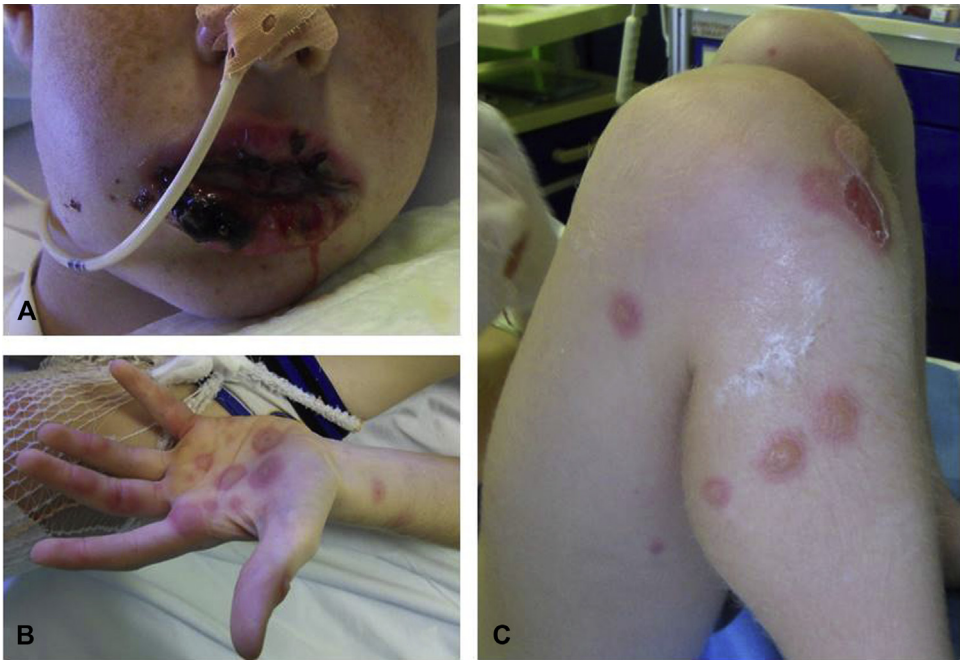

Fig 1. An 8-year-old boy presents with abrupt onset of extensive sero-heamatic crusts covering his lips, associated with de-epithelialization of the oral mucosa and tongue (**A**). Blisters and ulcerations with perilesional erythema are evident on the upper limbs including palmar regions (**B**) and lower limbs (**C**).

histopathologic findings suggested the diagnosis of HSV-related EM major.[4,5]

Systemic treatment with methylprednisolone at a dose of 1 mg/kg/d was started in association with acyclovir at a dose of 10 mg/kg/d. In the following days, a worsening with extension of de-epithelialization areas was observed. Intravenous immunoglobulin (IVIG) at a dose of 400 mg/kg/d for 5 days was started. A rapid improvement of signs and symptoms was observed, followed by complete resolution of mucocutaneous involvement within a week.

Because of the rapid disease progression with major extensive mucous membrane involvement, we performed HLA haplotype analysis to determine whether particular major histocompatibility complex alleles would predispose to this recurrent HSV-induced, severe EM. The presence of the HLA-B*5801 genotype was discovered. At a 3-month follow-up visit, the patient had maintained complete clinical resolution continuing to take acyclovir 400 mg/d to prevent herpetic recurrences.

DISCUSSION

EM is an acute inflammatory disease presenting with annular erythematous plaques or urticarial papules that may evolve in typical target lesions, mainly involving acral sites.[6] It occurs more frequently in young adults; however, a few pediatric cases have been reported in the literature.[2] Several etiologies have been associated with EM (eg, drugs, autoimmune disorders, malignancy, radiation); infectious processes are, however, the most common triggers, encompassing approximately 90% of cases. HSV is estimated to be involved in about 70% of cases of EM; *M pneumoniae* is also a prominent pathogen.[7,8]

In our patient, the close temporal relation between the onset of EM minor with a rapid worsening in EM major and its close relationship with recurrence of herpetic gingivostomatitis is highly suggestive for a causal role of HSV infection. Relapse of EM coinciding with HSV 1 or 2 infection relapses has been widely reported in the literature; the link between HSV and EM is probably caused by an autoimmune cross-reactivity mechanism, as a high number of peptides is shared between the HSV and human proteins.[9]

Prompt hydration, pain control, accurate skin care, and early identification and management of potential triggers are the mainstay of EM major treatment.[5] Although IVIG and systemic corticosteroids are the main therapy options, their effectiveness is still debated.[2,3] In our case, we observed a rapid improvement progress into a lasting resolution of the condition after the introduction of IVIG

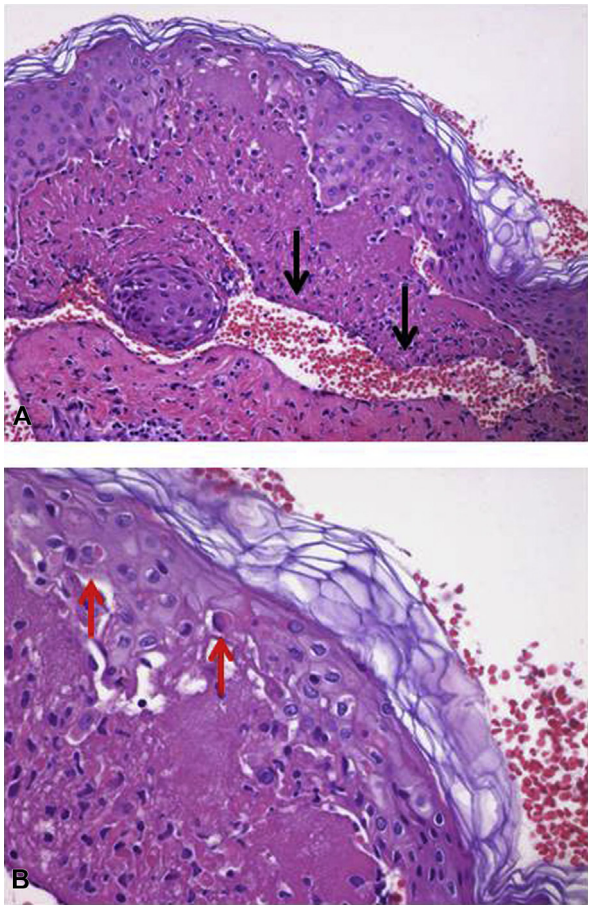

Fig 2. Biopsy performed from perilesional skin of left leg is characterized by blistering at the dermoepidermal junction (*black arrows*), epidermal spongiosis, and keratinocytes apoptosis (*red arrows*). (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×20; **B**, ×40.)

therapy. The efficacy of IVIGs depends essentially on their ability to interfere with ligand-induced keratinocytes apoptosis.[10]

Prognosis of EM major mainly depends on the extent of skin and mucosal involvement[2] and on a prompt treatment. Increasing evidence suggests a role of the immune system in the pathogenesis of EM reactions, but little was known about the predisposition to these reactions until recently.[11-13]

In our patient, because of the rapid disease progression with major involvement of mucous membranes, we performed HLA haplotype analysis to determine whether particular major histocompatibility complex alleles would predispose for this recurrent HSV-induced severe EM.

Malo et al[11] found that recurrent HSV-induced EM is strongly associated with the rare HLA allele DQB1*0402 in the disease form showing severe mucous membrane involvement. Recently, Olson et al[12] performed a retrospective chart review for cases of recurrent Stevens-Johnson syndrome in 9 children with mucous membrane—predominant phenotype, and HLA-B51 was found in 3 patients; HLA-B27 was found in 2 patients.

Furthermore, a strong association between some genetic variants of HLA regions and the onset of cutaneous hypersensitivity drug-related reactions was also found. Recently, some drugs have been identified as causing significant drug hypersensitivity reactions in patients who have the specific HLA alleles: abacavir and HLA-B*57:01, carbamazepine and HLA-B*15:02/A*31:01, and allopurinol and HLA-B*58:01.[13-15]

However, currently there is no information in the literature about the role of the HLA-B*5801 haplotype in the developing of EM/Stevens-Johnson syndrome triggered by viral infections. As it is known, immune response after HSV infection (in particular HSV1) can trigger numerous different autoimmune cross-reactions that depend mainly on the immunologic history and HLA-associated genetic background of the patient.[11,12,16] Therefore, we may speculate that HLA-B*5801 haplotypes observed in our patient may also be involved in the onset of HSV infection—related recurrent EM.

The question as to whether these HLA alleles are truly causative or acting as surrogate markers of predisposition, however, is still unanswered, and will require further investigations in larger patient cohorts.

REFERENCES

1. von Hebra F. *Atlas der Hautkrankheiten*. Vienna: Kaiserliche Akademie der Wissenchaften Wien; 1866.
2. Heinze A, Tollefson M, Holland KE, Chiu YE. Characteristics of pediatric recurrent erythema multiforme. *Pediatr Dermatol*. 2018;35(1):97-103.
3. Siedner-Weintraub Y, Gross I, David A, et al. Paediatric erythema multiforme: epidemiological, clinical and laboratory characteristics. *Acta Derm Venereol*. 2017;97(4):489-492.
4. Ferrandiz-Pulido C, Garcia-Patos V. A review of causes of Stevens-Johnson syndrome toxic epidermal necrolysis in children. *Arch Dis Child*. 2013;98(12):998-1003.
5. Ferrándiz-Pulido C, García-Fernández D, Domínguez-Sampedro P, García-Patos V. Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a review of the experience with paediatric patients in a university hospital. *J Eur Acad Dermatol Venereol*. 2011;25(10):1153-1159.
6. Olayemi S, Wetter DA. Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. *Int J Dermatol*. 2012;51:889-902.
7. Huff JC, Weston WL, Tonnesen MG. Erythema multiforme: a critical review of characteristics, diagnostic criteria, and causes. *J Am Acad Dermatol*. 1983;8:763-775.
8. Wetter DA, Davis MD. Recurrent erythema multiforme: clinical characteristics, etiologic associations, and treatment in a series of 48 patients at Mayo Clinic, 2000 to 2007. *J Am Acad Dermatol*. 2010;62(1):45-53.

9. Lucchese A. From HSV infection to erythema multiforme through autoimmune crossreactivity. *Autoimmun Rev*. 2018; 17(6):576-581.
10. Viard I, Wehrli P, Bullani R, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science*. 1998;282:490-493.
11. Malo A, Kämpgen E, Wank R. Recurrent herpes simplex virus-induced erythema multiforme: different HLA-DQB1 alleles associate with severe mucous membrane versus skin attacks. *Scand J Immunol*. 1998;47(5):408-411.
12. Olson D, Abbott J, Lin C, et al. Characterization of children with recurrent episodes of Stevens Johnson syndrome. *J Pediatric Infect Dis Soc*. 2017;6(3):e140-e143.
13. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T. Current perspectives on erythema multiforme. *Clin Rev Allergy Immunol*. 2018;54(1):177-184.
14. Amstutz U, Ross CJD, Castro-Pastrana LI, et al. HLA-A 31:01 and HLA-B 15:02 as a genetic markers for carbamazepine hypersensitivity in children. *Clin Pharmacol Ther*. 2013;94(1):142-149.
15. Lanjou C, Borot N, Sekula P, et al. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet Genom*. 2008; 18:99-107.
16. Chung WH, Hung SI. Recent advances in the genetics and immunology of Stevens-Johnsons syndrome and toxic epidermal necrolysis. *J Dermatol Sci*. 2012;66:190-196.