

Erythema Multiforme Following Live Attenuated Trivalent Measles-Mumps-Rubella Vaccine

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Sir,

Erythema multiforme (EM) is a fairly common skin reaction in children (1). It is often elicited by bacterial and viral infections (2). Only rarely is a vaccine the culprit agent. We wish to report such a case.

CASE REPORT

An 18-month-old boy underwent measles-mumps-rubella (MMR) vaccination under the usual schedule for routine childhood immunization in Italy. Approximately 8 days later he developed an itchy skin eruption, EM-like, consisting of targetoid lesions with erythematous-oedematous expanding borders, studded with tiny vesicles and pustules on an erythematous base, starting at the trunk and then rapidly involving the whole integument, including the face (with the presence of marked facial oedema). The patient had received no medications before vaccination or before the onset of his cutaneous eruption. Thereafter, the skin lesions gradually became confluent and polycyclic and within a few days were covered with tiny scales (Figs 1 and 2). Excoriations were also observed. There was no evidence of mucosal involvement, fever or respiratory symptoms.

Laboratory testing disclosed: absence of peripheral eosinophilia, normal inflammatory indices (anti-streptococcal and anti-staphylococcal titres were negative, normal erythrocyte sedimentation rate and C-reactive protein); normal urinalysis; normal immunoglobulin (IgE included) levels; negative RAST (RadioAllergo Sorbent Test); normal C3 and C4 levels and no anti-nuclear antibodies. Viral serological tests were negative (absence of herpes simplex virus (HSV) 1 and 2, cytomegalovirus (CMV), Epstein-Barr virus, enterovirus) and *Mycoplasma pneumoniae* IgM was negative by enzyme immunoassay. There were no *Toxoplasma gondii* (IgA, IgM, IgG) antibodies. Microbial cultures for bacteria and fungi were negative. Stool examinations for parasites and ova were negative. Anti-rubella IgM, anti-mumps IgM and anti-measles IgM were detected ap-

proximately 20 days after the MMR vaccination. High serological levels of anti-rubeola IgG, moderate levels of anti-mumps IgG and high levels of anti-measles IgG were detected 6 months after MMR vaccination.

The treatment regimen consisted of the administration of low-dose oral steroids, local cortico-antibiotic drugs, an antiseptic solution (eosin water solution 2%) followed by moisturizing creams. The skin lesions healed completely with abundant scaling after 3 weeks' therapy.

DISCUSSION

EM minor is usually a self-limiting process characterized by acute onset of acral and symmetrical erythematous papules evolving into the typical target lesions and absence of pronounced constitutional symptoms. Bullous elements are sometimes present. Mucosal involvement (usually of the lips) is rarely seen (1). It is most commonly caused by infections, especially by HSV and by *Mycoplasma pneumoniae* in children (2). Our patient's clinical manifestations included only diffuse targetoid skin lesions, resembling typical EM, and itch. There was no fever, general malaise, mucosal involvement or respiratory symptoms. No causative micro-organisms were identified and no drug had been taken by the patient during the previous 3 months. The only relevant data from the medical history was the administration of the MMR vaccination. Clinical differential diagnosis, based on polymorphic aspects of cutaneous lesions, might also include immune-



Fig. 1. Onset of skin eruption on the trunk, 8 days after measles-mumps-rubella vaccination.



Fig. 2. Twelve days after measles-mumps-rubella vaccination: targetoid confluent lesions are present over the entire integument.

mediated diseases, urticaria or even pustular psoriasis. Nevertheless, complement components C3 and C4 were within normal ranges and anti-nuclear antibodies were absent; RAST was negative. Moreover, there was no family history of psoriasis and no accompanying Koebner's isomorphic reaction. We were not able to perform skin biopsy and histological examination to confirm the clinical diagnosis as the patient's parents did not grant permission.

In Italy, as in many other European countries, the routine childhood immunization schedule uses a combined live attenuated multivalent MMR vaccine. The first dose of MMR vaccine is usually given at the age of 12 months. Childhood combination vaccines offer the convenience of a single injection and minimal local and systemic adverse reactions. The efficacy and safety of this kind of vaccine have been widely investigated. As with rubella antigens the measles components (3) used in various MMR vaccines (4) have been associated with various short- and long-term adverse events, although to a lesser extent. The mumps component (particularly the Jeryl Lynn strain), however, is thought to be virtually harmless (5). Pain, redness and swelling at the injection site have been described with different levels of incidence (3). Fever (37.5–39°C), with an onset 6 weeks after the injection, in addition to redness at the injection site, have been described in a high percentage of cases (more than 50% according to Nolan et al. (6)). According to Virtanen et al. (5), moderate or high MMR-associated elevation of temperature (higher than 38.5°C) occurs in 12% of vaccinees. Local reactions at the injection site were attributed by the same authors to mechanical trauma, since they found no difference between vaccinees and placebo recipients (5). According to Nolan et al. (6) the onset of a non-specific rash, particularly within the second week following vaccination, is much more frequent in the tetravalent MMR-varicella vaccine than in the MMR vaccine recipients, probably because of an enhanced measles immune response induced by the co-administration of varicella vaccine. Many authors (5–9) have described the development of a skin rash, often an aspecific febrile rash, sometimes a papular or vesicular rash, after MMR vaccination in young patients. To our knowledge, diffuse afebrile polymorphic erythema has not been described previously in relation to MMR vaccination. We hypothesize that the polymorphic

erythema in our patient is a consequence of MMR vaccination and that the pathogenetic mechanism is similar to that proposed by Aurelian et al. (10) to explain the association between polymorphic erythema and HSV, i.e. a combination of viropathic effects mediated by HSV proteins (DNA polymerase) and immunological reaction to viral antigens. According to these authors, viral DNA and proteins ingested by macrophages at lesion sites undergo fragmentation, processing and presentation to T cells with HSV memory. Activated T cells are recruited to the skin by viral DNA polymerase expression, resulting indirectly in the generation of an inflammatory cascade.

REFERENCES

1. Lam NS, Yang YH, Wang LC, Lin YT, Chiang BL. Clinical characteristics of childhood erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in Taiwanese children. *J Microbiol Immunol Infect* 2004; 37: 366–370.
2. Schofield JK, Tatnall FM, Leigh IM. Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol* 1993; 128: 542–545.
3. Enders JF, Katz SL, Milovanovic MV, Holloway A. Studies on an attenuated measles-virus vaccine: development and preparation of the vaccine-technics for assay of effects of vaccination. *N Engl J Med* 1960; 263: 153–159.
4. Redd SC, Markowitz LE, Katz SL. Measles vaccine. In: Plotkin SA, Orenstein WA, eds. *Vaccines*. 3rd edn. Philadelphia, PA: Saunders Company, 1999: p. 222–266.
5. Virtanen M, Peltola H, Paunio M, Heinonen OP. Day-to day reactogenicity and the healthy vaccinee effect of measles-mumps-rubella vaccination. *Pediatrics* 2000; 106: 62–67.
6. Nolan T, McIntyre P, Robertson D, Descamps D. Reactogenicity and immunogenicity of a live attenuated tetravalent measles-mumps-rubella-varicella vaccine. *Vaccine* 2002; 21: 281–289.
7. Jenkin GA, Chiba D, Kelly HA, Lynch PA, Catton MG. What is the cause of a rash after measles-mumps-rubella vaccination? *Med J Aust* 1999; 171: 194–195.
8. Lu MY, Huang LM, Lee CY, Lee PI, Chiu HH, Tsai HY. Evaluation of a live attenuated varicella vaccine in 15- to 18-month-old healthy children. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi* 1998; 39: 38–42.
9. Isozaki M, Kuno-Sakai H, Hoshi N, Takesue R, Takakura I, Kimura M, et al. Effects and side effects of a new trivalent combined measles-mumps-rubella (MMR) vaccine. *Tokai J Exp Clin Med* 1982; 7: 547–550.
10. Aurelien L, Kokuba H, Burnett JW. Understanding the pathogenesis of HSV-associated erythema multiforme. *Dermatology* 1998; 197: 219–222.