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**Atypical Gianotti-Crosti syndrome like skin lesions following vaccination**

**Short title:** GCS-like lesions

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24 vaccine, face, immunostaining

25

26 The ethics of our Hospital approved and both the patient and her mother made the  
27 written consent statement.

28

29 Y.O., N.H. and T.F. designed the study and contributed to data collection. Y.O., T.F., S.I.,  
30 N.H. and C.N. wrote the manuscript. All authors read and approved the final manuscript.

31

32     *Dear editor*

33     Gianotti-Crosti syndrome (GCS) was initially reported by Gianotti in 1955, as a  
34     papulovesicular exanthem following hepatitis B virus (HBV) infection<sup>1-4</sup>. Some similar  
35     cases without a history of HBV infection have been described as GCS<sup>2-4</sup>. Although the  
36     pathogenesis of GCS remains unclear, it is reportedly associated with viral infections or  
37     immunization with several types of vaccines<sup>2-6</sup>. Herein, we report an atypical early-  
38     onset case of GCS-like skin lesion that occurred 7 hours after measles-and-rubella (MR)  
39     vaccination and showed erythematous papules confined to the face.

40             The patient was a 13-year-old girl who had taken cyclophosphamide for  
41     relapsing nephrotic syndrome from 6 to 12 years of age, and had stopped the medication  
42     5 months previously, without experiencing a relapse. She presented with a sudden onset  
43     of erythematous papules on the forehead and the temples, 7 hours after being vaccinated  
44     with freeze-dried live attenuated MR vaccine (Fig. 1a). She consulted to our department  
45     3 days after vaccination, and a complete blood cell count and blood biochemistry results  
46     were within normal limits, and serum hepatitis B surface antigen was negative. Serum  
47     C3, C4, CH50, and C1q binding to immune complexes were within the normal range. A

skin biopsy performed 3 days after vaccination revealed the slight spongiotic changes in the epidermis and the perivascular lymphocytic infiltrates in the superficial dermis (Fig 1b,c). Consistent with a previous report<sup>3</sup>, immunostaining revealed patchy perivascular infiltration of CD3-positive lymphocytes, large numbers of CD4-positive and CD8-positive lymphocytes, and scant CD68-positive cells in the superficial dermis (Fig 1 e-g). Based on the clinical course and histopathological findings, we diagnosed her condition as GCS-like skin lesions. The eruption improved after 1 week of steroid ointment application.

GCS is relatively common in children between the ages of 3 months and 15 years<sup>3</sup>. The period from vaccination to onset varies from 1 day to 4 weeks<sup>3,4</sup>. This case had an early onset only 7 hours after vaccination with freeze-dried live attenuated MR vaccine. A patient who had experienced GCS by hepatitis B vaccination recurred GCS by MMR vaccination (measles, mumps and rubella)<sup>6</sup>. Same like this report<sup>6</sup>, sensitization phase might had been happened in our case.

We considered the possibility that a type IV hypersensitivity response might be involved<sup>3,4</sup>. In this case, the presence of abundant T cell lymphocytes, especially

64 CD4+ T cells, is consistent with this hypothesis; however, the time from vaccination to  
65 onset of the response in this patient (7 hours) was short. Thus, further research is  
66 needed.

67 Notably, the reported risk factors for GCS include combined vaccinations and  
68 a history of atopic dermatitis<sup>2, 3, 6</sup>, which were both present in the case patient. GCS  
69 typically manifests as a symmetrical rash on the face, limbs, and buttocks. Our patient  
70 presented with a rash confined to only the face. Lam<sup>5</sup> also reported two cases in which  
71 the rash was confined to only the face, both of which occurred after H1N1 vaccination.  
72 This case report can remind the risk of atypical GCS-like skin lesions following the  
73 vaccinations.

74 **Figure legend**

75

76 **Figure 1. Macroscopic and microscopic appearance of the skin lesions in a girl with**

77 **Gianotti-Crosti syndrome**

78 (a) Erythematous papules located on the forehead.

79 (b) Histopathological analysis showing the slight spongiotic changes in the epidermis

80 and the perivascular lymphocytic infiltrates in the superficial dermis (hematoxylin

81 and eosin staining, original magnification  $\times 40$ ; scale bar = 400  $\mu\text{m}$ ).

82 (c) Histopathological analysis showing perivascular lymphocytic infiltrates in the

83 superficial dermis (hematoxylin and eosin staining, original magnification  $\times 200$ ;

84 scale bar = 100  $\mu\text{m}$ ).

85 (d) CD3-stained tissue sample showing infiltration of CD3-positive cells (original

86 magnification  $\times 100$ ; scale bar = 200  $\mu\text{m}$ ).

87 (e) CD4-stained tissue sample showing infiltration of CD4-positive cells (original

88 magnification  $\times 100$ ; scale bar = 200  $\mu\text{m}$ ).

- 89 (f) CD8-stained tissue sample showing slight infiltrates of CD8-positive cells (original  
90 magnification  $\times 100$ ; scale bar = 200  $\mu\text{m}$ ).
- 91 (g) CD68 staining revealed very slight infiltrates of CD68-positive cells (original  
92 magnification  $\times 100$ ; scale bar = 200  $\mu\text{m}$ ).



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