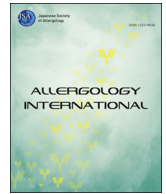




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Letter to the Editor

Localized cold urticaria after vaccination in a child: A case and literature review

Dear Editor,

Cold urticaria (CU), the second most frequent type of chronic inducible urticaria, is characterized by skin lesions and/or angioedema developing upon contact with cold air, liquids or solids, subsequent to the release of proinflammatory mast cell mediators on exposure to low temperatures.¹ CU can be subdivided into familial or acquired forms. The latter can be classified as primary or secondary to an underlying cause, such as infections (mainly viral pathogens), cryoglobulinemia, hypersensitivity vasculitis, drugs, neoplasms. Certain acquired CU (ACU), called atypical ACU syndromes, could not exhibit wheal formation after standard cold contact stimulation tests, and consequently their diagnosis must depend on history and other diagnostic procedures. Among them, have been included the systemic ACU, the cold-dependent dermatographism, the cold-induced cholinergic urticaria, the delayed cold urticaria, the localized cold reflex urticaria and the localized cold urticaria (LCU). In particular, LCU is defined by clinical manifestations only in a specific body area (sites of immunization/desensitization, site of insect bites or idiopathic).^{2,3}

Here we describe a unique case of LCU at the site of vaccine injection in a paediatric patient.

A 6-year-old child was referred to us for a 6-month history of an asymptomatic annular wheal on the left upper arm, which regularly appeared a few minutes after direct or indirect cold exposure (local cold exposure, cold shower, cold exposure while wearing clothes) and disappeared spontaneously after 30–60 min.

The lesion occurred in the site of injection of the first dose of Meningococcal B vaccine (Bexsero, GlaxoSmithKline Vaccines), one month after its administration. Similar lesions had not been noted elsewhere in his body and no systemic symptoms or angioedema occurred during the attacks. The patient had not history of atopy or recent infections. Complete blood test exam, including C-reactive protein, C3 and C4, cryoglobulin, total IgE, autoimmune and viral serology (Epstein–Barr virus, hepatitis B and C virus) panel showed normal results. At first examination no cutaneous lesions were present (Fig. 1a), so we performed an ice-cube test (ICT) and after 2 min the expected annular wheal appeared exactly in the same area as the previous times (Fig. 1b), disappearing within 1 h (Fig. 1c). Darier sign was negative at the vaccine administration site where the wheal appeared. Results of ICT on other body areas failed to induce lesions. Curiously, the urticarial rash had not occurred in the other arm, where the vaccine recall was performed 3 months after the first dose, even after ICT.

Echotomography, performed 1 h after ICT, showed an ill-defined isoechoic oedema of soft tissues, extending from the deep dermis to the subcutaneous tissue. The Color Doppler modality did not detect increased vascular signals. Based on these findings, vaccine-induced granuloma was ruled out, since it usually appears as hypoechoic and well structured⁴ (Fig. 1d).

We performed a punch biopsy from the annular wheal some minutes after inducing it and microscopic examination showed oedema, a sparse slight-moderate perivascular superficial, deep, interstitial mixed inflammatory infiltrate, predominantly consisting of lymphocytes, rare eosinophils, neutrophils and mastocytes between collagen bundles in the dermis (Fig. 1e). C-KIT(CD117) staining showed just few mastocytes in the dermis (Fig. 1f).⁵

Histological and immunocytochemical features were consistent with early stage urticaria.

To our knowledge, this is the first case of LCU induced by vaccine injection.

In fact, we are able to find only two different situations reported in the literature: (a) 4 cases of CU following vaccination and (b) 4 cases of LCU associated with immunotherapy (Table 1).

More precisely, in 4 cases CU occurred after vaccine injections: in 3 cases the wheals were localized on cold air-exposed areas, while the fourth experienced generalized urticaria and angioedema; none of them had cutaneous manifestations restricted to the site of injection only. In these cases, since different vaccines were incriminated, an immune allergic reaction to the vaccine viral strain itself and subsequent mast cell activation was suspected by the authors.⁶

On the other hand, in 4 cases the LCU was strictly confined to the site of subcutaneous immunotherapy (tree pollen extract) in patients with seasonal allergic rhinoconjunctivitis. ICT resulted strongly positive in the area of administration and negative in the rest of the body.^{7–9}

We hypothesized that in our case the pathogenetic mechanism underlying the clinical manifestations was more similar to the forms of LCU induced by immunotherapy: a local (immunologic or not) tissue injury which triggers a delayed cold-induced hypersensitivity.

In our young patient, we prescribed oral antihistamines (cetirizine 10 mg/day) with partial remission of his local symptoms.

In conclusion, we reported the first case of LCU developing after a vaccine injection in a child. Interestingly, the cutaneous manifestation has remained localized and no other symptoms have been reported even 6 months later.

However, it may be prudent to follow-up young patients with LCU for possible progression to systemic manifestation, including anaphylaxis, and keep in mind that a history of recent vaccination

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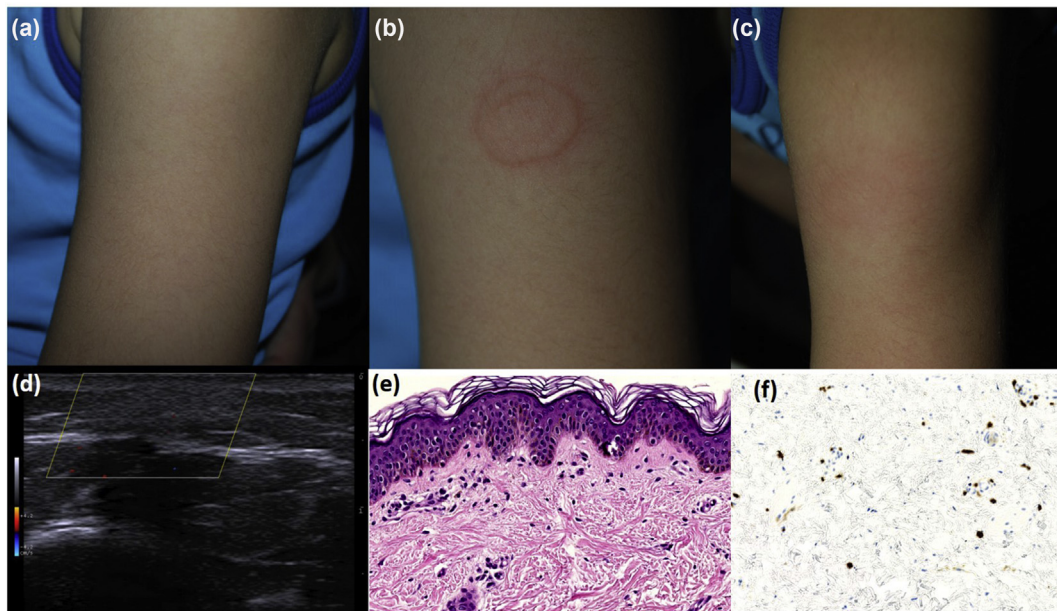


Fig. 1. No cutaneous lesion was present at first examination (a), occurrence of the annular wheal 2 min after performing the ice-cube test in the site of vaccination (b) and spontaneous disappearance of the lesion after 1 h (c). Echotomography showed an ill-defined isoechoic oedema of soft tissues, extending from the deep dermis to the subcutaneous tissue (d). Microscopic examination showed oedema, a sparse slight perivascular superficial, deep, interstitial mixed inflammatory infiltrate, predominantly consisting of lymphocytes, rare eosinophils, neutrophils and mastocytes between collagen bundles in the dermis (H&E, 44x) (e). C-KIT(CD117) staining revealed a few mastocytes around vessels of superficial and deep dermis (36x) (f).

Table 1
Case reports of cold-induced urticaria after immunotherapy or vaccination.

Reference	Age	Skin surface area involved	Trigger	Time between trigger and onset of symptoms	Test performed	Therapy	Laboratoristic abnormalities associated
Ducommun <i>et al.</i> , 2008	29	Localized (site of the injections)	Subcutaneous immunotherapy (for tree pollen allergy)	During 2 ^o year of immunotherapy	Ice-cube test: positive in few minutes only in the site of injection	Antihistamines	None
Solomon LM <i>et al.</i> , 1966	–	Localized (site of the injections)	Subcutaneous immunotherapy (for tree pollen allergy)	–	–	–	–
Garcia F <i>et al.</i> , 1998	29	Localized (site of the injections)	Subcutaneous immunotherapy (for gramineous pollen allergy)	During 2 ^o year of immunotherapy	Ice-cube test: positive in few minutes only in the site of injection	Antihistamines (no relapse at the following dose)	None
	36	Localized (site of the injections)	Subcutaneous immunotherapy (for gramineous pollen allergy)	During 4 ^o year of immunotherapy	–	Spontaneous remission in 6 months	None
Raison-Peyron N <i>et al.</i> , 2016	4	Cold-exposed areas	Vaccination anti N. meningitis serotype C	5 days after vaccination	Ice-cube test: positive	Antihistamines + montelukast	None
	29	Cold-exposed areas + angioedema	Vaccination anti yellow fever and hepatitis A	3 weeks after vaccination	Ice-cube test: positive	Antihistamines	None
	2	Cold-exposed areas	Vaccination anti S. pneumoniae + diphtheria, tetanus, poliomyelitis, H. influenzae B, pertussis	7 days after vaccination	Ice-cube test: positive	Antihistamines	None
	37	Cold-exposed areas	Vaccination anti H1N1 influenza virus	3 weeks after vaccination	Ice-cube test: positive	Antihistamines + prednisolone (no relapse at the following dose)	None

should be investigated to properly diagnose this rare and curious phenomenon.

Conflict of interest

The authors have no conflict of interest to declare.

Federica Filippi*, Andrea Sechi, Carlotta Baraldi, Cosimo Misciali, Annalisa Patrizi, Marco Adriano Chessa, Annalucia Viridi, Iria Neri

Dermatology Unit, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy

* Corresponding author. Dermatology Unit, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Via Massarenti 1, 40138, Bologna, Italy.
E-mail address: federicafilippi8@gmail.com (F. Filippi).

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