

Cutaneous Rosai-Dorfman disease after Covid 19 vaccination treated with thalidomide

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Dear Editor,

we report here, to the best of our knowledge, the first case of cutaneous Rosai-Dorfman disease observed following vaccination against coronavirus-19 disease.

Reports of COVID-19 vaccine-related skin reactions have become frequent. The most common reports concern injection site reactions and maculo-papular or urticarial rashes. However, many different skin manifestations have been observed.[1]

An otherwise healthy, 62-year-old individual came to our Dermatology Outpatient Clinic for a generalized, itchy, papular eruption which had lasted for 6 months. He reported no other systemic symptoms, and in his medical history nothing relevant emerged. He received his first dose of Pfizer® vaccination against COVID-19 in June 2021. After ten days, he noticed the appearance of small, itchy, purplish papules on his legs; a few days after the second dose, these lesions spread gradually on the trunk and upper limbs. On clinical examination we observed purpuric papules symmetrically distributed on the upper and lower limbs, trunk, and neck.(Fig 1a,1b,1c) Some of these lesions were keratotic. The patient had no enlarged lymphnodes. Histopathological examination showed large histiocyte-rich dermal infiltrate S100+ with emperipolesis, surrounded by lymphocytes, plasma cells, and neutrophils (Fig. 1d,1e) No BRAF or KRAS mutations were found. These findings were characteristic of a rare non-Langerhans cell histiocytosis of Rosai-Dorfman-Destombes type (RDD). Laboratory tests showed only a mild anemia 12,5 g/dl (normal range 14.0-

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17.0). As no internal abnormalities were recognized on the computed tomography scan and on the lymph nodes and abdominal ultrasound, we opted for the diagnosis of cutaneous Rosai-Dorfman disease (cRDD). Based on several reports on its safety-to-efficacy balance, we prescribed oral thalidomide [2] 100 mg/day and, after six months, we observed that lesions had cleared with no adverse effects.

To date, no cases of cutaneous histiocytosis have been reported after Covid-19 vaccination, while one case of cRDD has been described after Pneumococcal vaccination [1][3]. Primary cRDD is a form of non-Langerhans cells histiocytosis limited to the skin and mucosal surfaces (“group C histiocytoses”) in 3% of the cases. It may be indolent with a self-limiting course, but follow-up is indispensable, as systemic involvement cannot be excluded. Lesions are typically slow-growing, painless papules, nodules or plaques with color ranging from red to brown.[4] Etiopathogenesis is unknown but it may be secondary to a malignant, infectious (i.e., Epstein-Barr Virus, Cytomegalovirus, parvovirus B19), or autoimmune/autoinflammatory stimulus [5]. The frequent presence of monoclonality of histiocytes raises the question whether it should be considered a neoplasm. The histological marker is the presence of large, pale histiocytes with emperipolesis, while immunohistochemistry shows positivity for S100 protein and for histiocytic markers – CD68 and CD163 – and OCT2, but negativity for Langerhans cell markers – CD1a and CD207.[6] In most cases, mutations of BRAF, KRAS, and NRAS are detected. For the treatment of refractory or extensive disease, there is some evidence of effectiveness for thalidomide, dapsone and low-dose weekly methotrexate as monotherapy, or combined with steroids.[7] Histiocytes perform phagocytic functions against numerous antigens, so different stimuli can trigger their activation and proliferation. However, the precise mechanism that determines the appearance of these lesions after vaccination against Covid-19 has not yet been clarified. Another condition that links histiocytes to COVID-19 is a macrophage hyperactivation syndrome called Hemophagocytic lymphohistiocytosis (HLH), found both post-COVID-19 infection and post-vaccination. This could be due to an altered response of macrophages against virus-infected cells with modification of their cytotoxic function.[8] We report this association for the first time, given that the strict temporal relationship between vaccination and development of this dermatosis may be of a causal nature.[9]

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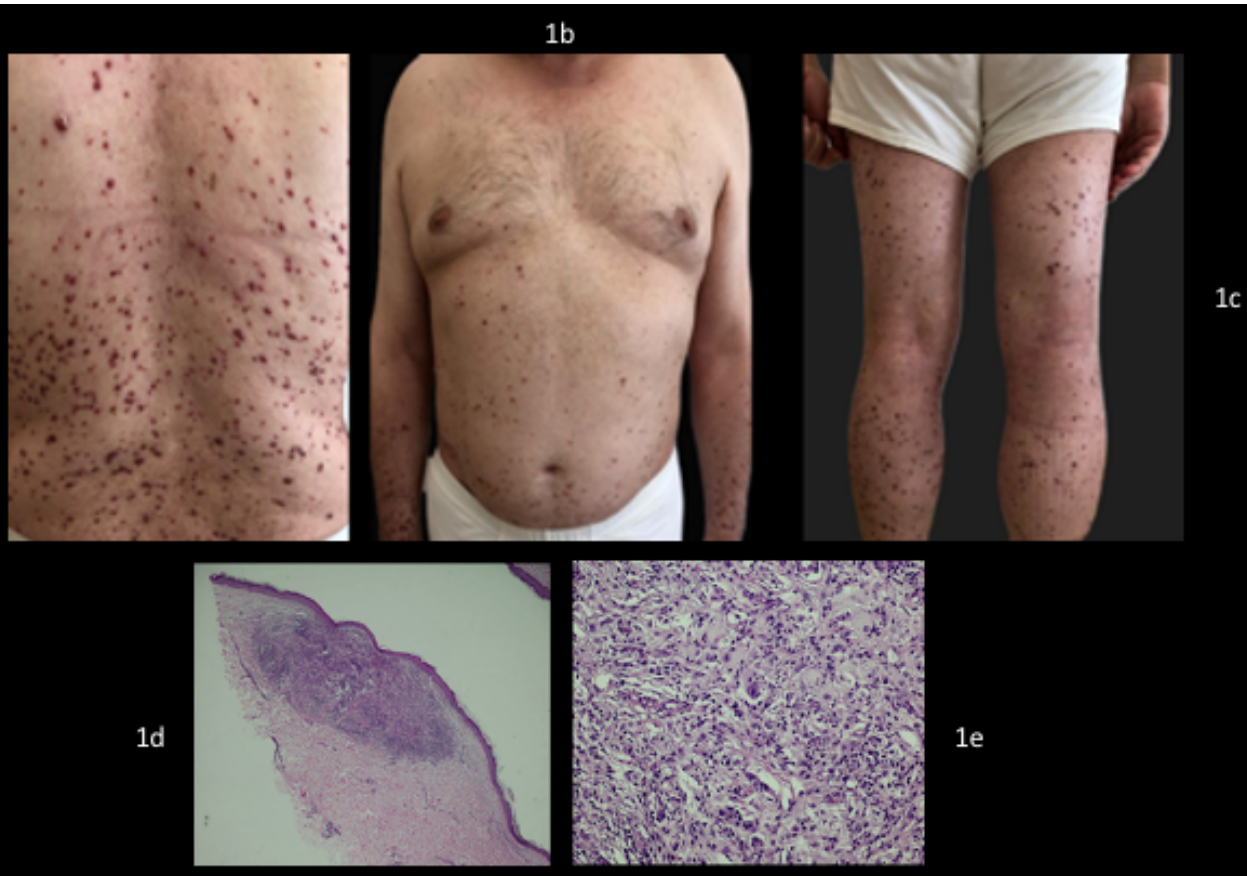
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Legend of figure:

Figure 1: Purpuric papules symmetrically distributed on the back (**a**), and the front of the trunk (**b**), and the back of the legs (**c**); Histological examination of cutaneous lesion in Rosai-Dorfman disease characterized by dermal accumulation of histiocytes (hematoxylin and eosin) (**1d**); Histiocytes show enlarged round or oval hypochromatic nuclei and abundant eosinophilic cytoplasm, often containing engulfed intact inflammatory cells (emperipolesis) hematoxylin and eosin 20x (**1e**).



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