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Case report

Cutaneous Rosai Dorfman disease harboring RET and MAP2K1 mutations, successfully treated with methotrexate

Maria P. Konstantinou[1], MD and Emilie Tournier[2], MD

[1]Dermatology Department, Paul Sabatier University, University Hospital of Toulouse, Toulouse, France, [2]Pathology Department, University Institute of Cancer Toulouse Oncopole and University Hospital of Toulouse, Toulouse, France

Correspondence
Maria Polina Konstantinou, MD
Dermatologie
CHU de Toulouse – Larrey
24 Chemin de Pouvourville TSA 30030
31059 Toulouse
France
E-mail: mariepaulinek@gmail.com

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Introduction

Rosai-Dorfman disease (RDD), also known as histiocytosis with massive lymphadenopathy, is a histiocytic proliferative disorder with lymph nodes and occasional extranodal involvement. Purely cutaneous RDD is a rare entity with distinct clinical and histopathological features.[1] We present a case of cutaneous RDD with head and neck involvement harboring both RET and MAP2K1 mutations, successfully treated with methotrexate.

Material and methods

A 66-year-old male with no past history was consulted for the progressive appearance during a 12-month period of multiple, dome-shaped, violaceous papulonodules of the face, hair, and anterior thorax (Fig. 1a). Skin biopsy revealed a dense dermal infiltrate compounded by lymphocytes, plasma cells, and histiocytes with abundant pale cytoplasm (Fig. 2a). Emperipolesis was observed with a significant number of histiocytes containing lymphocytes and red blood cells (Fig. 2b). Immunohistochemistry revealed a PS100+ (Fig. 2c), CD68+, CD1a–, pERK+, and VE1- histiocytic proliferation. The patient was diagnosed with RDD. The whole positron emission tomography was normal. Genomic DNA was extracted from formalin-fixed and paraffin-embedded skin biopsies. Next-generation sequencing identified a mutation of RET c2371T > A, p. (Tyr791Asn), (Roche sequencing, Kapa/SeqCap) of unknown significance and a pathogenic, activating mutation of MAPR2K1 c308T > A, p. (Ile103Asn), (Illumina, MiSeq). The patient received methotrexate at 15 mg once weekly associated with medium-potency topical corticosteroids once daily and achieved significant improvement at 9 months (Fig. 1b). At this point, the methotrexate dose was increased to 25 mg/week (0.3 mg/kg), and an intralesional injection of 10 mg/ml triamcinolone was performed. Complete remission was noted at the 12-month follow-up (Fig. 1c).

Discussion

Mutually exclusive KRAS and MAP2K1 mutations have been identified in one-third of patients with RDD.[2] Their presence correlates clinically with a younger age at presentation and pediatric patients, with head and neck involvement and a multifocal disease but not with the response rates to conventional treatment.[2] MAP2K1 mutations can be selectively targeted by

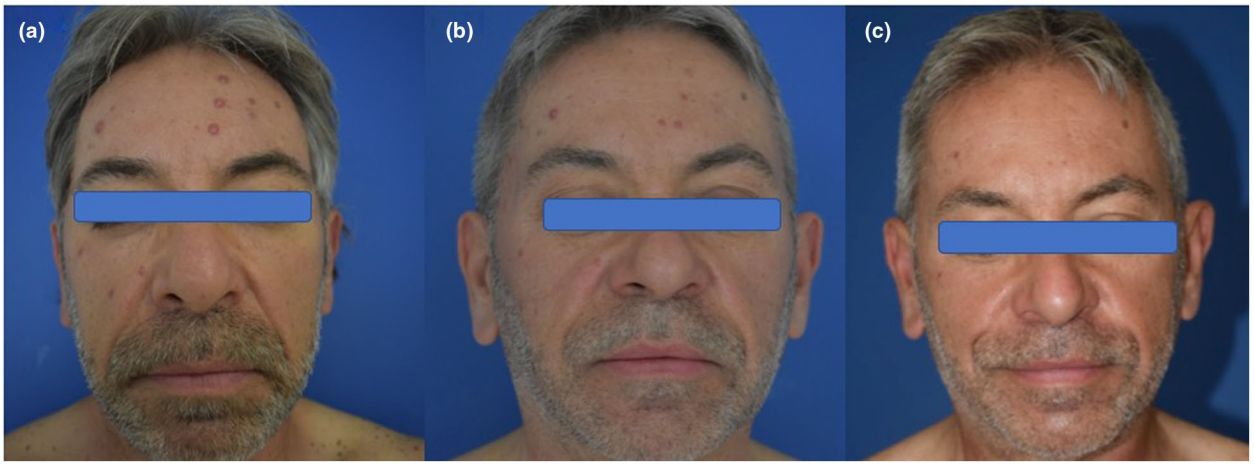

Figure 1 (a) Multiple, papulonodular, dome-shaped, violaceous lesions of the face; (b) Partial clinical response at 9 months of methotrexate treatment at 15 mg/week and medium-potency topical corticosteroids; (c) Complete response at 12 months of methotrexate treatment at 25 mg/week

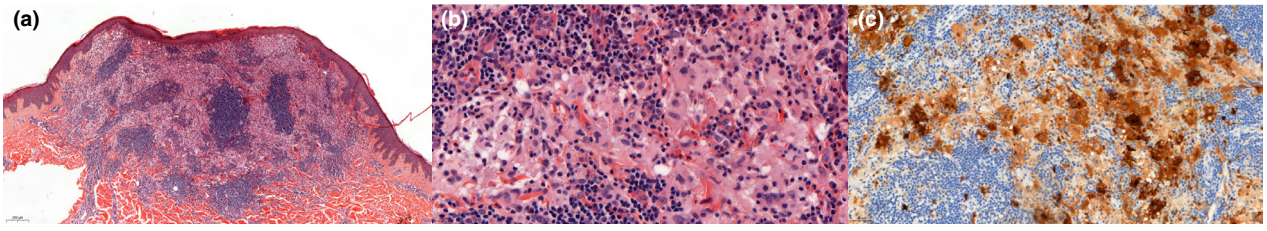

Figure 2 (a) Dense dermal infiltrate compounded by lymphocytes, plasma cells, and histiocytes with abundant pale cytoplasm (Hematoxylin and eosin, x50); (b) Pale histiocytic cells characterized by emperipolesis (Hematoxylin and eosin, x400); (c) Immunostaining anti-PS100, x200

currently approved MAP2K1/2 inhibitors such as cobimetinib and trametinib.[3,4] In a proof-of-concept study, 18 patients with $BRAF^{V600E}$ wild-type histiocytic neoplasms were treated with cobimetinib, achieving an overall response rate of 89%.[4] This study further confirmed the remarkable dependence of histiocytic neoplasms from the MAPK pathway.

The particularity of our case is the synchronous identification of two mutated genes. New genomic drivers have been recently identified in histiocytic neoplasms including rearrangements in RET (fusion gene *NCOA4-RET*) and ALK (fusion gene *KIF5B-ALK*).[5] These RET and ALK rearrangements responded to selective inhibition with selpercatinib and crizotinib, respectively, confirming their pathogenic potential.[5] RET rearrangements are primarily associated with papillary thyroid carcinoma and non-small cell lung cancer. The RET proto-oncogene contains 21 exons and encodes for a tyrosine kinase receptor. In normal conditions and upon activation, RET interacts via the phosphorylation of its intracellular domain Y1062 and activates the MAPK/RAS/ERK downstream pathway.[6] The pathogenic role of the RET c2371T > A variant, identified in our case, is well reported in lymphoid tumors (COSMIC database). Targeting RET mutations could represent a new therapeutic approach in RDD.

Cutaneous RDD treatment is not well codified. As a result of the normally self-limited course, aggressive therapies are not recommended. In our case, the limited extension of lesions prompted the use of methotrexate over MAP2K1/2 inhibitors as a first-line treatment, mainly because of the restricted access and the greater risk of toxicities of the latter. Low-dose methotrexate has been used in several case reports of cutaneous RDD leading to partial or complete responses in the majority of cases.[7] Methotrexate increases the inhibition of isoprenylcysteine carboxyl methyltransferase inducing the hypomethylation of RAS by almost 90%[8] and thus could act by inhibiting directly the MAPK pathway.

We report the first case of primary cutaneous RDD harboring two, non-mutually exclusive, RET and MAP2K1 mutations that were successfully treated with methotrexate.

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