CASE REPORT

Special variant of histiocytosis

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Accepted 17 October 2017

SUMMARY

Indeterminate cell histiocytosis is a rare variant of histiocytosis. The diagnosis is currently based on presence and absence of immunohistochemical markers. The current case described an indeterminate cell histiocytosis with *ETV3-NCOA2* translocation.

BACKGROUND

Indeterminate cell histiocytosis is a rare histiocytic disorder with immunohistochemical features that overlap with non-Langerhans cells and Langerhans cells of the monocyte-macrophage-dendritic cell lineage. The disease was first described in 1985 by Wood *et al.*¹ Currently, the gold standard to differentiate Langerhans cell histiocytosis from indeterminate cell histiocytosis is the presence of CD1a transmembrane glycoprotein and the absence of Birbeck granules (determined by CD207 immunohistochemistry or by electron microscopy). New insights into genetic alterations in Langerhans cell histiocytosis and non-Langerhans cell histiocytosis observed mutations

in the MAPK pathway.² Nevertheless, indeterminate cell histiocytosis remained an unexplored area.

CASE PRESENTATION

A 67-year-old man presented with a 6-month history of progressive asymptomatic waxy skin lesions located on his trunk, arms and upper legs (figure 1). His medical history mentioned type 2 diabetes and hepatocellular carcinoma. He had no rheumatic complaints or other systemic symptoms. Over time, the skin lesions did not resolve spontaneously.

DIFFERENTIAL DIAGNOSIS

Under the differential diagnosis of a Langerhans cell histiocytosis, a generalised eruptive histiocytosis (or other variants of non-Langerhans cell histiocytosis), a mastocytosis and a leukaemia cutis, a skin biopsy was taken.

INVESTIGATIONS

A skin biopsy revealed a non-epidermotropic mononuclear histiocytic infiltrate (figure 2a), which expressed CD68 (figure 2b) and CD1a (figure 2c), but no CD207/Langerin (figure 2d), suggestive for indeterminate cell histiocytosis. Electron microscopy confirmed the absence of Birbeck granules, which was in line with the negative CD207/Langerin staining and excluded Langerhans cell histiocytosis. Genetic analyses with the Taqman hotspot mutation panel for the RAS-RAF-MEK pathway revealed no mutations in the MAPK pathway, as suggested by the literature.³ Nevertheless, in paraffin-embedded representative tumour tissue, we detected a gene fusion of *ETV3* exon 4 (NM_001145312.1): *NCOA2* exon 14 (NM_006540.2). The fusion of *ETV3* with *NCOA2* was detected by using the commercial available FusionPlex Sarcoma Kit (ArcherDX). For reference sequence, see NM codes.

Furthermore, full blood count, bone marrow biopsy and CT of the thorax and abdomen were performed, showing no internal involvement or underlying haematological malignancy.

TREATMENT

Literature regarding treatment of indeterminate cell histiocytosis is scarce. Good responses to combinations of *BRAF* and *MEK* inhibitors have been described in histiocytosis patients with a *BRAF* V600E mutation, but our patient was not carrying this mutation. Disease-modifying anti-rheumatic drugs or ultraviolet B therapy can be tried, but results might be disappointing. Our patient received ultraviolet B radiation therapy with minimal improvement of the skin lesions but

Figure 1 Waxy, skin-coloured papules on the trunk photographed by floodlight to increase the visibility.

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To cite: Quint KD, Cleven AH, Vermeer MH. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-221538

Figure 2 (A) H&E staining (100×) showing a highly cellular dermis with a prominent infiltrate of monomorphic histiocytic cells admixed with a scarce lymphocytic infiltrate. (B) CD68 staining (100×) was positive in the monomorphic histiocytic cells. (C) CD1a (100×) also showed an abundant positive staining pattern in the monomorphic histiocytic cells. (D) The CD207/Langerin (100×) staining was negative in the histiocytic cells with a positive internal control (Langerhans cells in the epidermis).

no progression. Routine follow-up will be performed to evaluate the disease course.

DISCUSSION

Currently, two separate genetic abnormalities (mutations in *BRAF* gene and *ETV3-NCOA2* translocation) are known for indeterminate cell histiocytosis, leading to the same histological phenotype of CD207[−]/CD1a⁺ histiocytes.

ETV3-NCOA2 translocation is recently described in *BRAF* V600E-negative indeterminate cell histiocytosis patients.⁴ Normally, the *ETV3* gene encodes a transcriptional repressor (Ets variant 3) involved in macrophage growth arrest, while the *NCOA2* gene encodes the transcription factor nuclear receptor coactivator 2 that is involved in the balance between brown and white adipose tissue. Translocations of *NCOA2* gene can be observed in different types of sarcoma, acute leukaemia and colon cancer and in benign angiofibromas. The exact role of this translocation has to be elucidated, but possibly the malfunction of ETV3 protein leads to an increase in RAS-dependent cell proliferation. This specific gene fusion is an important marker in confirming the rare diagnosis of indeterminate cell histiocytosis and can even be an interesting target for future therapies.

Learning points

Indeterminate cell histiocytosis is a rare variant within the histiocytic proliferations.

The histiocytes in indeterminate cell histiocytosis express CD68 and CD1a, but no CD207 and Birbeck granules are not observed by electron microscopy.

Indeterminate cell histiocytosis can have a specific *ETV3-NCOA2* translocation.

Contributors All authors contributed to patient care. KDQ an MHV wrote the report and prepared the figures. AHC did the histopathology and molecular analysis. Written consent to publication was obtained.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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