Disseminated non-Langerhans cell histiocytosis with an IRF2BP2-NTRK1 gene fusion identified by next-generation sequencing

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INTRODUCTION

The histiocytoses are rare myeloid disorders characterized by the accumulation of dendritic cell, macrophage, or monocyte-derived cells in tissues and organs. Based on the revised 2016 classification of histiocytoses, non-Langerhans cell histiocytosis of skin and mucosa (C group) is a subclass that includes various forms of xanthogranulomas (XGs) and several non-XG family disorders.1 Because these histiocytoses have overlapping clinical and histologic presentations, a definitive diagnosis and appropriate therapy regimen is often difficult to ascertain.2

We present a case report describing the use of targeted next-generation sequencing (NGS) with the Stanford Solid Tumor Actionable Mutation Panel (STAMP) to identify a rare case of IRF2BP2-NTRK1—associated progressive nodular histiocytosis (PNH)/xanthogranulomatosis after autologous hematopoietic cell transplantation (HCT) for diffuse large B-cell lymphoma (DLBCL). STAMP targets 198 genes based on their known impact as actionable targets of existing and emerging anticancer treatments. This case of IRF2BP2-NTRK1 fusion-related histiocytosis demonstrates the applicability of NGS to the diagnosis and treatment of clinically ambiguous pathologic conditions.

CASE REPORT

A 50-year-old white man with a history of double-hit (MYC and BCL2) stage IV DLBCL status post—autologous HCT with complete remission presented to the dermatology clinic with an 11-month history of asymptomatic papules on his face, chest, back, and extremities. The lesions first developed 3 months after HCT as small bumps on the face, which quickly generalized to the chest and back (Fig 1).

Physical examination found hundreds of yellow-orange 3- to 9-mm smooth papules studding his face, trunk, and extremities. Skin punch biopsies found an exuberant dermal proliferation of histiocytes, including several Touton-like multinucleated giant cells (Fig 2). Cholesterol clefts, necrosis, mitotic activity, and angiodestructive features were not present. On immunohistochemical staining, the dermal infiltrate showed CD163 and factor 13a positivity and was negative for CD1a, S100, and BRAF V600E, consistent with PNH, eruptive XG, and other cutaneous histiocytoses.1,2 Although the storiform architecture, occasional spindle cells, and immunohistochemistry favored the diagnosis of PNH, the patient lacked the larger nodules that are often characteristic of PNH; thus, other diagnoses such as eruptive XG, generalized eruptive histiocytoma, and reactive granulomatous dermatitis remained in the differential diagnosis. Additional laboratory testing, including complete blood count, peripheral blood smear review, comprehensive metabolic panel,
serum protein electrophoresis, and immunofixation were all within normal limits. Review of systems for histiocytosis-related complications, including diabetes insipidus, were unremarkable, and whole-body positron emission tomography/computed tomography scan did not show signs of histiocytosis or lymphoma.

Because of the challenge in diagnosis and to determine treatment options, molecular mutation analysis was performed, which found an IRF2BP2-NTRK1 gene fusion. An IRF2BP2-NTRK1-associated cutaneous histiocytosis was diagnosed and the patient was referred to a histiocytosis center. He was treated with hydroxyurea, 1000 mg/d, for 2 months without improvement and is under consideration for chemotherapy or targeted therapy with an oral NTRK inhibitor.

DISCUSSION

The histiocytoses have traditionally been categorized as Langerhans cell histiocytosis (LCH) and non-Langerhans cell histiocytosis (non-LCH). However, in light of recent insight into the cellular origin, molecular pathology, and clinical features of histiocytic disorders, a revised classification into 5 groups is now widely accepted: L (Langerhans), C (cutaneous and mucocutaneous histiocytoses), M (malignant histiocytoses), R (Rosai-Dorfman disease), and H (hemophagocytic lymphohistiocytosis and macrophage activation syndrome). The L group consists of LCH and Erdheim-Chester disease (ECD), whereas the C group includes the juvenile and adult XGs, PNH, generalized eruptive histiocytosis, xanthoma disseminatum, and necrobiotic xanthogranuloma, among others. The term non-LCH is still used to describe any histiocytosis that is not LCH specifically, including ECD. Given the similarity in pathologic features between ECD and cutaneous histiocytosis, ECD symptoms were evaluated and excluded. For our patient, his histologic findings are compatible with an early lesion of PNH, but his clinical morphology is not nodular and appears to be
congruent with generalized eruptive XGs. Our patient had a non-LCH, C-type histiocytosis, most likely PNH, XG, or an overlap of PNH/XG. All histiocytosis subtypes, including the C group, have been associated with lymphoid malignancies.

Recent molecular advances have shown that mutations involving the MAPK and PI3K-AKT pathways are implicated in the pathophysiology of a large proportion of histiocytosis patients, especially those with the L-type histiocytoses. Gene fusions involving the NTRK1 tyrosine kinase led to constitutive activation of the MAPK and PI3K-AKT pathways and have been reported in 7 histiocytosis patients in the literature. Histiocytosis type in all of these reports was non-LCH, particularly ECD (L type) or generalized eruptive histiocytosis (C type). Our patient had an NTRK1 fusion in PNH/XG, which has been previously reported with non-LCH-type disease and, to our knowledge, is the first case of an IRF2BP2-NTRK1 fusion in any histiocytosis. He is also the first patient with suspected PNH associated with DLBCL.

PNH is categorized as a rare variant of the XG family of histiocytoses, as PNH and XG share a common immunohistochemical profile and many microscopic characteristics. An important distinguishing feature of PNH, however, is that PNH often shows relentless clinical progression, with almost no evidence of spontaneous or induced regression in the literature. Our patient appears to have exhibited continuously progressing lesions since the first appearance of his lesions 1.5 years ago.

It is important to consider the use of NGS technologies for mutation identification, especially in cases such as ours for which the specific diagnosis and therapeutic options are unclear. STAMP targets 130 genes selected based on their known impact as actionable targets of existing and emerging anti-cancer therapies. Using STAMP, we identified an NTRK1 fusion that supports the consideration of NTRK inhibition in our patient, irrespective of the definitive diagnosis of cutaneous histiocytosis subtype and the initial projected clinical course of his PNH/XG. However, not all NGS tests are designed to test gene fusions, amplifications, or deletions, and the limitations of the specific assay should be identified prior to testing.

The identification of an NTRK1 fusion in our patient suggests that constitutive activation of the MAPK and PI3K-AKT pathways may lead to cellular proliferation and differentiation in not only L-type, but also C-type histiocytoses. An equally important consideration is that other suspected PNH cases may also harbor NTRK1 gene fusions or other actionable MAPK and/or PI3K-AKT–associated mutations that may qualify them for more effective therapies. We therefore recommend the inclusion of NGS technologies such as STAMP in the clinical workup of challenging histiocytosis cases in addition to continued efforts to discern the underlying genetic and molecular landscape of the histiocytoses.

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