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

Warren H. Chan, BS,[a] Aatman Shah, MD,[a] Gordon Bae, MD,[a] Caely Hambro, MD,[a] Beth A. Martin, MD,[b] Ryanne Brown, MD, MBA,[a,c] Roberto Novoa, MD,[a,c] and Bernice Y. Kwong, MD[a]
Stanford, California

Key words: *BCL2*; histiocytosis; MYC; non-Langerhans; sequencing.

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.

Abbreviations used:

DLBCL:	diffuse large B-cell lymphoma
ECD:	Erdheim-Chester disease
HCT:	hematopoietic cell transplantation
LCH:	Langerhans cell histiocytosis
NGS:	next-generation sequencing
PNH:	progressive nodular histiocytosis
STAMP:	Solid Tumor Actionable Mutation Panel
XGs:	xanthogranulomas

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,

From the Departments of Dermatology,[a] Hematology,[b] and Pathology,[c] Stanford University.
Funding sources: None.
Conflicts of interest: None disclosed.
Correspondence to: Bernice Y. Kwong, MD, 780 Welch Road, Palo Alto, CA 94304. E-mail: bernicek@stanford.edu.
JAAD Case Reports 2020;6:1156-8.
2352-5126

https://doi.org/10.1016/j.jdcr.2020.05.032

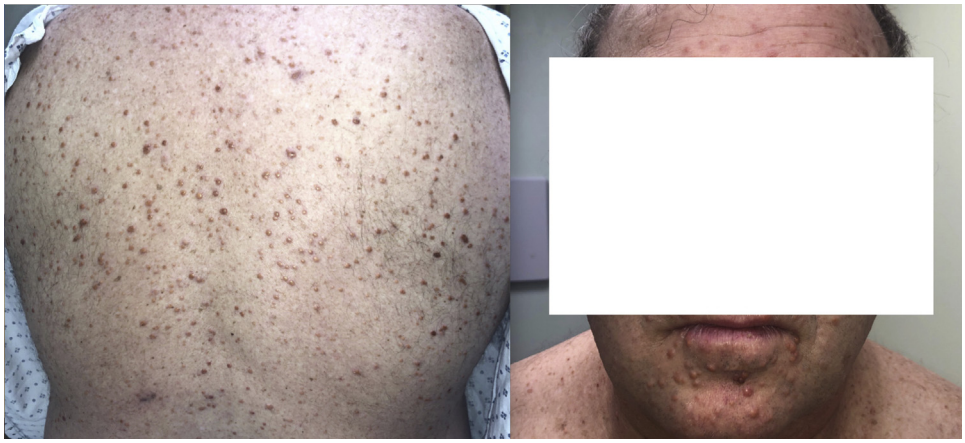

Fig 1. Hundreds of smooth dermal yellow-orange 3- to 9-mm papules studding the patient's face, trunk, and extremities.

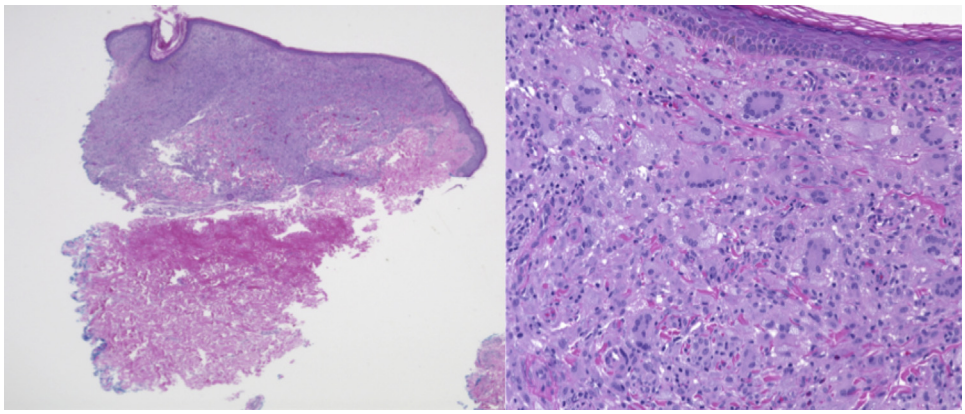

Fig 2. An exuberant dermal proliferation of histiocytes, including several Touton-like multinucleated giant cells at low (×4) and high (×40) power. Cholesterol clefts, necrosis, mitotic activity, and angiodestructive features are not present.

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).[3] 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).[1] 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.[1] 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.[1,3,4] 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.[5-9] 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.[1,10] 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.[3,10] 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 anticancer 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.

REFERENCES

1. Emile J-F, Abla O, Fraitag S, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. *Blood*. 2016;127(22):2672-2681.
2. Glavin FL, Chhatwall H, Karimi K. Progressive nodular histiocytosis: a case report with literature review, and discussion of differential diagnosis and classification. *J Cutan Pathol*. 2009;36(12):1286-1292.
3. Durham BH. Molecular characterization of the histiocytoses: neoplasia of dendritic cells and macrophages. *Semin Cell Dev Biol*. 2019;86:62-76.
4. Durham BH, Diamond EL, Abdel-Wahab O. Histiocytic neoplasms in the era of personalized genomic medicine. *Curr Opin Hematol*. 2016;23(4):416-425.
5. Diamond EL, Durham BH, Haroche J, et al. Diverse and targetable kinase alterations drive histiocytic neoplasms. *Cancer Discov*. 2016;6(2):154-165.
6. Janku F, Diamond EL, Goodman AM, et al. Molecular profiling of tumor tissue and plasma cell-free DNA from patients with non-Langerhans cell histiocytosis. *Mol Cancer Ther*. 2019;18(6):1149-1157.
7. Lee LH, Gasilina A, Roychoudhury J, et al. Real-time genomic profiling of histiocytoses identifies early-kinase domain BRAF alterations while improving treatment outcomes. *JCI Insight*. 2017;2(3):e89473.
8. Pinney SS, Jahan-Tigh RR, Chon S. Generalized eruptive histiocytosis associated with a novel fusion in LMNA-NTRK1. *Dermatol Online J*. 2016;22(8).
9. Taylor J, Pavlick D, Yoshimi A, et al. Oncogenic TRK fusions are amenable to inhibition in hematologic malignancies. *J Clin Invest*. 2018;128(9):3819-3825.
10. Nofal A, Assaf M, Tawfik A, et al. Progressive nodular histiocytosis: a case report and literature review. *Int J Dermatol*. 2011;50(12):1546-1551.