CASE REPORT

Progressive nodular histiocytosis with dramatic response to cobimetinib

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INTRODUCTION

Progressive nodular histiocytosis (PNH) is a rare subtype of non-Langerhans cell histiocytosis (non-LCH) first described as characterized by the presence of yellowish papules and dermal nodules with or without mucosal involvement.1 Though difficult to treat, there have been significant developments in describing the pathogenesis and mutational landscape of histiocytic disorders.2,3 We describe a woman with PNH with a remarkable response to targeted therapy identified by mutational analysis.

CASE REPORT

A 71-year-old woman presented to dermatology with a 10-year history of evolving skin eruptions, which initially started as purpuric patches and resolved with topical corticosteroids. Approximately 6 years later, she developed papules and nodules with histopathology demonstrating noncaseating granulomatous inflammation consistent with sarcoidosis; further workup with imaging and ophthalmology evaluation were unremarkable. Several treatments resulted in progressive worsening of her skin lesions, including hydroxychloroquine 400 mg daily and triamcinolone 0.1% ointment, methotrexate 15 mg weekly for 3 months, prednisone 40 mg daily for several months, and infliximab 5 mg/kg once, limited by admission for sepsis. Eighteen months later, she presented with extensive violaceous nodules and plaques with notable sparing of the palms and soles (Fig. 1). Punch biopsies of arm lesions demonstrated diffuse proliferation of epithelioid histiocytes with focal lymphocytes extending to subcutaneous tissue (Fig 2, A and B). Immunohistochemical stains were performed, and the histiocytes were positive for CD68, CD4, and PU.1 (Fig 2, C and D) and negative for S100, CD1a, Langerin, and factor XIIIa. BRAF V600E mutation and PD-L1 were negative. A bone marrow biopsy and positron emission tomography scan were negative, with exception of hypermetabolic activity of the superficial skin nodules. Based on clinical, histopathologic, and systemic workup negative for systemic disease, a diagnosis of PNH was made.

Next-generation sequencing on the skin biopsy was performed and demonstrated mutations with an allele frequency of more than 40% in several genes, including MAP3K1 and JAK2, prompting initiation of treatment with the MEK inhibitor, cobimetinib, which was titrated to 60 mg daily for 21 days in 28-day cycles. Within 5 months, there was a noticeable response to therapy, although improvement of face and neck nodules were not noted until 10 months of treatment (Fig 1, C and D). Dosing was adjusted for elevated creatine phosphokinase during treatment. Monitoring for ocular and cardiac toxicities was performed.

DISCUSSION

Histiocytic disorders comprise a heterogeneous group of more than 100 subtypes that were recently classified into 5 categories: Langerhans (L), cutaneous and mucocutaneous (C), malignant (M), Rosai-Dorfman disease (R), and hemophagocytic
lymphohistiocytosis (H). The C group are non-LCH with broad clinical spectrums and overlapping histopathologic features. PNH is a group C histiocytosis characterized by the presence of progressive and nonremitting yellowish papules (normolipemic xanthomas) and dermal nodules (spindle-cell xanthogranulomas) found most commonly in older patients aged 40 to 60 years. PNH is differentiated from LCH by CD68 positivity, S100 and CD1a negativity, and mucocutaneous-restricted lesions. The management of PNH is challenging. Surgical ablation and excision have been recommended but are not always feasible, as in this case, and may have esthetic and/or functional impact. There are cases of successful medical management; yet, the regimens used—methotrexate, systemic steroids—remain an unreliable approach, with treatment failures reported both in the literature and with our patient.

More recently, mutational analysis-directed therapy has shown promising results. In patients with BRAF V600E mutations, vemurafenib has proven to be effective, particularly in patients with LCH and Erdheim-Chester disease. In 50% of the patients with histiocytic neoplasms without BRAF mutations, MAPK signaling is the primary driver of unregulated cellular proliferation. In a phase II clinical trial of MEK inhibition (ie, cobimetinib), the overall response and 1-year progression-free rates were 89% and 94%, respectively. The remarkable response of our patient to cobimetinib further supports the dependence of histiocytic neoplasms, including PNH, on MAPK signaling. Mutational analysis and molecular-directed therapy offer a promising treatment approach to patients with this heterogeneous group of disorders and uncommon diseases.

Fig 1. Clinical photographs of progressive nodular histiocytosis and improvement with cobimetinib therapy. Dermal nodules coalescing into plaques on the upper portion of the back and neck (A) and shoulders (C) with improvement after 10 cycles of cobimetinib (B, D).
Conflicts of interest
None disclosed.

REFERENCES

Fig 2. Histopathology of progressive nodular histiocytosis. Proliferation of epithelioid histiocytes in the dermis with focal infiltration of lymphocytes in the subcutaneous tissue (A, Hematoxylin-eosin stain; original magnifications: ×2). Epithelioid histiocytes in the dermis (B, Hematoxylin-eosin stain; original magnification: ×20). Immunohistochemical stains demonstrated that the cells were positive for CD4 (C, Original magnification: ×20) and PU.1 (D, Original magnification: ×20).