CASE REPORT

Generalized indeterminate cell histiocytosis successfully treated with methotrexate

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INTRODUCTION

Histiocytic diseases are a group of disorders characterized by the proliferation of monocytes, macrophages, and dendritic cells. First described by Wood et al1 in 1985, indeterminate cell histiocytosis (ICH) is a very rare histiocytic disease with clinical and histopathologic overlap with both Langerhans cell histiocytosis (LCH) and non-LCH. Clinically, the lesions present as either solitary or multiple papulonodules on the face, neck, trunk, or extremities. ICH has been described in both children and adults with no sex predilection. Here, we describe a case of generalized ICH in a male patient who responded to low-dose methotrexate therapy. This is, to our knowledge, the second case described in the literature.2

CASE REPORT

A 70-year-old male peanut farmer presented to our clinic for an evaluation of disseminated mildly pruritic papules. The skin lesions began 3 years prior to presentation and had progressively increased in both number and affected area over time without signs of regression. A skin biopsy performed by an outside dermatologist demonstrated granulomas, and the patient was given a diagnosis of sarcoidosis. He was treated with topical steroids and hydroxychloroquine without improvement prior to presenting to our clinic. His past medical history was significant for lumbar stenosis status postlaminectomy complicated by Pseudomonas-associated osteomyelitis and now on lifelong ciprofloxacin therapy. He also had a remote history of bladder cancer status postintralesicular Bacillus Calmette-Guérin immunotherapy.

A total body skin examination revealed numerous, firm, nontender, erythematous papules ranging in size from 0.5 to 0.7 cm on the face, neck, trunk, and extremities (Fig 1). No palpable lymphadenopathy or organomegaly was appreciated. We performed a repeat skin biopsy, which demonstrated a diffuse and nodular nonepidermotropic dermal infiltrate composed of crowded histiocytoid cells and a minor inflammatory component featuring lymphocytes, histiocytes, plasma cells, and rare eosinophils (Fig 2). Based on immunohistochemistry studies, the tumor cells were positive for CD1a and S100 (Fig 3, A and B), but negative for langerin or CD207 (Fig 3, C). His clinical presentation and histopathologic findings supported the diagnosis of ICH.

His laboratory workup, which included a complete blood count, complete metabolic panel, immunoglobulin panel, lactate dehydrogenase, bone marrow studies (aspirate, flow cytometry, and fluorescence in-situ hybridization), and whole-blood flow cytometry were all normal. Serology tests for HIV and viral hepatitis were negative. A test for the BRAF V600 mutation was negative in the neoplastic cells (sequencing analysis of BRAF gene mutations technique). Whole-body positron emission

Abbreviations used:
ICH: indeterminate cell histiocytosis
LCH: Langerhans cell histiocytosis
PUVA: psoralen and ultraviolet A
tomography—computed tomography showed no evidence of malignancy.

The patient initially underwent psoralen and ultraviolet A therapy (PUVA) for 4 months with minimal response. We then discontinued PUVA and commenced treatment with methotrexate 15 mg weekly. After 6 months on methotrexate, the patient showed significant improvement with flattening of his skin lesions in all affected areas: the face, neck, trunk, and extremities (Fig 4).

DISCUSSION

ICH is a very rare, clinically diverse, proliferative disorder of the histiocytes. Clinical features, immunophenotype, and histopathology are all key to making a diagnosis of ICH. Given the unclear relationship with Langerhans cells and the origin and maturation state of indeterminant cells, the classification of ICH has remained in flux since its initial description. The clinical differential diagnosis includes generalized eruptive histiocytosis, which is a non-LCH that likely represents a variant of juvenile xanthogranuloma. Indeterminant cells demonstrate positivity for CD68, an antigenic marker of non-LCH. However, indeterminant cells are positive for CD1a and S100, which are sensitive, but nonspecific markers for Langerhans cells. Interestingly, indeterminant cells are negative for CD207 (langerin) and lack the typical Birbeck granules on electron microscopy that are highly specific and pathognomonic for Langerhans cells. Taken together, the histopathological features of ICH suggest that it likely
represents multiple entities that exist on a spectrum of LCH and non-LCH.

Given the limited number of reported cases, ICH is often misdiagnosed initially, as was the case with our patient. The course of ICH is variable, ranging from spontaneous remission to stable disease, with remission followed by recurrence also reported in the literature. ICH is primarily a cutaneous condition, but 1 in 5 reported cases have been associated with the presence of a second hematopoietic malignancy, such as chronic myelomonocytic leukemia and low-grade B-cell lymphoma. Overall, however, the scarcity of cases makes it difficult to establish a definitive association with malignancy at this time. Additionally, while not found in our patient, the presence of a BRAFV600E mutation, prevalent in LCH and Erdheim-Chester disease, has also been reported for ICH, but given the rarity, the role of this mutation in the biology of ICH remains to be elucidated.

ICH is generally a benign indolent condition, and aggressive treatment is often not necessary. Given the rarity of this condition, there is currently no standard treatment protocol. Chemotherapies used with reported success include cyclophosphamide, etoposide, vinblastine, and 2-chlorodeoxyadenosine. More recently, there have been reports of success with PUVA, narrow-band ultraviolet B, thalidomide, pravastatin, low-dose methotrexate, and surgical excision for solitary lesions. Although often effective, phototherapy appears to be less successful for treating lesions on the face. Low-dose methotrexate may represent an effective alternative with a more favorable side-effect profile compared with other antineoplastic treatments for ICH, especially in individuals with facial involvement who may not respond well to phototherapy or surgeries. The risk of recurrence following discontinuation of methotrexate remains to be determined.

After failing to improve on PUVA therapy, our patient switched to low-dose methotrexate and demonstrated significant clinical improvement following 6 months of therapy, with diffuse flattening of all lesions on his face, neck, trunk, and extremities.

Fig 3. Immunohistochemical stain of punch biopsy specimen of the left part of the chest. CD1a diffusely positive in dermal histiocytoid cells and epidermal Langerhans cells. S100 (Langerin) negative in dermal infiltrate and positive in epidermal Langerhans cells. (A, CD1a stain; original magnification, ×40; B, S100 stain; original magnification, ×40; C, CD207 stain; original magnification, ×40)
Conflicts of interest
None disclosed.

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Fig 4. Six months after treatment with low-dose methotrexate, diffuse flattening of the papules on the face (A), chest (B), and back (C, D) were observed.