Drug-induced sarcoidosis in a patient treated with an interleukin-1 receptor antagonist for hidradenitis suppurativa

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Key words: anakinra; interleukin; sarcoidosis.

INTRODUCTION

Numerous reports document cases of iatrogenic sarcoidosis or sarcoidlike granulomatosis in the setting of biologic therapy with interferon (IFN)-α, tumor necrosis factor (TNF)-α inhibitors, and, most recently, immune checkpoint inhibitors. Anakinra, an interleukin (IL)-1 receptor antagonist (IL-1Ra), has only been reported once in the literature to induce sarcoidlike granulomatosis in a patient with TNF receptor–associated periodic syndrome.[1] In this report, IL-1Ra–induced sarcoidal granulomas are postulated to be caused by the upregulation of type 1 IFN and IL-1 cytokine pathway inflammation.

Abbreviations used:

IFN:	interferon
IL:	interleukin
IL-1Ra:	interleukin-1 receptor antagonist
Th1:	T helper cell type 1
TNF:	tumor necrosis factor

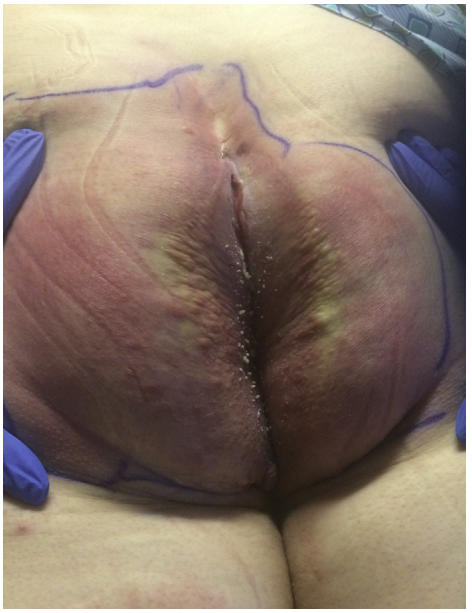

Fig 1. Anakinra-induced sarcoidosis. Buttock erythematous plaque eruption while on anakinra for hidradenitis suppurativa.

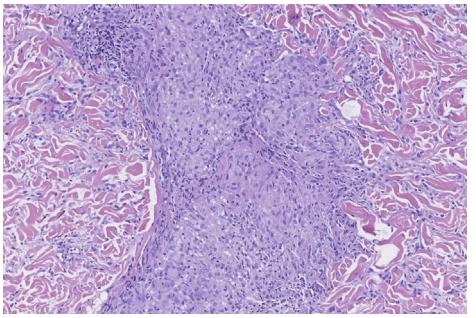

Fig 2. Anakinra-induced sarcoidosis. Histologic confirmation on noncaseating epithelioid granulomas. (Hematoxylin-eosin stain; original magnification: ×10.) Courtesy of Jonathan Ho, MD UPMC Dermatopathology.

CASE REPORT

A 48-year-old woman with long-standing pathology-confirmed chronic hidradenitis suppurativa (Hurley stage III), sequentially treated with doxycycline, minocycline, clindamycin-rifampin, cyclosporine, and adalimumab, was taking anakinra monotherapy (100 mg/d subcutaneous injection for 9 months followed by 200 mg/d subcutaneous

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Table I. Drugs that induce cutaneous sarcoidosis and proposed biologic mechanisms of induction

Drug	Biologic mechanism
IL-1Ra: anakinra[1]	• Unopposed type I IFN production • Failure of immune regulatory mechanisms • Immunosuppression favoring infection with bacterium implicated in sarcoidosis
Interferon-α[3]	• Induction of Th1 cytokines
anti-TNF agents[4,5]: entanercept,[6] infliximab,[7] adalimumab[8]	• Unopposed type I IFN production • Move toward a Th1/Th17 profile • Decreased TNF-mediated suppression of Treg expansion/activity • Alteration in ratio of membrane bound to soluble TNFR2 • Process of anti-IFX antibody production • Predisposition secondary to genetic variation of TNF-α gene
PD-1 inhibitors: pembrolizumab,[9] nivolumab[10]	• Increased T-cell proliferative capacity • Note: PD-1 up-regulation has also been associated with sarcoidosis with a proposed mechanism of decreased T-cell proliferative capacity leading to immunologic derangements conducive to sarcoidosis
BRAF inhibitor: vemurafenib[11]	• Increased TNF-α and IFN-γ levels • Note: Study suggests patients who have sarcoidosis with vemurafenib therapy carry a better prognosis
anti-CTLA4 mAb: ipilimumab[12]	• Enhanced T-cell responses
anti-IgE mAb: omalizumab[13]	• Decreased expression of dendritic cell IgE high affinity receptor/Th2 cytokine production with subsequent shift from Th2 to Th1 cytokine profile • Unmasking of sarcoidosis with prednisone taper accompanying omalizumab treatment initiation
Fillers for aesthetic procedures: hyaluronic acid[14]	• Tissue injury and foreign body reaction to filler
Insulin[15,16]	• Traumatic induction (Koebnerization) and foreign body reaction to materials introduced with insulin injection • Inflammatory response to zinc component of insulin formulation
Botulinum neurotoxin A[17]	• Foreign body reaction after deposition of crystalline preparation of botulinum neurotoxin A in the skin • Foreign body reaction after accidental inoculation of a separate material during injection
Desensitization injections[18]	• Inoculation of antigens (aluminum and others) into the subcutaneous tissue at time of injection
Ophthalmic drops with sodiumbisulfate[19]	• Foreign body reaction to known sensitizer implicated in delayed type hypersensitivity reactions (sulfur)
Leuprorelin injections[20]	• Subcutaneous granulomatous hypersensitivity reaction

injection for 15 months) when she presented with acute onset of a tender, warm, erythematous, plaque-like eruption on the bilateral buttocks (Fig 1). The patient was admitted to the hospital for a presumed soft tissue infection from chronic immunosuppression. Blood cultures and IFN-γ release assay were negative. A skin biopsy found an exuberant granulomatous process comprised predominantly of naked noncaseating granulomas throughout the dermis (Fig 2). Fite, acid-fast bacilli, fungal, and bacterial stains were negative. A workup for sarcoidosis was initiated. The patient's complete blood count with differential, basic metabolic panel, serum Ca^{2+}, and thyroid function tests were all within normal limits. Electrocardiogram, transthoracic echocardiogram, chest radiography, and dilated fundal examinations found nothing consistent with sarcoidosis. The patient deferred colonoscopy, as she had no signs or symptoms of inflammatory bowel disease. Anakinra was discontinued, as the treatment was only moderately successful and because of new literature on anti—IL-17 effectiveness in hidradenitis suppurativa. The buttock eruption improved over 4 months with no therapy until secukinumab was approved. The eruption showed no residual activity at the last clinical evaluation performed 11 months after the cessation of anakinra.

DISCUSSION

Granulomatous drug eruptions consist of drug-induced reactive granulomatous disease, accelerated rheumatoid nodulosis, drug-induced granuloma annulare, and drug-induced sarcoidosis.[2] Drug-induced sarcoidosis (Table I) may cause polymorphic skin lesions and possible systemic involvement weeks to months after drug initiation.[1,20] Diagnosis of isolated single-organ sarcoidosis or sarcoidlike granulomatosis depends on the evolving definition of sarcoidosis and acknowledgement of a single organ variant.[20] The most frequently cited cause of drug-induced sarcoidosis is IFN-α, a type I IFN thought to induce sarcoid granuloma formation via induction of a predominant T helper cell type 1 (Th1) cytokine response.[2] Granuloma formation is predominantly Th1, with IFN and TNF critical cytokines; however, TNF inhibitor–induced granulomas are more confusing. The formation of anti-TNF drug-induced psoriasis and sarcoid granulomas, theoretically results from imbalances in TNF receptor 2–mediated activation of regulatory T cells and eventual Th1 T cells or enhancement of local IFN-γ.[4,5] Immune checkpoint inhibitors can induce sarcoidosis by modifying cytotoxic, Th1/17 and regulatory T-cell ratios.[10,21]

A similar mechanism may underlie the induction of sarcoidosis in the setting of anakinra, a recombinant IL-1 receptor antagonist that competitively blocks IL-1. Studies support a strong counter-regulation effect between IL-1 and type I IFN cytokine pathway, with elevated levels of IL-1b potently antagonizing type I IFN.[22] Thus, anakinra therapy may mitigate regulatory mechanisms on type I IFN leading to a paradoxical increase in granulomatous inflammation and a predominant Th1 cytokine response.

In this case, resolution of cutaneous symptoms after cessation of anakinra therapy suggests anakinra-induced sarcoidosis. As such, this report supports expansion of the classes of drugs associated with drug-induced sarcoidosis to include IL-1 receptor antagonists. The diagnosis of drug-induced sarcoidosis is complicated both by the variable time lapse between drug initiation and lesion presentation and the heterogeneous clinical presentation of the disease.[19] Thus, it is important to maintain a high index of suspicion for drug-induced sarcoidosis in patients on biologic therapies including anakinra.

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