Idiopathic Granulomatous Mastitis as a Complication of Interferon-alpha Therapy

Sir,

Idiopathic granulomatous mastitis (IGM) is a benign, disfiguring, chronic, inflammatory breast disease of unknown etiology.[1,2] It was first described by Kessler and Wolloch in 1972.[3] Histologically, it is characterized by an inflammatory infiltrate with Langerhan's giant cells. It has been associated with hormonal contraceptive use and hyperprolactinemia, and is thought to be an autoimmune phenomenon. Other etiologies of granulomatous disease, such as tuberculosis, sarcoidosis, Wegener's granulomatosis, syphilis, mycotic infections, foreign body reaction, giant cell arteritis and polyarteritis nodosa, can cause a similar clinical picture and must be excluded. Glucocorticoids and other immunosuppressive therapies are often helpful in the management of IGM. We present a case of IGM occurring in the setting of therapy for HCV with interferon alpha-2a and ribavirin.[4]

A 40-year-old African American woman presented with painful and erythematous nodules on both breasts one month after starting the treatment for hepatitis C with pegylated interferon alpha-2a and ribavirin. She also had a history of human immunodeficiency virus (HIV) infection, with CD4 cell count 412 (26%) and an undetectable viral load on tenofovir/emtricitabine and boosted fosamprenavir, hepatitis C virus (HCV), and diabetes. She was not married and had never been pregnant before. However, within 10 days, the nodules started to ulcerate, and she developed serous drainage from both breasts. She was empirically treated with trimethoprim/sulfamethoxazole. Culture from the drainage grew *Pantoea agglomerans*, which was sensitive to trimethoprim. A week later, the breast drainage became more purulent. Physical examination revealed tender ulcers on bilateral breasts as shown in Figure 1a. Mammogram showed benign fibronodular elements in both breasts. Ultrasound revealed multiple complex cystic masses of varying sizes. Biopsy [Figure 2] revealed severe acute and chronic inflammation, with scattered multinucleated giant cells and fat necrosis consistent with granulomas. Acid-fast bacilli (AFB), periodic acid-Schiff (PAS), and gram stains were all negative. The non-caseating granulomas were not consistent with sarcoidosis. Rapid plasma regain (RPR), antinuclear antigen (ANA), p-ANCA, c-ANCA, prolactin levels (20 ng/ml) and chest X-ray were unremarkable. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were not elevated. Pegylated interferon alpha-2a and ribavarin therapy were stopped for the fear of aggravating an infectious process. The breast lesions progressively improved [Figure 1b]. One month later, her symptoms and signs had completely resolved. Our patient represents a probable case of interferon-alpha-induced severe idiopathic granulomatous mastitis with Naranjo adverse drug reaction probability score of five.

IGM typically affects women of childbearing age. The true prevalence of IGM is not really clear. Baslaim *et al*., reviewed their cases of IGM and concluded that they represented 1.8% of cases out of 1106 women with benign breast diseases.[5]

This disease entity has to be considered in the differential diagnosis for ulcerative disfiguring breast lesions. It may mimic a malignancy,[6] resulting in extensive and expensive diagnostic investigations. IGM is usually unilateral. However, it may be bilateral,[7] as in the case we have presented here. IGM is a diagnosis of exclusion with classic histopathological findings such as lobular non-caseating granulomas with epithelioid histiocytes, multinucleated giant cells, and a predominantly neutrophilic background with attendant lymphocytes, plasma cells and eosinophils in varying numbers without necrosis and negative microbiological investigation.[5]

Corynebacterium kroppenstedtii breast infection has recently been hypothesized to be associated with IGM but remains unconfirmed.[8] In our patient, the cultures grew *Pantoea agglomerans*, which is an emerging pathogen that causes systemic infections in immunosuppressed and localized infections in immunocompetent hosts. We propose that infection with this Gram negative organism could have potentially been the antigenic trigger that contributed to the development of the granulomatous mastitis.

Pegylated interferon-alpha, used in the therapy of hepatitis C, is synthesized by adding a polyethylene glycol molecule to the standard interferon structure, and it has antiviral, antiproliferative in addition to its immunomodulating properties. The most notable adverse effect of interferon therapy is flu-like symptoms and fatigue. Interferon has been well described to

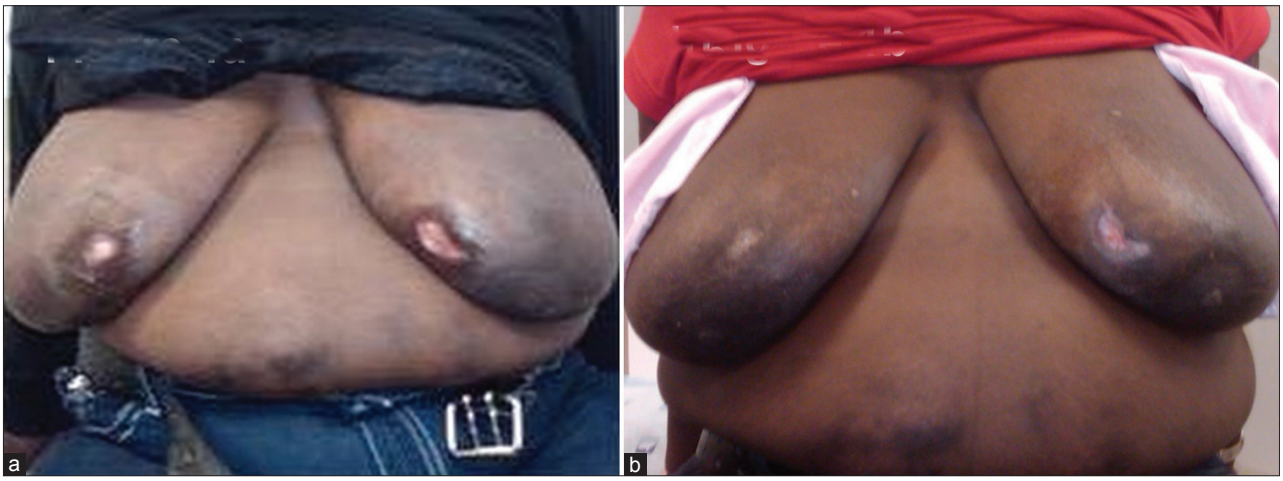

Figure 1: Bilateral ulcerated breast lesions that appeared after initiation of interferon therapy

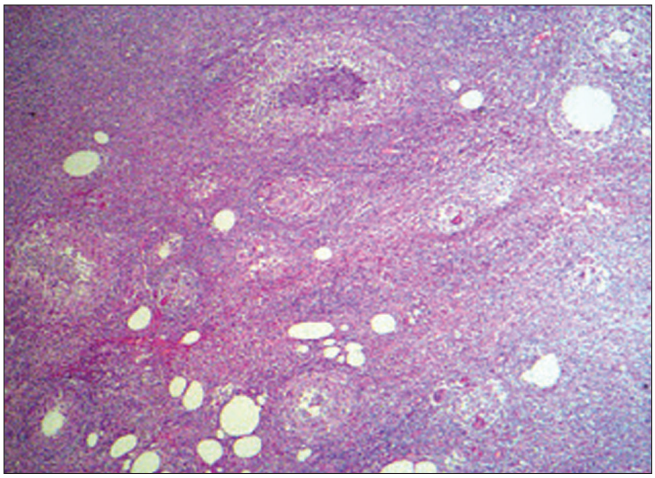

Figure 2: Histological findings showing idiopathic granulomatous mastitis characterized by epithelioid and multinucleated giant cell granulomas within a neutrophilic infiltrate (enlarged × 10)

cause autoimmune, cardiovascular, dermatological, endocrinological, hematological, neurological, psychiatric, and renal side effects. Interferon-alpha augments the differentiation of Th1 lymphocytes and the down-regulation of Th2 lymphocyte activation, favoring the formation of granulomas in susceptible patients. Pegylated interferon-alpha has clearly been demonstrated to be superior to classic interferon-alpha for the intensification of Th1 immune response and it increases the likelihood of developing a granulomatous reaction. This is the first case of IGM that occurred during pegylated interferon and ribavarin therapy.

The initial management should be conservative, since a significant proportion of patients will improve without intervention.[9] Al-Khaffaf *et al*., retrospectively reviewed cases of IGM over 25 years and concluded that regardless of the therapeutic management, which included steroids, antibiotics, and surgical intervention alone or in combinations, this disease entity resolves completely in 6 to 12 months.[1] Proposed treatments have included 0.8 mg/kd/day of prednisone for 2 weeks and immunosuppressive therapies, such as methotrexate and azathioprine. Surgical excision should be considered in refractory cases of IGM.[10] Complications may include sinus tract and fistula formation. Recurrence is common.

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References

1. Al-Khaffaf B, Knox F, Bundred NJ. Idiopathic granulomatous mastitis: A 25-year experience. J Am Coll Surg 2008;206:269-73.
2. Rowe PH. Granulomatous mastitis associated with a pituitary prolactinoma. Br J Clin Pract 1984;38:32-4.
3. Kessler E, Wolloch Y. Granulomatous mastitis: A lesion clinically simulating carcinoma. Am J Clin Pathol 1972;58:642-6.
4. Sato N, Yamashita H, Kozaki N, Watanabe Y, Ohtsuka T, Kuroki S, *et al*. Granulomatous mastitis diagnosed and followed up by Fine-needle aspiration cytology, and successfully treated by corticosteroid therapy: Report of a case. Surg Today 1996;26:730-3.
5. Baslaim MM, Khayat HA, Al-Amoudi SA. Idiopathic granulomatous mastitis: A heterogeneous disease with variable clinical presentation. World J Surg 2007;31:1677-81.
6. Tuli R, O'Hara BJ, Hines J, Rosenberg AL. Idiopathic granulomatous mastitis masquerading as carcinoma of the breast: A case report and review of the literature. Int Semin Surg Oncol 2007;27:4:21.
7. Carmalt HL, Ramsey-Stewart G. Granulomatous mastitis. Med J Aust 1981;1:356-9.
8. Taylor GB, Paviour SD, Musaad S, Jones WO, Holland DJ. A clinicopathological review of 34 cases of inflammatory

breast disease showing an association between corynebacteria infection and granulomatous mastitis. Pathology 2003;35:109-19.
9. Raj N, Macmillan RD, Ellis IO, Deighton CM. Rheumatologists and breasts: Immunosuppressive therapy for granulomatous mastitis. Rheumatology (Oxford) 2004;43:1055-6.
10. Erozgen F, Ersoy YE, Akaydin M, Memmi N, Celik AS, Celebi F, *et al*. Corticosteroid treatment and timing of surgery in idiopathic granulomatous mastitis confusing with breast carcinoma. Breast Cancer Res Treat 2010;123:447-52.

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