

## An Unusual Cause of Oligoarthritis and Erythema Nodosum: Idiopathic Granulomatous Mastitis

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### ABSTRACT

Idiopathic granulomatous mastitis (IGM) is an unusual benign inflammatory disease of breast. Breast cancer mimics IGM both radiologically and clinically. However, IGM is a benign disease and awareness of such an entity prevents unnecessary surgical procedures. Although its etiology is unknown, it may be an autoimmune disease. There are few patients reported in the literature presenting with reactive arthritis and/or erythema nodosum accompanying IGM of breast. Granulomatous mastitis should be considered as a possible underlying cause of arthritis and erythema nodosum. In this article, we report this interesting association of IGM as an underlying cause of arthritis and generalized erythema nodosum in a 32-year-old female patient. Comprehensive examination for granulomatous mastitis showed no apparent underlying cause. Indomethacin was beneficial in treatment of arthritis and erythema nodosum. Resistant IGM was responsive to colchicine treatment. Clinical management and therapeutic approach have been discussed in detail.

**Keywords:** Arthritis; erythema nodosum; idiopathic granulomatous.

Idiopathic granulomatous mastitis (IGM) is an unusual chronic inflammatory panniculitis of breast characterized by non-caseating granulomas.<sup>1</sup> Although IGM is a rare disease, it is highly important to consider IGM in differential diagnosis of breast lesions due to its imitation of breast cancer both clinically and radiologically.<sup>2</sup> Disease has a chronic course; it begins with a tender mass in breast, proceeding to fistulae, sinus tract, and scar formation. There are many theories about the etiology of IGM, including autoimmunity, trigger with trauma, prolactinemia, hormonal, alpha-1 antitrypsin deficiency, and infections; however, these theories have not been proven yet.<sup>3</sup> It has been rarely associated with oligoarthritis and erythema nodosum (EN) in the literature.<sup>4-10</sup>

In this article, we discuss the diagnostic, clinical, and therapeutic approach to a unique case with granulomatous mastitis, EN, and arthritis

that may be of interest to clinicians who are not readily familiar with this condition.

### CASE REPORT

A 32-year-old multiparous female patient was admitted to dermatology department with one-month history of a palpable mass in breast and multiple red tender nodules on extremities and polyarthralgia (Figure 1a, b). Medical history of the patient was insignificant. There was no history of parturition, breastfeeding, or oral contraceptive drug use in the past two years. A written informed consent was obtained from the patient.

Tender red mass with skin retraction (3x2 cm diameter) was located on superior of right areola. Two lymph nodes at right axillary region were palpable. Widespread erythematous tender

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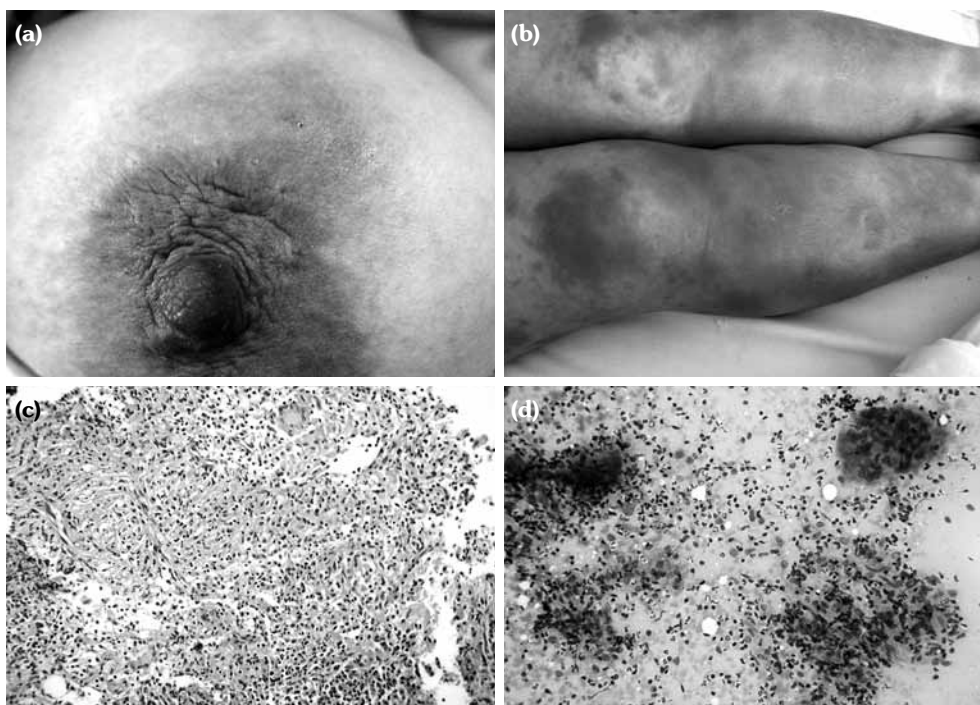
nodules on extensor surfaces on extremities consistent with EN were observed. Patient had arthritis of the left ankle with swelling and polyarthralgia.

Vital examination for fever was normal. Acute phase reactants were elevated [erythrocyte sedimentation rate: 105 mm/hour (normal, 0-20)], [C-reactive protein levels: 241 mg/L (normal, 0-3)]. Leukocyte count was normal ( $9.6 \times 10^{12}/L$ ).

Ultrasound examination of breast excluded breast abscess. Diagnostical fine needle aspiration biopsy was performed to rule out malignancy. Cytological examination was compatible with non-necrotizing granulomatous inflammation consisting of neutrophils, lymphocytes, and multinucleated histiocytic giant cells (Figure 1c, d).

Protein purified derivative intradermal test on flexural area of forearm was anergic (0 mm). QuantiFERON®-TB Gold In-Tube test (QFT, Qiagen, Valencia, USA) was also negative. Extrapulmonary tuberculosis of breast was

excluded with negative tuberculosis cultures (repeated three times), polymerase chain reaction test (repeated three times), and acid fast bacilli staining from aspiration material of the lesion. On thorax computed tomography, there was a 6 mm nodule in left lower lobe located in subpleural area and few nodules smaller than 4 mm in diameter compatible with intrapulmonary lymph nodes in left fissure were observed. Angiotensin converting enzyme level was within normal range [14 U/L (normal, 8-52 U/L)]. Sarcoidosis and tuberculosis were excluded with these findings. Bacterial and fungal cultures were negative. Patient did not have signs of a systemic disease. Autoimmune markers (antinuclear antibody, anti-neutrophil cytoplasmic antibody) were negative and rheumatoid factor level was within normal range [ $<10$ , (normal, 0-14)]. Prolactin level was normal [5.44 ng/mL (normal, 3.3-26.7)]. Through biopsy and exclusion of other possible diseases leading to granulomatous inflammation, patient was diagnosed as IGM accompanied by EN and arthritis.



**Figure 1.** (a) Right breast superior of areola, palpable hard nodule, with erythema on skin. (b) Diffuse erythematous nodular lesions on lower extremities. (c) Granulomatous inflammation infiltrating normal breast tissue (H-E  $\times 200$ ). (d) Cytological smear reflecting granulomatous reaction with dense neutrophil leukocyte infiltration, epithelioid histiocytic cell layers, and multinucleated histiocytic giant cells (May-Grunwald-Giemsa,  $\times 200$ ).

Initial treatment was indomethacin (50 mg three times a day) and potassium iodide saturated solution (6 drops x3/day). EN and arthritis regressed with this therapy. Indomethacin and potassium iodide solution was discontinued and colchicine (3x0.5 mg/day) was started for IGM. On follow-up of three months; EN and arthritis regressed completely and IGM regressed partially (50%) in size. Patient was free of symptoms and no relapse was observed through colchicine monotherapy (2x0.5 mg/day) in follow-up of 20 months.

### DISCUSSION

Nodular relapsing panniculitis of unknown origin with associated lipoatrophy, fever and lipophagia was originally described as “Weber-Christian disease”.<sup>11,12</sup> When previously published Weber-Christian Disease cases were reevaluated, most of them were diagnosed with new diagnoses including cytophagic panniculitis, calciphylactic panniculitis, fat necrosis with pancreatitis, connective tissue panniculitis and others.<sup>13</sup> With improved ability to identify these conditions, the term “Weber-Christian disease” has largely been abandoned in favor of the more specific diagnoses.<sup>13,14</sup> IGM is a subtype of panniculitis with granulomatous inflammation, which was first described by Kessler and Wolloch as an uncommon disease of females in reproductive years which can mimic various inflammatory and malignant

disorders.<sup>1,3</sup> IGM is a diagnosis of exclusion once infection, malignancy, foreign body reaction, and other autoimmune disorders have been ruled out. In our case, underlying causes were excluded with medical history, laboratory tests, radiology, and pathology. Many etiological factors including local irritation, oral contraceptive use, viruses, parasites, mycotic diseases, hyperprolactinemia, diabetes mellitus, smoking, alpha-1 antitrypsin deficiency, and autoimmunity have been suggested in pathogenesis of IGM, but none of them have been proven yet.<sup>2</sup>

Usually, IGM presents with unilateral mass, breast pain, nipple inversion, and axillary lymphadenopathy. Histopathological examination of biopsy material from the center of lesion is valuable for accurate diagnosis.<sup>15</sup> Granuloma formations, dense neutrophilic infiltration on the background without necrosis are pathological findings of IGM. Granulomatous lobular mastitis with exclusion of other causes of granulomatous inflammation of breast (infections (tuberculosis, actinomyces) and systemic diseases (sarcoidosis, Wegener granulomatosis) is necessary for diagnosing IGM.<sup>2</sup> It has been suggested that a microorganism that has not been isolated with current techniques in cultures may lead to microabscess formation of IGM.<sup>2</sup> Taylor et al.<sup>16</sup> detected *Corynebacterium* in 41% of 34 isolated IGM lesions. Causal relationship was not confirmed since *Corynebacterium* is a member of normal flora. In our patient,

**Table 1.** Patients with triad of idiopathic granulomatous mastitis, erythema nodosum, and arthritis

	Age (year)	Hormonal status	Arthritis	Erythema nodosum	Evidence of underlying cause	Treatment	Treatment response	Relapse
Our case	32	-	Left ankle Polyarthralgia	UE LE	None	Indomethacin Colchicine	PR R	No
Salesi et al. <sup>5</sup>	23	Pregnant 28 weeks	Both knees and ankles Polyarthralgia	LE	None	Prednisolone  Colchicine Azathioprine	R	No follow-up
Nakamura et al. <sup>7</sup>	23	-	Polyarthralgia	LE	None	Prednisolone Prednisolone + methotrexate	PR R	Relapse during tapering No
Nakamura et al. <sup>9</sup>	27	-	Polyarthritits	UE LE	None	Oral antibiotics Prednisolone	No response R	No
Binesh et al. <sup>8</sup>	40	-	Oligoarthralgia	LE	None	Prednisolone	PR	No
Adams et al. <sup>22</sup>	24	-	Polyarthralgia	LE	ARB from breast positive Culture: negative	Rifampicin + isoniazide Indomethacine	No response R	No
Olfatbakhsh et al. <sup>4</sup>	30	Pregnant 32 weeks	Right ankle	LE	None Chest X-ray not done	Corticosteroid 45 mg/day		Relapse at postpartum period
Zabetian et al. <sup>10</sup>	43	-	Bilateral knees and ankles	UE LE	None Cough (+)	Prednisolone 80 mg/day tapering in 3 months Azathioprine 100 mg/day maintenance		No

UE: Upper extremity; LE: Lower extremity; PR: Partial response; R: Complete response; ARB: Acid-resistant bacilli.

*Corynebacterium* was not detected in the cultures.

In the literature, association of EN, IGM, and arthritis has been reported in seven cases up until now including the presented case (Table 1).<sup>4-10</sup> Two of these reports were associated with pregnancy and lesions had appeared in third trimester.<sup>4,5</sup> Arthritis accompanying IGM regresses concurrently with resolution of IGM, which suggests that arthritis in these cases was the result of a reactive process.<sup>6,8,10</sup>

Mild IGM usually resolves spontaneously with drainage. Resolution time may prolong up to 9 to 12 months. Moderate and severe disease require systemic treatment.<sup>17,18</sup> Surgery is not recommended due to slow wound healing after the operation. Methotrexate is reported as an effective treatment option in a few studies.<sup>19,20</sup> In case series regarding IGM therapy, colchicine, hydroxychloroquine and systemic steroids were reported to be equally efficient treatment modalities.<sup>21</sup> Despite therapy, relapses may be observed. IGM in our case was unresponsive to non-steroid anti-inflammatory drugs. Colchicine was preferred to suppress neutrophilic inflammation.

Idiopathic granulomatous mastitis is a rare neglected diagnosis which is important in differential diagnosis of breast cancer. Colchicine is an optimal therapy with low side effect profile in severe cases without spontaneous resolution. Even though current knowledge does not allow us to definitely claim that EN, arthritis, and accompanying IGM triad is an autoimmune reactive process, successful treatment with immunosuppressives and lack of an underlying cause may suggest an autoimmune mechanism.

#### Declaration of conflicting interests

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