IDIOPATHIC GRANULOMATOUS MASTITIS ASSOCIATED WITH ERYTHEMA NODOSUM: CASE REPORT AND LITERATURE REVIEW

Ferhat Arslan[1], Ergenekon Karagöz[2], Birsen Yiğit Arslan[3], Bahadır Ceylan[1], Gülhan Ertan[4], Ali Mert[5]

[1]Department of Infectious Diseases and Clinical Microbiology, Istanbul Medipol University Hospital, Istanbul
[2]Department of Infectious Diseases and Clinical Microbiology, GATA Haydarpasa Training Hospital, Istanbul
[3]Department of Anesthesiology and Reanimation, Esenyurt State Hospital, Istanbul
[4]Department of Radiology, İstanbul Medipol University Hospital, Istanbul
[5]Department of Internal Medicine, İstanbul Medipol University Hospital, Istanbul

ABSTRACT

Idiopathic granulomatous mastitis (IGM) is an uncommon inflammatory disease of the breast. Differential diagnosis and exclusion of breast cancer is the most challenging issue for patients and physicians. IGM may be differentiated from cancer and other diseases with histopathological evaluation; however, the response to empirically initiated steroid therapy may sometimes be useful to distinguish it from other diseases. In this context, whether erythema nodosum may assist in the IGM diagnosis is an unasked question. Here we present the case of a 30-year-old woman presenting with tenderness, redness and discharge in her left breast accompanied by a mass, together with pain in her ankles, the findings of IGM and erythema nodosum (EN). We aim to review the medical literature regarding the association between IGM and EN. IGM should be primarily considered when a patient presents with signs of inflammatory breast disease and EN.

Keywords: *Idiopathic granulomatous mastitis, erythema nodosum, inflammatory breast disease.* ***Nobel Med 2016; 12(1): 101-105***

ERİTEMA NODOSUM'UN EŞLİK ETTİĞİ İDİYOPATİK GRANÜLOMATÖZ MASTİT VAKASI: OLGU SUNUMU VE LİTERATÜR DERLEMESİ

ÖZET

İdiyopatik granülomatöz mastit (İGM), memenin etyolojisi çok iyi bilinmeyen ve nadir görülen bir inflamatuar hastalığıdır. Meme kanserini taklit edebilmesiyle önem kazanan bu durum, ayırıcı tanı ve meme kanserlerinin dışlanması aşamasında hasta ve klinisyen açısından zorlayıcı olabilmektedir. İGM tablosu kanser ve diğer hastalıklardan histopatolojik inceleme ile ayırt edilse de, ampirik başlanılan steroid tedavisinden alınan olumlu yanıt da İGM'nin diğer hastalıklardan ayırt edilmesinde klinisyene yarar sağlayabilir ve hekim açısından yol gösterici olabilir. Bu bağlamda, eritema nodozumun (EN) da İGM'nin tanısında destekleyici bir bulgu olup olamadığı hususu daha önce sorgulanmamış bir konudur. Burada, sol memede kitlenin de eşlik ettiği ağrı, kızarıklık, hassasiyet ve akıntı yakınmaları olan, beraberinde her iki ayak bileğinde ağrının var olduğu eritema nodozum ve idiyopatik granülomatöz mastit bulguları ile presente olan 30 yaşındaki bir kadın hasta sunulmuştur. Bu yazıda aynı zamanda medikal literatürdeki İGM ve EN arasındaki birliktelik ve ilişkiyi de tartışmayı amaçladık. İnflamatuar meme hastalığı ve EN bulguları ile prezante olan olgularda İGM ayırıcı tanılar arasında ilk planda düşünülmelidir.

Anahtar kelimeler: İdiyopatik granülomatöz mastit, eritema nodozum, inflamatuar meme hastalığı. **Nobel Med 2016; 12(1): 101-105**

INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is an uncommon inflammatory disease of the breast. In fact, its similarity to inflammatory breast cancer - which is a rare type of breast cancer with poor prognosis - may lead clinicians to apply unnecessary interventions and patients to experience extra anxiety. In addition, granulomatous diseases such as tuberculous mastitis and sarcoidosis must be considered in the differential diagnosis of IGM. IGM may be differentiated from cancer and other diseases with histopathological evaluation; however, the response to empirically initiated steroid therapy may sometimes be useful for distinguishing it from other diseases. In some studies, the presence of erythema nodosum and arthritis has been reported as a predictor for finding IGM, before the pathological sampling has been established.[1,2] In this article we present our IGM patient, in whom we have detected the co-occurrence of erythema nodosum, tenosynovitis and granulomatous mastitis, and evaluate the case in association with similar cases in the literature.

CASE

A 30-year-old woman presented with tenderness, redness and discharge in her left breast accompanied by a mass, together with pain in her ankles. Her complaint had started nearly two years after her last delivery and had been ongoing for two months. Physical examination revealed a nodular lesion with discharge under the areola of the left breast at the horizontal line, approximately 3 cm in diameter. Arthritis and tenosynovitis accompanied by edema were detected at the medial surface of the right ankle, while a painful lesion which was consistent with erythema nodosum was observed at the pretibial area. Breast ultrasound (US) examination revealed a 12x15x16 mm irregular heterogeneous hypoechoic solid mass with tubular extensions. Skin thickening and hyperechogenicity of subcutaneous fat were also seen. A few lymph nodes were found in the left axilla, which seemed to be pathological. A breast magnetic resonance image (MRI) revealed a hyperintense solid mass of 16x18x24 mm with tubular extensions and evidence of edema, and thickening of the overlying skin on T2 weighted images in the lower outer quadrant. Dynamic contrast enhanced MR imaging of lesions showed an intensely enhancing mass with rapid enhancement and plateau (type 2 time curve) (Figure). A fine-needle aspiration biopsy (FNAB) was obtained from the breast and a punch biopsy was obtained from the pretibial region. Pathology from the needle biopsies revealed the formation of microabcesses without caseification necrosis, compatible with granulomatous mastitis. A punch biopsy of a lesion on the right leg showed a lobular panniculitis which, in some areas, extends into expanded interlobular septa (compatible with erythema nodosum). The infiltrate is slightly atypical and predominantly lymphocytic, but contains scattered histiocytes and plasma cells. Laboratory test results were as follows: WBC: 11.400/mm³ (4.000-10.000/mm³), Hgb:9.8 g/dL (13.5-18 g/dL), PLT:335.000/mm3, erythrocyte sedimentation rate (ESR): 101 mm/hour (0-30 mm/hour), CRP: 7.77 mg/L (0-5 mg/L), ALT:6 U/L (5-40 U/L), AST:9 U/L (5-40 U/L), Albumin:3.82 g/dl (3.5-5.2 g/dl), Globulin:4.16 g/dl. The serum angiotensin-converting enzyme (ACE) level was 10 U/L; (8-52 U/L). ANA, Anti dsDNA, RF, Anti CCP, c-ANCA, p-ANCA, Anti HIV, Rose Bengal and hepatitis serology were found to be negative. Few leukocytes were seen in a gram stained discharge sample. No acid-fast bacilli were detected with Eilich-Ziehl-Neelsen staining, and the tuberculosis culture remained negative. The patient's tuberculin skin test was 0 mm; a booster shot was administered one week later and repeated. The PPD skin test was evaluated as 0 mm once again. The

Table: Clinical and laboratory findings of granulomatous mastitis associated with erythema nodosum

Reference	Y/G	FUO Duration/ Type	Erythema Nodosum Appearance	Lesion Location/ Size/Character	Extra Mammary Findings	Pathology	Treated With/ Duration	Complication	Complete Resolution
Adams et al. 1987[4]	24 F	24 month recurrent	After 4 weeks	Left breast areola/ 12x9 cm / painful mass	Bilateral EN + arthritis	Granulomata and micro abscess	6 weeks anti TB İndomethacin	Persisted sterile discharge (6 weeks)	5 months
W Donn et al. 1994[5]	36 F	Nursing	After 8 weeks	Left breast upper outer part 8x10 cm / mass	Bilateral EN	GM	Multiple antibiotics long time Prednisone 60 mg/day 2 weeks	Non resolved Prednisone 10 mg/day Excisional surgery	After surgery
RJ. Yaghan. 2004[6]	34 F	None	After 2 weeks	Right breast Upper part/8x5 cm/ painful mass	Bilateral EN	GM	15 mg/day prednisolone + Surgical excise	None	1 month
AT. Erdemir et al. 2007[7]	31 F	None	Simultaneously	Right breast Multiple deep nodules discharging fistula and sinus formation	Bilateral EN	Noncaseating granulomatous inflammation	32 mg/day prednisolone 30 days	None	3 months
C Bes et al. 2010[1]	34 F	None	Simultaneously	Left breast upper part 5x5x4 cm / painful and fluctuated mass	EN	Granulomata and micro abscess	Prednisolone 32 mg/day (Tapered)	None	6 months
C Bes et al. 2010[1]	27 F	Nursing	After 3 weeks	Left breast/ 8x6 cm / painful mass	Bilateral EN	GM	12 weeks anti TB Metil Prednisolone 32 mg tapered	Relapsed Metil Prednisolone 32 mg tapered	12 months
M Salesi et al. 2011[9]	23 F	Pregnant	Simultaneously	Right breast periareola / 5x5 cm / painful and purulent discharge mass	Bilateral EN	Necrotisan GM	Prednisone 15 mg, Colchicine 1 mg Azathio-prine 100 mg	None	15 days
T. Nakamura et al. 2012[2]	23 F	None	Simultaneously	Swelling and pain in the left breast	EN	Noncaseating Granuloma composed of epithelioid cells	Prednisolone 40 mg/day	Relapsed Prednisolone 50 mg/day (8 months) MTX 4 mg/ week (1 Year)	2 years
F Binesh et al. 2013[10]	40 F	None	Simultaneously	8x5 cm firm mass in her left breast	Bilateral EN + arthritis	Epithelioidhis-tiocytes with multinucleated giant cells	Prednisolone 30 mg	None	NA
Noma et al. 2014[11]	31 F	None	After 3 weeks	Left breast upper outer quadrant/7x10 cm painful mass	Bilateral EN + arhritis	GM and abscesses	Prednisolone 10 mg/day	None	3 months
Hida et al. 2014[12]	26 F	None	After 5 days	Right breast lateral region	Bilateral EN	GM	Minocycline 150 mg/day	None	6 months
Present case	30 F	None	Simultaneously	Left breast areola / 3 x4 cm/ painful and purulent discharge mass	Bilateral EN + arthritis+teno-synovitis	GM and abscesses	Multiple antibiotics long time Anti TB (10 days) Prednisone 60 mg tapered 3 months	None	3 months

GM: Granulomatous mastitis, **EN:** erythema nodosum, **MTX:** methotrxate, **NA:** non available, **Y/G:** year/gender

QuantiFERON TB Gold test result was <0.35 IU/ml; therefore, a diagnosis of tuberculosis was excluded. Chest radiography and chest computed tomography (CT) were also performed and both of them were found to be normal. As the patient had no history of recurrent oral and genital aphthae, and her autoimmune markers were identified as negative, she was considered to have IGM and was started on treatment with oral prednisolone 1mg/kg/day and tapered in two months. At the end of the first week of treatment, the mass in the breast was reduced, the discharge had was decreased and pretibial lesions disappeared; no recurrence was observed in the patient during the six-month follow-up. Her laboratory test results were found to be normal.

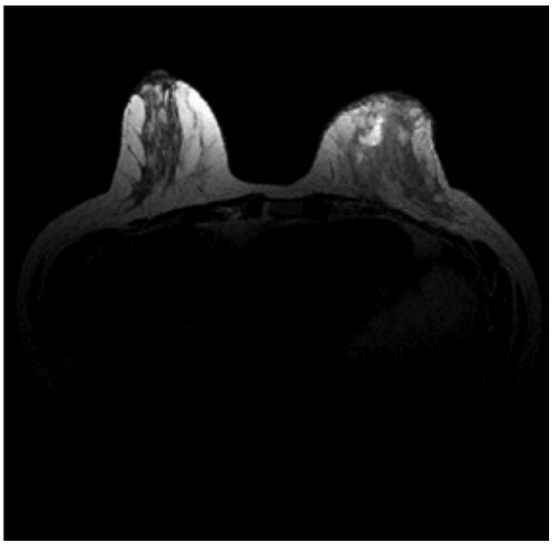

Figure: A breast magnetic resonance image (MRI) revealed a hyperintense solid mass of 16x18x24 mm with tubular extensions and evidence of edema, and thickening of the overlying skin on T2 weighted images in the lower outer quadrant. Dynamic contrast enhanced MR imaging of lesions showed an intensely enhancing mass with rapid enhancement and plateau (type 2 time curve)

DISCUSSION

IGM should be differentiated from breast cancer (especially inflammatory breast cancer), granulomatous diseases (tuberculosis, brucellosis, sarcoidosis) of the breast and bacterial mastitis.[1,2] IGM may be differentiated from these diseases with histopathological evaluation and microbiologic studies. However, the response to empirically initiated steroid therapy may sometimes be useful to distinguish it from other diseases.

Although recent studies indicate that Corynebacteria may play role in the pathogenesis of the disease, the etiology has not been clearly elucidated. Clinically, patients may often refer with solid masses and abscess-related signs accompanied by inflammatory findings at the breast. In addition to fistula formation, nipple retraction, peau d'orange changes, and axillary lymphadenopathy may be associated with these findings. Cases having a predominantly inflammatory character may be confused with bacterial mastitis, and this may lead to unnecessary and prolonged use of antibiotics, while lesions with a different character may raise suspicion of malignancy. In addition, sarcoidosis, tuberculosis - in endemic countries - and brucella mastitis must be considered in differential diagnosis. The diagnosis of IGM is often established with the exclusion of these other diseases. A sample obtained from the breast is examined both cytopathologically (caseification necrosis, the presence of dysplasia) and microbiologically (acid-fast bacilli, tuberculosis culture) with the intention of excluding other diseases; however, ensuring a definitive diagnosis is often difficult. The presence of extra-mammary findings such as erythema nodosum and arthritis may be a predictive finding for IGM. Indeed, no scientific data is available examining the co-occurrence of erythema nodosum with the diseases that must be differentially diagnosed from IGM and breast involvement.

Erythema nodosum is the most common panniculitis, which is often located in the pretibial area. Although its etiopathogenesis has not been completely understood, its association with many infections and the inflammatory process that leads to granulomatous and neutrophilic reactions has been reported. Inflammatory bowel disease (IBD) is the most commonly reported disease associated with erythema nodosum in the medical literature. In a retrospective study conducted by Farhi et al., 2402 IBD cases were evaluated; the rate of erythema nodosum was found to be only 4%.[3] No studies are available regarding incidence, prevalence and extra-mammary findings of IGM, which is considered to be an auto-inflammatory disease. With our medical literature search in the English language (PubMed, Google Scholar) we have found twelve cases emphasizing the co-occurrence of granulomatous mastitis and erythema nodosum (Table).[1,2,4-12]

Except for one case, EN appears concurrently or within a few weeks of the occurrence of breast symptoms or signs. The association between the case reported by Olfatbakhsh et al. and granulomatous mastitis is very controversial.[8] EN and arthritis findings observed in the patient appear more consistent with seronegative spondylitis experienced during pregnancy. In another patient for whom only indomethacin was used, IGM continued in the form of sterile discharge and improved within five months, whereas erythema nodosum was completely resolved.[4] After primary treatment, erythema nodosum resolved in all patients and EN did not recur in any patient, including the recurrent IGM cases.This indicates that the relationship between IGM and EN is a direct association, which evolves through an initial antigenic stimulus of unknown etiology.

Relevant information about an optimal therapeutic option for the treatment of IGM and optimal treatment duration is not available. For many years, the patients who underwent surgical excision and mastectomy were concurrently treated with steroids, since the disease has come to be considered as auto-inflammatory. Reports are available for the use of additional methotrexate therapy in patients who do not respond to steroid therapy alone. In three cases, relapse occurred during treatment and the dose of steroid therapy had to be increased. In one case, methotrexate had to be added to the therapy, while surgical intervention was required in *another* case. The time required for full recovery of the cases varied within a wide range, from 2 weeks to 2 years.

In conclusion, IGM should be the primary consideration when a patient presents with signs of inflammatory breast disease and EN. In treatment, the addition of anti-inflammatory drugs to steroid therapy may contribute to preventing recurrences and shortening the duration of treatment.

* The authors declare that there are no conflicts of interest.

CORRESPONDING AUTHOR: Ergenekon Karagöz GATA Haydarpasa Training Hospital Dep. of Infectious Diseases and Clinical MicrobiologyIstanbul, Türkiye ergenekonkaragoz@hotmail.com

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