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AUTOIMMUNE MASTITIS AS A CLINICAL MANIFESTATION OF BEHÇET'S DISEASE: A CASE REPORT AND A SYSTEMATIC LITERATURE REVIEW

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ABSTRACT – ***Objective:*** Behçet's disease (BD) is a rare autoimmune disorder of unknown origin that causes chronic and systemic inflammation in blood vessels. The condition is traditionally defined by oral and genital ulcers and uveitis; however, cutaneous, articular, neurologic, vascular, gastrointestinal, and pulmonary manifestations may also be observed. It is more prevalent throughout the Silk Road, such the Mediterranean basin and the East Asia. There have been reported only four cases of BD targeting the breast. We herein present a case report of an autoimmune mastitis (AM) in a 23-year-old patient diagnosed for BD treated surgically.

Case Presentation: The patient is a 23-year-old Italian female who reported recurrent aphthous ulcers of the oral mucosa, occasional vaginal dryness, and genital lesions, diagnosed for BD according to the International Study Group (ISG) criteria and the skin biopsy. The patient referred to our department for examination of a painful and ulcerating lump at the 5 o'clock position of the right breast, which had been present for one month.

Results: In our case, we opted for a surgical approach, which proved to be effective in treating the lesion. Considering the relapsing and remitting nature of BD, surgical intervention is questionable when compared to appropriate conservative treatment.

Conclusions: A conservative approach should be evaluated first, in order to have regard to the recurrent course of the disease and to the risk that numerous surgical procedures may result in irreversible aesthetic damage.

KEYWORDS: Autoimmune mastitis, Behcet's disease, Breast neoplasms, Case report, Review.

INTRODUCTION

Behçet's disease (BD) is a rare autoimmune disorder of unknown origin that causes chronic and systemic inflammation in blood vessels. It is characterized by variable-vessel vasculitis, affecting both arterial and venous vessels of any size throughout the body[1]. While the condition is typically defined by oral and genital ulcers and uveitis, it can also manifest as cutaneous, articular, neurological, vascular, gastrointestinal, and pulmonary symptoms. The prevalence of BD is influenced by the geographical distribution of HLA-B51[2]. It is more commonly observed in regions along the Silk Road, such as the Mediterranean basin and East Asia. Prevalence rates have been reported as 370/10,000 in Turkey, 11.9/10,000 in Israel, 13.5/10,000 in Japan, 0.64/10,000 in England, 5.2/10,000 in the United States, and 3.8-15.9/10,000 in Italy[3]. The exact etiology of BD remains unclear. Alpsoy et al[4] suggest that genetic factors like HLA and non-HLA associations, epigenetic mutations, environmental factors, infectious agents, and specific microbiome alterations may be involved to its development.

The diagnosis of BD is established based on the presence of pathognomonic manifestations, after excluding other potential causes. Aphthous ulcers are observed in 95-97% of patients and are often the initial clinical sign of the disease. The most commonly used diagnostic criteria are the International Study Group (ISG) criteria from 1990, although the International Criteria for BD (ICBD) introduced in 2014 have higher sensitivity (85.0% *vs.* 94.8%) but lower specificity (96% *vs.* 90.5%)[5] (Table 1).

Table 1. The International Study Group criteria for diagnosis of Behçet's disease.

Major criteria (required)	Minor criteria (at least 2 required)
Recurrent oral ulceration (at least 3 times in a 12-month period)	Recurrent genital ulcers
	Eye lesions uveitis or retinal vasculitis.
	Skin lesions Erythema nodosum-like, pseudo folliculitis, papulopustular or acneiform lesions.
	Positive pathergy test Test interpreted positive by a physician at 24-48h and performed by the insertion of a 20G needle or smaller under sterile conditions.

Autoimmune mastitis (AM) is rarely associated with a well-defined autoimmune disease. Only four cases of BD affecting the breast have been reported, presenting symptoms such as soreness, ulcers, or ductal ectasia rather than vasculitis[6-9]. The increasing interest in the literature in recent years and the absence of a standardized diagnostic approach for AM suggest that it is an underdiagnosed or misdiagnosed condition[10]. Additionally, challenges arise in determining the most appropriate treatment approach for the inflammatory lesions, weighing between conservative and surgical options.

In this case report, we present a surgical treatment for mastitis in a 23-year-old patient diagnosed with BD. After ruling out breast cancer, clinical and diagnostic data supported the diagnosis of BD-related AM.

CASE PRESENTATION

The patient is a 23-year-old Italian female who presented with recurrent aphthous ulcers of the oral mucosa, occasional vaginal dryness, and genital lesions (Figure 1). In February 2023, she was diagnosed with BD based on the ISG criteria and a skin biopsy.

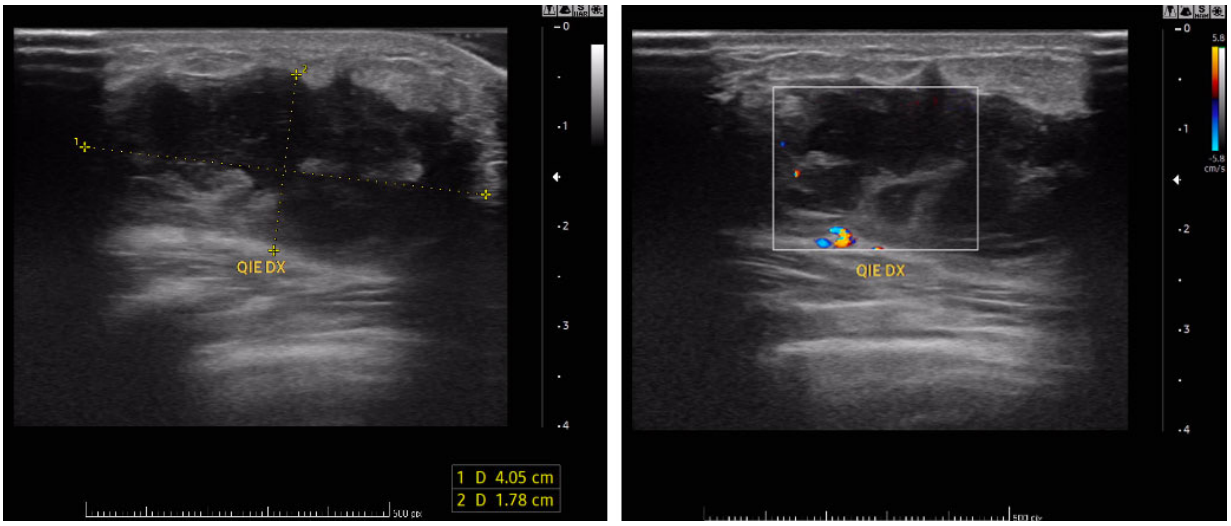

Figure 1. A 23-year-old female with Behçet's disease. The Ultrasound (US) image of the palpable nodule at the outer-lower quadrant of the right breast: (a) structural alteration with corpuscular fluid in the context (b) perilesional vascularity.

In March 2023, the patient visited our department due to a painful and ulcerating lump at the 5 o'clock position of the right breast, which had been present for one month. The lesion appeared swollen, tender, and red, raising suspicion of mastitis. Ultrasound (US) examination revealed an area with an irregular echo-structure and unclear boundaries measuring 4.05x1.78 cm at the right breast, corresponding to the palpable lesion (Figure 1). Although the imaging findings were not indicative of breast cancer, surgical drainage of the abscess was performed as a day-surgery procedure. Given the patient's positive family history of breast cancer, a diagnostic biopsy and microbiological assessment were conducted.

The patient received broad-spectrum antibiotic therapy, leading to symptom improvement and complete resolution within 14 days through secondary intention healing. Bacteriological examination yielded negative results, and pathological analysis of the specimen showed fibrino-necrotic material with rare epithelial elements, preserved myoepithelial layer, eosinophilic infiltrate, and lymphocytic small-vessel vasculitis, ruling out malignancy.

Follow-up ultrasound at 6 months showed complete resolution of the mastitis. Due to the absence of any other identifiable cause, acute mastitis was attributed as a clinical manifestation of BD.

DISCUSSION

BD is a chronic inflammatory disease of blood vessels, affecting both arteries and veins, with an unknown etiology as defined in the revised Chapel Hill Consensus[1]. The classic "triple symptom complex" described by Behçet in 1937 includes muco-cutaneous ulcers of the mouth and genitals, as well as uveitis. While BD has a global distribution, it is particularly prevalent along the "Silk Road" in regions such as the Mediterranean basin and Eastern Asia[4]. The vasculitis associated with BD is characterized by granulomatous necrotizing inflammation of blood vessels and can potentially affect any organ system. BD often follows a relapsing and remitting course, with recurrent episodes of clinical manifestations. The diagnosis of BD is based on the ISG criteria, which require the presence of oral aphthosis and at least two additional conditions such as recurrent genital ulcers, eye lesions, skin lesions, or a positive pathergy test. Our patient was diagnosed with BD based on these criteria one month prior to the onset of the breast nodule.

Mammary involvement in BD is uncommon and typically unilateral. Acute mastitis can be categorized as lactational or non-lactational mastitis. Lactational or puerperal mastitis, which affects breastfeeding women, is the most common subtype and is characterized by prolonged milk duct engorgement and infection. Non-lactational mastitis includes periductal mastitis, which occurs in reproductive-aged women and is often associated with smoking, and idiopathic granulomatous mastitis, which can mimic breast cancer and primarily affects parous women within 5 years of giving birth[11]. AM primarily affects

young to middle-aged women and its histopathological pattern varies depending on the autoimmune disease targeting the breast. The clinical manifestations of AM can be broad, including painful nodules or masses, recurrent breast inflammation, nipple discharge or retraction, and lymphadenopathy[11].

When faced with a breast lump, it is crucial to rule out malignancy as an autoimmune disease like BD and its immunosuppressive therapy may increase the risk of neoplastic degeneration[12]. Since those patients are exposed to the risk of developing breast cancer (BC), the risk reduction strategy by affecting modifiable factors, such as the diet, should be considered[13]. In support to this assumption, Mohamed et al[14] proved there is a correlation between higher body mass index (BMI) and negative BC prognosis, and many randomized clinical trials also showed a positive impact of regular physical activities on quality of life (QoL)[15]. All these data should be taken into advice through health awareness programs.

Although the relationship between BD and BC is still unclear, some studies have reported a 3-fold increased cancer risk in patients with BD compared to age- and sex-matched controls[15]. Differential diagnosis with breast cancer requires histological evaluation, although a specific histopathological finding for BD-related mastitis has not been described yet. Chun et al[16] described Behçet's histological pattern as non-specific small-vessel vasculitis characterized by leukocytoclastic and lymphocytic inflammation and peri-vascular infiltration by mononuclear cells. In severe cases, such as in our patient, there may be necrosis of breast tissue and the formation of abscesses.

Given the patient's positive family history of breast carcinoma, the clinical presentation of the breast nodule, and the aggressive nature of the ulceration, excisional biopsy was chosen as the diagnostic and therapeutic strategy to exclude malignancy. The first suspect was driven by the breast US, since mammography couldn't be performed due to the high density of the patient's breast[17]. The therapeutic strategy must take into account the psychological care, since a somatic disease's diagnosis, such as BC, has its impact on the emotional condition of the patient and may trigger the development of a psychological disorder[18]. Predictive and prognostic factors are crucial for determining the appropriate treatment for breast cancer[19,20]. The molecular classification, which can be predicted by imaging, and the gene expression profile are nowadays the drivers of precision oncology for individualized therapeutic approaches in order to spare patients of unnecessary treatments[21-23].

An alternative to histological examination for diagnosing cancer is the use of reverse transcriptase-polymerase chain reaction (RT-PCR), which analyzes blood samples to detect mRNA expressed in tumor cells[24].

In our case, the unilateral aseptic abscess and the presence of vasculitis signs in the excisional biopsy reinforced the correlation with BD. In clinical practice, a combined surgical and conservative approach has been reported in patients with autoimmune mastitis, resulting in no recurrence and complete regression. Currently, there is no standardized diagnostic and therapeutic protocol for autoimmune mastitis. Some studies recommend surgical excision or incision and drainage, while others suggest conservative treatments such as corticosteroids, antibiotics, and other anti-inflammatory medications.

In our case, we opted for a surgical approach, which proved to be effective in treating the lesion. However, the differential diagnosis with breast cancer required a two-week wait for the final histopathological results and involved significant healthcare resources for the surgical regimen. Considering the relapsing and remitting nature of BD, surgical intervention is questionable when compared to appropriate conservative treatment. Furthermore, surgical trauma itself poses a risk for post-operative complications in patients with BD, including wound dehiscence, infection, graft occlusion or failure, particularly in patients with a positive pathergy test[25]. Avoiding surgery would also minimize the risk of unfavorable aesthetic outcomes in case of AM recurrence (Figure 2). Considering the course of BD, our future direction would favor a conservative approach. Ultrasound-guided fine-needle aspiration cytology (FNAC), core-needle biopsy (CNB), or ultrasound-guided vacuum-assisted excision (VAE) could have been decisive in ruling out a tumor, reducing healthcare costs, and avoiding post-operative complications while providing a definitive diagnosis[26,27].

CONCLUSIONS

In conclusion, although rare, autoimmune granulomatous mastitis is an emerging clinical manifestation of BD. After excluding infections and breast cancer, physicians should consider mastitis as a clinical manifestation of an autoimmune disease, particularly in patients with a personal or family history of autoimmune diseases. A conservative approach should be considered first, such as FNAC, CNB, or VAE, to account for the relapsing course of the disease and the potential risks associated with multiple surgical procedures, including irreversible aesthetic damage.

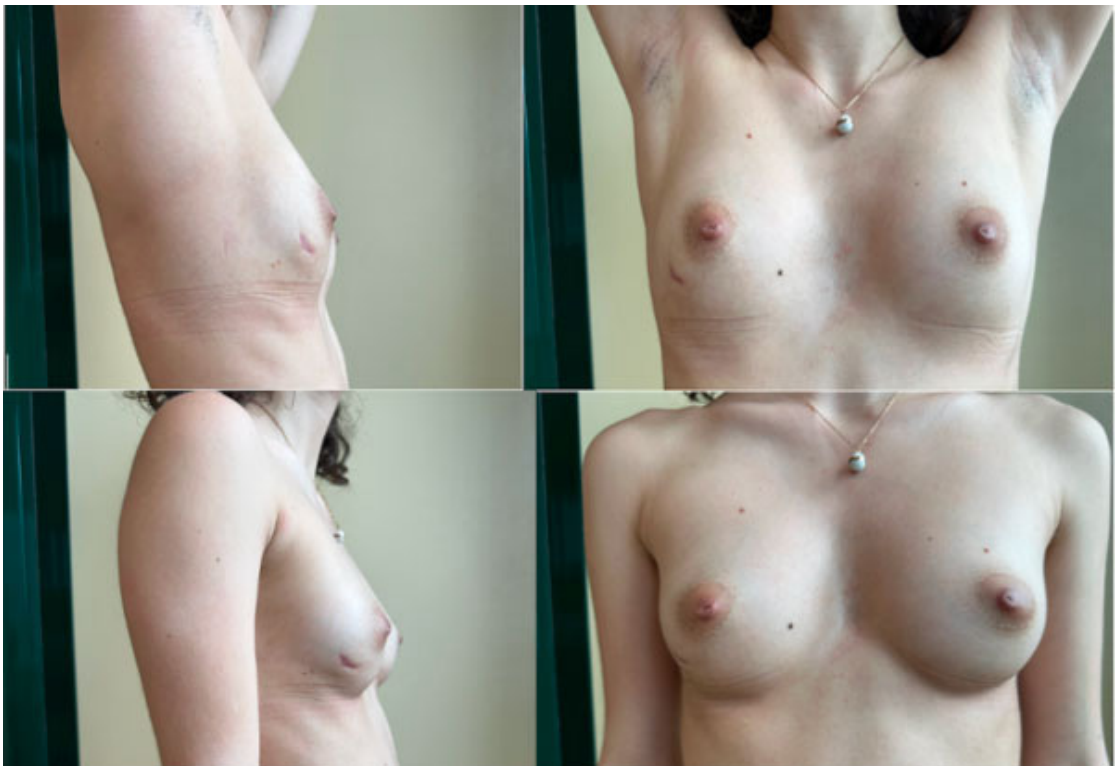

Figure 2. A 23-year-old female with Behçet's disease. The Ultrasound (US) image of the palpable nodule at the outer-lower quadrant of the right breast: (a) structural alteration with corpuscular fluid in the context (b) perilesional vascularity.

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Conflict of interest:
The authors declare there is no conflict of interest in this case report.

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