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Review

Diagnostic techniques and multidisciplinary approach in idiopathic granulomatous mastitis: a revision of the literature

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Summary. Idiopathic granulomatous mastitis (IGM) is a chronic benign inflammatory disease of the breast that may mimic breast cancer. It is most common in parous young fertile women, although it can occur in nulliparous women and in men. IGM is an idiopathic disease due to the influence of some environmental factors in genetically predisposed subjects. Several pathogenic hypothesis have been proposed in the last years (autoimmune, hormonal, infective genesis). IGM presents as a painful palpable mass located in one of the two udders. The skin is usually normal but could present signs of inflammation with or without lymph nodes involvement. Ultrasonography, mammography, magnetic resonance can be diagnosed an IGM, but pathognomonic radiological signs has not yet reported in literature. Biopsy findings show granulomatous lesion centered on the breast lobule, as in granulomatous mastitis induced by tuberculosis or sarcoidosis. The aim of this review of literature is to verify the development of new advanced diagnostic techniques and multidisciplinary approach for this condition. In the last years innovative approaches have modified IGM diagnosis and therapy, avoiding surgery in most of cases, introducing a more conservative medical approach based on recent etiopathological hypothesis. (www.actabiomedica.it)

Key words: breast cancer, chronic benign inflammatory disease, idiopatic mastitis

Introduction

Idiopathic granulomatous mastitis (IGM), also known as idiopathic granulomatous lobular mastitis, is a chronic benign inflammatory disease of the breast with unknown etiology. It was first described by Kessler and Wolloch in 1972 (1-10).

IGM is most commonly seen in parous young women, often within a few years of pregnancy, although it can occur in nulliparous women and in men (6, 11, 129.

Although most articles have mentioned that IGM is rare, numerous recent studies with large number of patients, that are continuously published especially in developing countries, make a doubt about the rarity of IGM. This could be due to under-diagnosis or misdiagnosis or due to a possible increasing prevalence among developing nations (3).

There is no increased risk of subsequent breast cancer in IGM patients, but, clinically and radiologically, it may mimic breast cancer and awareness of surgeons, pathologists, and radiologists is essential to avoid unnecessary mastectomies (14, 15). For these reasons, although IGM is considered a benign condition, most of studies has been concentrated on disease management, which is still very controversial (2, 16-18).

Our review has the aim to verify how, in the last 30 years, the development of new advanced diagnostic techniques and multidisciplinary approach, have modified IGM diagnosis and therapy, avoiding surgery in most of cases.

In this work, literature was reviewed from 1972, when IGM was discovered, until now. In general, reported cases were represented by young adult fertile female patients (mean age 35 years), multiparous. A few percent of cases was represented by over 50 patients. In rare cases, IGM was described in an 11-year-old female patient, in an 80-year-old woman and in some male patients. Interestingly, in almost all reported cases, patients delivered five year before, and interrupted breastfeeding one year before disease diagnosis (10-12, 16, 19). Usually, IGM presents as a painful palpable mass located in one of the two udders. The skin is usually normal but could present signs of inflammation with or without lymph nodes involvement. Diagnosis is bases on ultrasonography (US), mammography, magnetic resonance (MR), fine needle aspiration cytology (FNAC), fine needle ago-biopsy (FNAB) (20-24). In this review, IGM medical and surgical treatment options were evaluated (16-18, 25-28).

Discussion

IGM represents a benign inflammatory disease of the breast. It is an idiopathic disease due to the influence of some "environmental stimulus" in genetically predisposed subjects. Some authors proposed that a local granulomatous inflammatory response to epithelial damage describes the pathogenesis of IGM (29). However, the trigger in the development of the epithelial damage remains unknown. Although several triggers have been proposed, the etiologic association of neither of them has been documented with IGM. It has been postulated that extravasated lactational secretions may be responsible for eliciting a granulomatous inflammatory response (30).

To date, three main hypotheses have been postulated to explain IGM (31):

1) autoimmune genesis;
2) infectious disease;
3) hormonal disorder.

Currently, the most accredited hypothesis recognizes IGM as an *autoimmune disease*; in many studies, some IGM patients could be also affected by erythema nodosum and arthritis, a lymphocyte-rich immunohystochemicl pattern, and present a good clinical response to steroid or immunosuppressant administration (32).

Hormonal disorder hypothesis rises from the evidence of high prolactin serum levels in IGM patients; furthermore, prolactin could affect disease severity and prognosis and increase disease relapse rate. IGM presents frequently in fertile female patients, especially in those who use oral contraceptives or are near to delivery or breastfeeding. However, IGM is uncommon during pregnancy. To date, few are hyperprolactinaemia-related cases and new studies should be aimed to clarify the role of this hormone in IGM pathogenesis and analyse its prognostic significance to better address treatment (15). Cases of IGM have been recognized in patients submitted to Selective Serotonine Reuptake Inhibitors (SSRI). Interestingly, it has been reported that antipsychotic therapy can be associated with hyperprolactinemia and that the onset of breast enlargement can occur during chronic antidepressant therapy (33, 34), suggesting a possible side effect of SSRI. Maione et al demonstrated that SSRI could exert a perturbation in dopamine secretion, counteracting its role in repressing prolactin gene expression, leading finally to hyperprolactinemia and associated IGM. In this regard, it seems worthy of noting the findings about a functional crosstalk between serotonin and dopamine receptors (35). In a study on 18 patients, Ehran et al. used prolactin serum levels to address the IGM treatment: they performed surgery + steroids when IGM relapsed and prolactinaemia was in normal range, whereas they used medical therapy alone when prolactin serum levels where higher (34).

Infectious hypothesis is not supported by a causality relation between IGM and infectious agents; however, a granulomatous inflammation is typical in response to specific strains of bacteria, fungi and parasites. Corynebacterium is the most recognized bacterium of the breast granulomatous diseases, unfortunately its etiologic role in IGM has not been yet established. Some cases of IGM in developing Countries could be associated to tuberculous bacterial infections (36-39).

IGM may present as a peripheral inflammatory breast mass; it can also present as multiple simultaneous areas of peripheral (and rarely central) infection with abscesses and/or overlying skin inflammation and ulceration (2, 4-8). Nipple retraction, sinus formation, peau d'orange-like changes, and axillary adenopathy may accompany these findings (1, 11, 19, 38). Some patients have extramammary signs and symptoms, while others have disease confined to the breast(s). IGM patients could develop repeated abscesses over weeks to months. These findings may be confused with breast abscess or malignancy (4).

There are not pathognomonic signs on US, mammography and MR. Irregular tubular hypoechoic lesions, lobulated hypoechoic masses, parenchymal irregularities without a mass, fistulisation to skin or axillary lymphadenopathies, could be recognized on US. Typically, US examination demonstrates a solid mass, often with one or more abscesses. Multiple irregular hypoechoic masses and collections with tubular connections with fingerlike aspects and skin fistulae in patients with breastfeeding history, suggests IGM rather than carcinoma (39).

A focal asymmetric opacity, enhancement of density, diffuse enhancement of fibroglandular mass density, an irregular mass, ellipsoid mass, retraction and heterogeneity of breast parenchyma, could be identified on mammography. Cases with micro-calcifications are confused with cancer (40, 41). In IGM, radiology findings are nonspecific and mammography may be easily suggestive of malignancy (39, 41-45).

A pathognomonic imagination for IGM on MR has not yet been reported in the literature. Yildiz et al. described T2-weighted hyperintense masses in 4 out of affected patients but no conclusions were reached because of the short amount of cases (39).

Overtime, excisional biopsy has acquired a diagnostic and therapeutic role. Biopsy findings typically show granulomatous lesions centered on the breast lobule (14, 23, 24). The biopsy should be sent for acid-fast bacilli and fungal stains in addition to histopathology; other diseases such as tuberculosis or sarcoidosis may induce a granulomatous mastitis. However, biopsy is the gold standard for its diagnosis and should be taken in any patient even with a mild suspicion of cancer (20, 46). On the other side, some Authors have introduced a more conservative medical approach, against a more or less aggressive surgical approach (16-18, 25, 27, 28). Due to its possible autoimmune aetiology, immunosuppressors have been proposed for the treatment of IGM. There is no role for steroid use; systemic glucocorticoid therapy and local depot steroid injections have been used for the treatment of IGM, although there are no randomized controlled trials that demonstrate their efficacy (4, 26, 42, 47, 48). Altintoprak et al reviewed the effect of topical steroids in patients with IGM characterized by skin changes (49). Methotrexate is another option (31, 50-53). In the experience of Sheybani et al., 16 out of 22 patients (72.7%) suffering from IGM took advantages from a combined treatment of prednisone and methotrexate (31). Discontinuation of these drugs has been associated with rebound inflammation.

IGM is a self-limiting inflammatory condition but commonly takes 9 to 12 months to resolve (54), that is why its therapeutical management is still controversial: recent studies showed that expectant conservative management with no medical or surgical treatment resulted with high rates of spontaneous remission in IGM patients as well (54-56). Therefore, there exists different valid management options for these patients (56, 57). When considering the high success rates of nonsurgical modalities for IGM, it seems that surgical treatment might be reserved for those in whom other modalities are not effective or who ask to have a rapid amelioration (49).

Conclusion

To date, IGM has lost its surgical identity (except for rare cases of relapsing or complicated disease) and it could be considered a medical condition. Taking into account the three main aetiological hypotheses, the treatment can be oriented to different targets (immune system, endocrine system or infectious agents) in a multimodal fashion. Therefore, involved drugs vary from immunosuppressors to steroids to those medications which interact with endocrine system. Because of its multimodal and complex therapeutic management, IGM has been identified as a complex, multifactorial disorder that should involve different specialized

figures, such as endocrinologists, radiologists, immunopathologists, infectivologists. Only addressing the right aetiology it is possible to address the right treatment, avoiding invasive decisions and reducing hospital stay and social costs.

Conflict of interest: None to declare

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