Idiopathic granulomatous mastitis associated with risperidone: case report

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Aim. **Granulomatous mastitis is a rare benign inflammatory disease of the breast, characterized by non-caseating granulomas without any evidence of infection, pathologically mimicking carcinoma. The differential diagnosis with malign breast disease is often not easy, so it is often initially misdiagnosed and proper treatment is delayed. Surgical biopsy is needed for correct diagnosis and there is still no generally accepted optimal treatment. In our experience a conservative approach seems to be adequate in most cases and in our opinion, surgical treatment is the best therapy. Another option is a long/middle-term steroid treatment. It is mandatory to exclude infectious causes of granulomatous mastitis before corticoid therapy is started.**

Methods. **In our patient the surgical treatment was planned; excision of the entire lesion, and subsequently neoadjuvant corticosteroid therapy was performed.**

Results. **The patient has benefit from the operation immediately, with resolution of the disease. The follow-up (on-going), up to now, showed no recurrence of the pathological and no complications, making sure the authors of the efficacy of the surgical treatment.**

Conclusion. **The purpose of this study is describe the clinical, imaging, and pathologic features of granulomatous lobular mastitis of our patient and discuss diagnostic and therapeutic protocols that we used to diagnose and treat this rare disease. The authors noted that believe in the surgical treatment as the only procedure, performed alone or combined with corticosteroid therapy, to the cure of the patients.**

KEY WORDS: Granulomatous mastitis - Risperidone - Breast neoplasms.

Idiopathic granulomatous mastitis (IGM) is a rare benign inflammatory disease of the breast, characterized by non-caseating granulomas without any evidence of infection, awareness of this condition is important because it can clinically mimic breast carcinoma.

A granulomatous inflammatory response can be a reaction to either a specific agent, for example mycobacterium tuberculosis or agent of sarcoidosis.

The entity was first described by Kesler and Wolloch in 1972, elaborated by Cohen in 1977. They found a discrete granulomatous lobulitis and because of the morphological resemblance to granulomatous thyroiditis and orchitis, suggested that it might be immunologically mediated.

Patient usually presents with symptoms of a painful mass, chronic sinus drainage, erythematous breast mass with an abscess, fever and associated conditions like tachycardia and tenderness, with laboratory in-

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vestigations suggesting no infectious etiology.

For this reasons the clinical and radiological features of this benign entity are frequently mistaken-misdiagnosed as a breast abscess or as carcinoma.

Definitive diagnosis is based on histological examination.

The absence of guideline for the treatment for patients diagnosed with IGM, has left to surgery, steroids, immunosuppressants, and antibiotics a role not defined, with varying degrees success therapy. Recurrence is common in the absence of surgical treatment, and a long-term follow-up is generally recommended.

Here we represent a rare literature case of granulomatous mastitis associated with risperidone induced hyperprolactinemia[1].

The most common presentation is a focal asymmetric density on mammography and an irregular hypoechoic mass with tubular extensions on ultrasound. The imaging findings of granulomatous lobular mastitis overlap with those of malignancy. Core biopsy is typically diagnostic. Once the diagnosis is established by tissue sampling, surgical treatment and corticosteroids are the first line of treatment.

Case report

In our case-history, we treated a 41-year-old woman presented with a painful inflammatory breast mass (ultrasound examination-lump in her left breast 4.52 centimetres), a discrete nipple retraction and no palpable axillary nodes. She had a history of schizophrenia for over 15 years and had been receiving risperidone 2 mg (serotonin and dopaminergic antagonist) for more than 5 years. She had never consumed tobacco, alcohol, oral contraceptive pills, she hadn't any family history of breast cancer or receiving any breast surgery, finally she breastfed one children.

On physical examination, slight ulcerated peau d'orange skin and cherry-like mass of breast with localized redness over the left breast lateral aspect with an ill defined margin was noted with no palpable lymphadenopathy at the axilla.

There was no splenomegaly or hepatomegaly.

During tac, we found an incidental finding, a liver mass of 3 cm any side, initially considered likely metastasis from breast cancer (Figure 1); further investigations like scintigraphy and ultrasound investigations allowed us to conclude that it was liver-hemangioma (2.66 cm) (Figure 2).

She did not have fever, joint pain, air way or urinary tract bleeding and no other skin lesion was found.

Serological and haematological investigations were normal, no sign of inflammation or positive tumour markers; the only relevant laboratory data was the finding of hyperprolactinemia.

Breast ultrasound, mammography (Figure 3) and tac of the breast revealed a diffuse lesion, very suggestive for breast cancer.

Breast ultrasound images revealed lobulated and hypoechoic mass (4.52 cm), with ill-defined area and heterogeneous echoes in the left upper and lower outer quadrants, associated with increased vascularity, micro-calcification and tissue edema (Figure 4).

Mammography showed asymmetry with increasing radiodensity at the outer upper and outer lower

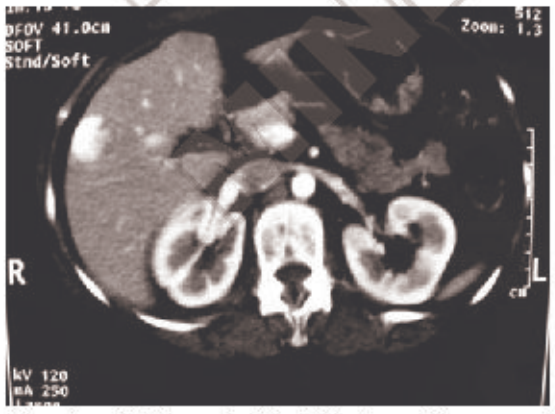

Figure 1.—TAC shows incidental finding, a liver mass of 3 cm any side, initially considered likely metastasis from breast cancer.

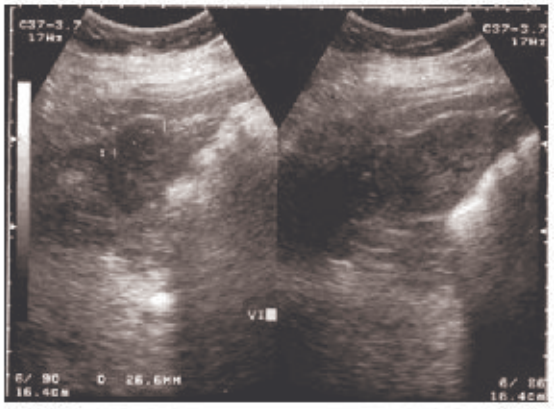

Figure 2.—Ultrasound investigations show liver-hemangioma.

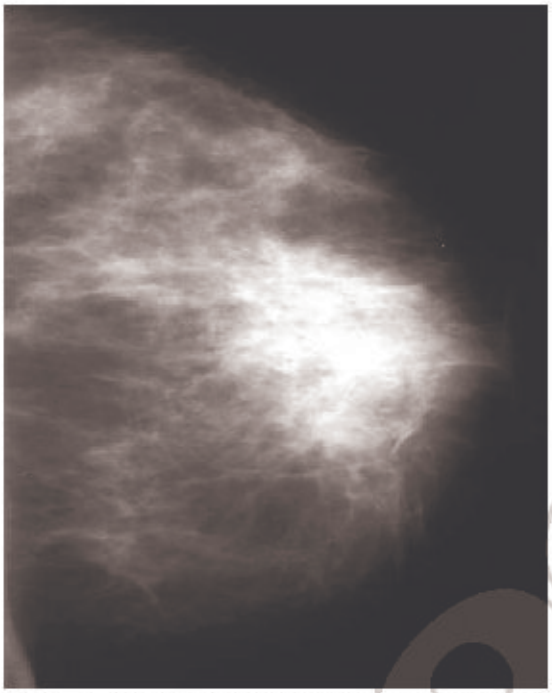

Figure 3.—Mammography shows asymmetry with increasing radiodensity at the outer upper/lower quadrants of the left breast, very suggestive for breast cancer.

quadrants of the left breast with nipple retraction.

For studied the breast mass and exclude metastases, was performed scintigraphy, showed negative metastatic disease and contemporary occasional spondylotic image (Figure 5).

The patient received a presumptive diagnosis of breast cancer and was treated with breast biopsy, which revealed an non-caseating granulomas with Langhans and bodytype giant cells within fibrous background tissue. These exhibited a distribution respecting the lobules, but at some sites completely destroying these structures. A few micro-abscesses and microgranulomas were found. Microscopic examination revealed adipose tissue with acute and chronic inflammation and macrophage, giant histiocyte, and epithelioid-like cellular infiltration, with cytologic features suggestive of a granulomatous process.

Aspiration culture showed no evidence of bacterial or mycobacterial growth (no evidence of tuberculosis or sarcoidosis was found).

The differential diagnosis, based on the histological features, included autoimmune response, undetected organisms, systemic granulomatous disease with breast involvement, granulomatous reaction in a carcinoma and foreign body reaction.

Considering patient's clinical history, all laboratory findings and imaging studies, the diagnosis was interpreted as IGM.

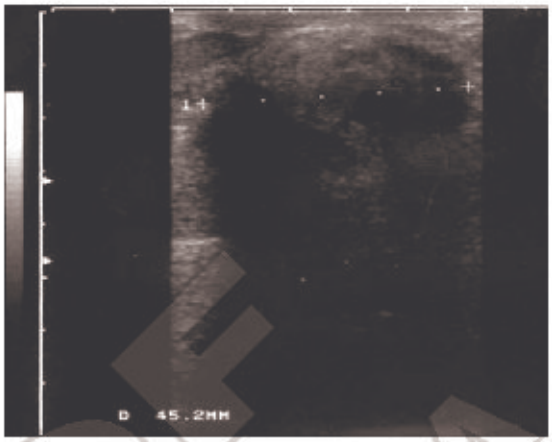

Figure 4.—Breast ultrasound image shows lobulated and hypoechoic mass, with ill-defined area and heterogeneous echoes in the left upper and lower outer quadrants, associated with increased vascularity, micro-calcification and tissue edema.

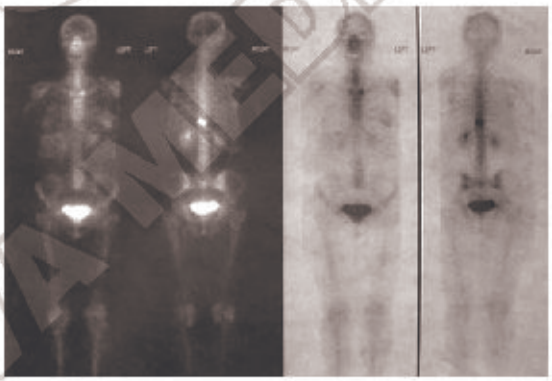

Figure 5.—Scintigraphy shows negative metastatic disease and contemporary occasional spondylotic image(arrow).

Our case is one of the few cases in the literature of hyperprolactinemia risperidone-induced.

Discussion

Idiopathic granulomatous mastitis is a disease characterized by unknown aetiology and is diagnosed by exclusion.

Possible infectious etiology are mycobacterium tuberculosis, blastomycosis, cryptococcosis, histoplasmosis, actinomycosis and filarial infection.

The presumptive causes of IGM, including alpha-1- antitrypsin deficiency, oral con-

traceptives usage, pregnancy, lactation, and hyperprolactinemia have been reported in literature.

Primary or secondary hyperprolactinemia, play an important role in IGM; previous hyperprolactinemia may cause IGM like results localized autoimmune protein secretion in the breast ducts during childbearing age.

Without a history of recent pregnancy, the serum prolactin level and the pathogenesis of IGM in non-pregnant outlines a role in the disease for hyperprolactinemia, and some trigger agents like environmental contaminants, pituitary adenoma and increase of hormone receptors, can promote cell proliferation.

Clinically, patients with IGM present a unilateral hard lump in the absence of any systemic signs of infection, and for these reasons, mimic carcinoma.

Approximately 200 cases of IGM "Risperidone-Induced Hyperprolactinemia" have been reported in the literature and more than 50% of the reported cases of IGM were initially mistaken for breast carcinoma, even with a combined diagnosis by mammography and ultrasound. A definitive diagnosis can be made only through histological evidence of granuloma formation with the absence of any infection[2].

During the diagnosis, diseases to be excluded are duct ectasia, sarcoidosis, Wegener's granulomatosis, giant cell arteritis, polyarteritis nodosa, tuberculosis, syphilis, corynebacterial infection, cat-scratch disease in breast lymph node tissue, mycotic infection, granulomatous reaction in a carcinoma and foreign body reaction, whether infectious or non-infectious, that can mimic IGM.

Granulomatous response to carcinoma is unusual and characterized by multinucleated giant cells restricted to the carcinoma or osteodastic giant cells (OGCs) at peripheral hypervascular stroma.

Foreign body reaction may be due to silicon leakage from breast implant.[2]

Many antipsychotic agents are known to increase prolactin secretion because of their inhibitory effect of dopamine; risperidone is known to increase serum prolactin level to a greater extent than other antipsychotics, such as quetiapine. Studies suggest that prolactin contributes to a wide variety of both physiological and pathological granulomatous cutaneous lesions, especially those of immune response, such as the non-caseating granulomas.

IGM usually appears during lactation, as a firm, discrete and unilateral mass;[3] in specific case, we suspected that the dopaminergic effect of risperidone [1] was the cause of hyperprolactinemia and IGM in our patient, and for this reason the prescription was shifted to prolactin-sparing second line agent (clozapine), during the postoperative period and follow-up.

Patients with psychiatric disorders and elevated prolactin levels while receiving risperidone, may require additional medication, in persisting psychiatric symptoms or to acclimate them to a second antipsychotic, or risperidone could be stopped due to metabolic problems. Aripiprazole, alternative drug, can be added concomitant to the risperidone treatment. Risperidone can cause gynecomastia with generalized breast enlargement and glandular; when to the treatment is added aripiprazole, patients prolactin normalized in 2 to 12 weeks.[4]

A conservative non-operative treatment is usually recommended for IGM patients with mild symptoms.[5]

Surgical treatment (surgical technique consist of wide surgical excision and/or mastectomy) is recommended for patients with symptoms of moderate and severe extent. Postoperative wound infection, fistulas, chronic suppuration and recurrence are often seen, and require surgical re-interventions; limited excision has a strong tendency for persistence or recurrence.[6]

According to our actual guide-lines the gold-standard treatment for patients with more severe symptoms, also may provide oral prednisolone [6] and immunosuppressive treatment (some cases the only curative treatment), especially in refractory cases.

In our case, the patient was treated with surgical excision of the affected lobe of the breast, with additional neoadjuvant prednisolone, 20 mg/d.

Follow-up last 2 years, still in progress, showed no recurrence of the disease, both clinically and by imaging studies positivity.

Conclusions

Idiopathic granulomatous mastitis is an uncommon benign entity of the breast, clinically and diagnostically characteristics similar to breast carcinoma.

In this study, we report a case of a non-pregnant woman, with a laboratory evidence of hyperprolactinemia due to risperidone usage.

The Authors emphasize the importance of an accurate clinical and instrumental examination, as a fundamental act for exclude other agents of diseases, principally thanks to biopsy.

In our case, treatment with steroids like neoadjuvant, before surgical management appears to be beneficial.

Our patient has benefit from the operation immediately, with resolution of the disease.

The follow-up (on-going), up to now, showed no recurrence of the pathological and no complications, making sure the authors of the efficacy of the surgical treatment.

The Authors believe in the surgical treatment as the only procedure, performed alone or combined with corticosteroid therapy, to the cure of the patients.

Riassunto

Mastite granulomatosa idiopatica associata a risperidone: segnalazione clinica

Obiettivo. La mastite granulomatosa è una rara malattia infiammatoria benigna del seno, caratterizzata dalla presenza di granulomi non caseosi non di origine infettiva, patologicamente non dissimile da un carcinoma. La diagnosi differenziale con la malattia tumorale maligna del seno non è facile, quindi spesso inizialmente si giunge a una diagnosi errata, tardando il trattamento corretto. La biopsia è necessaria per la corretta diagnosi e non vi è ancora alcun trattamento generalmente accettato. Nella nostra esperienza un approccio conservativo sembra essere adeguato nella maggior parte dei casi e, a nostro avviso, il trattamento chirurgico è la migliore terapia. Un'altra opzione è un lungo/medio trattamento steroideo. È obbligatorio escludere cause infettive di mastite granulomatosa prima di avviare una terapia corticosteroidea.

Metodi. Nella nostra paziente il trattamento chirurgico è stato effettuato eseguendo una escissione della lesione intera, e successivamente è stata eseguita una terapia neoadiuvante con farmaci corticosteroidei.

Risultati. La paziente ha mostrato un beneficio immediato, con risoluzione clinica-strumentale della malattia. Il follow-up (in corso) non ha mostrato recidiva del quadro patologico, non ha mostrato complicazioni, rendendo sicuri gli autori della efficacia del trattamento chirurgico.

Conclusioni. Lo scopo di questo studio era descrivere la clinica, l'imaging, le caratteristiche patologiche della mastite granulomatosa lobulare della nostra paziente, discutere dei protocolli diagnostici e terapeutici che abbiamo usato per la diagnosi e infine analizzare il trattamento di questa rara malattia. Gli autori ribadiscono che credono nel trattamento chirurgico, come unica procedura, eseguita da sola o in combinazione con la terapia corticosteroidea, per la cura dei pazienti.

Parole chiave: Mastite granulomatosa -Risperidone - Carcinoma della mammella.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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