

Case Report

Tuberculous mastitis presenting as a lump: a mimicking disease in a pregnant woman case report and review of literature

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Tuberculosis (TB) of the breast is a rare entity, and can be confused with many other breast disorders, like mamma carcinoma or inflammatory breast cancer. When finding granulomatous mastitis (GM) on histology, it is important to make a differential diagnosis and seek actively for clues on the presence of tuberculosis, sarcoidosis, Wegener's granulomatosis, or idiopathic granulomatous mastitis, since treatment strategies differ and maltreatment has major implications on morbidity and mortality. An extensive clinical evaluation, laboratory work up, and imaging will lead in most cases to the right diagnosis. Anti-tuberculous therapy is the core treatment for breast TB, and surgery is indicated for extensive or persistent residual disease. Here we present a case of tuberculous mastitis and a review of literature on GM.

Keywords: Granulomatous mastitis, Breast mass, Tuberculosis, Pregnancy

Introduction

Tuberculosis (TB) is responsible for a high global disease burden. In 2012 the WHO reported 8.7 million new cases, most of them present in Asia and Africa.¹ Breast TB is a form of extra-pulmonary TB which is rarely seen. It was first described by Sir Astley Cooper in 1829² and accounts for 0.1% of all mammary lesions in western countries, but up to 4% in TB endemic regions.^{3,4} Breast TB is usually diagnosed in young lactating multiparous women.^{5,6} Clinical features are diverse and can mimic carcinoma, abscess, or infectious mastitis. Additionally, radiological findings are nonspecific.⁷ Diagnosis can be presumed when finding granulomas on histopathology of FNAC, or core or open biopsy specimen. However, it is of high importance to differentiate between several pathologies causing granulomatous mastitis (GM), like TB, sarcoidosis, Wegener's disease, or idiopathic granulomatous mastitis (IGM). Since maltreatment with corticosteroids will brisk up existing TB, and omitting proper treatment for Wegener's disease can even lead to death.⁸ Acid-fast bacilli (AFB) staining or culture can confirm the presence of *Mycobacterium tuberculosis*; however, it is often found to be negative.^{5,9} Here we present a case of breast TB in a pregnant woman,

which was only diagnosed after multiple surgical interventions.

Case Report

A 33-year-old Moroccan woman presented at the Breast Clinic of our hospital with a painful mass in her left breast. She reported a history of the sudden appearance of the mass a few weeks before, and being sub fibril only once. There was no history of systemic diseases or surgery, nor was there a family history of breast cancer. She was not on medication. Furthermore, she had three healthy children whom she breastfed for 20, 20, and 7 months.

Physical examination showed an ill-defined lump in the upper quadrant of the left breast, measuring about 3 cm, without any skin abnormalities, nor nipple discharge. An enlarged left axillary lymph node was observed. Laboratory workup was essentially normal including absence of inflammatory parameters. We tested for pregnancy and a positive human chorionic gonadotropin of 72 U/l was found. It turned out she was pregnant for four weeks. Ultrasound investigation showed significant swelling and engorgement of the tissue in the upper part of the breast, without any sign of malignancy or abscess, nor pathological lymph nodes. Confirming the idea of hormonal engorgement, she was treated with paracetamol and close follow up.

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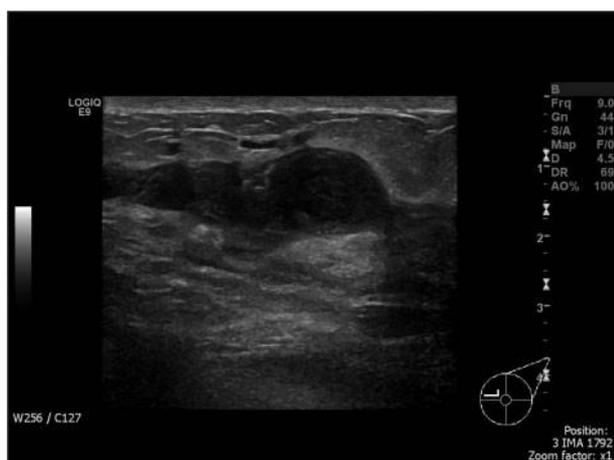


Figure 1 Ultrasound image of the left breast showing diffuse oedematous induration of the skin and sub cutis. Irregular hypoechoogenic masses and an abscess collection, which was on Doppler surrounded by hyperaemia.

After two weeks she went to Morocco for six weeks, where she visited the local hospital with 39°C fever, skin vasculitis, erythema nodosum, and arthralgia. She underwent resection of the lump and was hospitalized for two weeks. Post-operative, the patient received antibiotic treatment and multiple evacuations for residual haematoma. Histopathology in Morocco showed GM, though no staining or culture was performed.

Back in Belgium the patient presented at the emergency department with a wound infection and abcedation. Besides pain and redness on her left breast, she had high grade fever of 39°C, erythema nodosum on both legs, and arthralgia. At this moment she was pregnant for 13 weeks. Ultrasound showed extensive and irregular polylobular abscess collections, of which one with imminent skin breakthrough (Fig. 1). The patient had a drainage of the abscess together with a debridement of the entire

infected area, creating an open wound of 10 cm. The wound was treated with vacuum assisted closure therapy. Specimen was sent for histopathology.

The systemic symptoms of fever, vasculitis, erythema nodosum, and arthralgia pointed towards Wegener's disease or IGM; however, anti-neutrophil cytoplasmic antibodies (ANCA) were negative and there was no proteinuria or haematuria. Repeated, detailed questioning revealed the possibility of TB, as the patient was treated for cervical lymph node enlargement for 6 months, while living in France 10 years ago. Furthermore, the Mantoux showed an induration of 12 mm. There was no clinical indication for pulmonary TB and chest X-ray turned out negative. The diagnosis of breast TB was supported by histopathological findings; however, staining and cultures for bacteriology, yeasts, and mycobacterium remained negative. Histological sections showed extensive GM with expansion of the infiltrate over the ductal and lobular epithelia, and destruction of the parenchyma. Granulomas contained central necrosis and Langhans giant cells were present (Fig. 2). Subsequently, the T-spot test turned out positive, and PCR confirmed the presence of *M. tuberculosis*.

Meanwhile, the wound was improving until a new inflammatory focus appeared in the under-outer quadrant, which was marked with an erythematous skin lesion and subcutaneously linked to the existing wound. In total, nine vacuum assisted closure renewals every 4 days were needed before closure of the wound was possible.

The difficult diagnostic process, delayed proper treatment. Finally at 17 weeks of pregnancy the patient started with anti-tuberculous therapy (ATT). She was treated with isoniazid, rifampicin, ethambutol, and pyrazinamide for two months, followed by

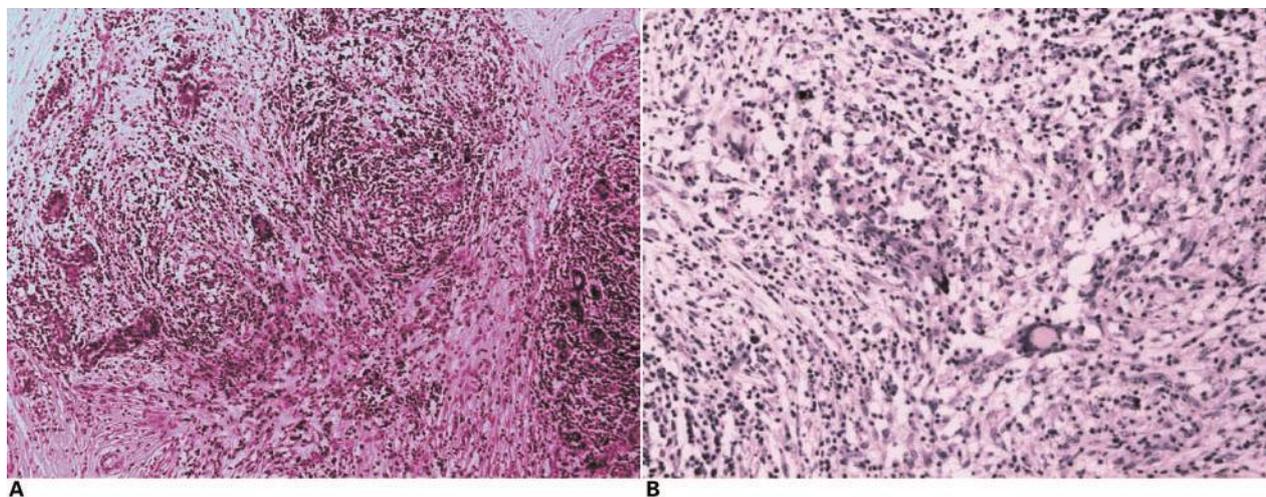


Figure 2 (A) Histological sections showing extensive GM with expansion of the infiltrate over the ductal and lobular epithelia, and destruction of the parenchyma (40 ×). (B) Granulomas containing central necrosis and multi-nucleated Langhans giant cells (200 ×).

four months of isoniazid and rifampicin alone. After six weeks of therapy, there was clinical improvement and the wound was healing well.

At 39 weeks of pregnancy the patient delivered a healthy son, and four weeks later she accomplished ATT. Remarkably, two weeks after finishing therapy, the patient developed two new asymptomatic granuloma's, which both on ultrasound and MRI appeared as well defined encapsulated inhomogeneous nodules. Currently, the patient is having close follow up, with monitoring of the breast.

Discussion

Presentation

Breast TB is an extremely rare manifestation of extrapulmonary TB. This may be due to mammary gland tissue, as well as the spleen and skeletal muscle, being more resistant against mycobacterial infection.^{4,5,10,11} Additionally, primary breast TB is even more infrequent, since these infections arise from direct contamination, which may be associated with some lactation-related infections.¹⁰ Overall, it is more likely that breast TB is secondary; however, the location of primary infection is often unknown.^{7,9} Secondary breast TB is suspected in women diagnosed with TB

before. Therefore detailed history questioning, especially when originating from endemic countries, is essential.

Localisation is often central or in the upper-outer quadrant of the breast, associated with axillary lymph node involvement.⁷ Breast TB can present in various forms, based on radiological and clinical characteristics (Table 1). First, a nodular or lump variant, which is most common.^{5,10} This is a well circumscribed, slow growing mass that progresses to involve the overlying skin, may ulcerate, and form sinuses.⁹ The nodular form is often mistaken for fibroadenoma in earlier stages, while later on it may present as an oval tumour shadow on mammography, mimicking breast carcinoma.^{4,9} Yet, pain in the lump is more present in breast TB compared to breast carcinomas.⁵ Second, mammary TB frequently presents as a breast abscess.^{9,11} The disseminated variant is characterized by multiple lesions which, in later stages, caseate leading to sinus formation. The skin is thickened and tense, sometimes with painful ulcers.⁹ Disseminated breast TB might be mistaken for inflammatory breast cancer on mammography.⁴ This form is also referred to as diffuse nodularity or multiple sinuses.^{5,7} Lastly, a rare sclerosing form is

Table 1 Differential diagnosis of tuberculous mastitis

	Tuberculosis	Tumour	Other GM
Presentation	Lump or nodular form <i>well circumscribed, painless, slow growing may ulcerate, form sinuses, or become painful</i> Dissiminated or diffuse nodularity <i>multiple lesions, may evolve to multiple sinuses and skin ulcers</i> Breast abscess Sclerosing form <i>hard, painless, slow growing</i>	Fibroadenoma or carcinoma Inflammatory breast cancer	Sarcoidosis: firm mass, lymphadenopathies Wegener's: lump, usually tender, painful IGM: firm breast mass; sometimes nipple retraction, pain, skin inflammation, or lymphadenopathies; associated with lactation
Imaging	MX	Spiculated mass Increased parenchymal density	Definable or spiculated mass Heterogenous, increased parenchymal density
	US	Microcalcification	Heterogenous, increased parenchymal density
	Doppler	Irregular, inhomogeneous and hypoechogenic masses Breast abscesses without caverns	Irregular, inhomogeneous and hypoechogenic masses
Histology	Increased vascularity of lesions/surrounding tissue Granulomas, Langhans giant cells, lymphocyte aggregates with caseation and necrosis AFB or culture (low positive rate) Tuberculin skin test, T-spot test, PCR	Increased vascularity of lesions/surrounding tissue Malignancy	Increased vascularity of lesions/surrounding tissue Granulomas, Langhans giant cells, lymphocyte aggregates without caseous necrosis or calcification
Treatment	ATT, surgery is indicated in some cases	Surgery and/or systemic therapy	Sarcoidosis: none, except when symptomatic Wegener's: corticosteroids and cyclophosphamide IGM: observation (immunosuppressants or surgery)

Note: MX: mammography; US: ultrasound; IGM: idiopathic granulomatous mastitis; ATT: anti-tuberculous therapy.

described.⁴ Our patient presented with a single painful lump, which did not involve the overlying skin at first consultation. Furthermore, hormonal changes were seen in her breast, due to pregnancy. Gradually she was thought to have secondary breast TB, since her history suggested TB; however, we were not able to demonstrate a primary infection.

Differential diagnosis

Besides benign anomalies and malignant lesions, breast lumps can exist of inflammatory or infectious diseases (Table 1). GM can be differentiated into infectious causes like TB, fungal infection, actinomycosis, or histoplasmosis, and primary inflammatory diseases such as sarcoidosis, Wegener's granulomatosis, and IGM.^{3,12} However, malignancy is far more common than inflammatory or infectious breast tumours. Several imaging methods are used to differentiate carcinoma from GM. On mammography malignant lesions have varied appearances, from the obvious spiculated masses, to subtle asymmetries in parenchymal density. The same is true for inflammatory and infectious breast masses.¹² In accordance with other case reports, our patient showed an ill-defined dense heterogeneous parenchyma, associated with two speculated focal masses, without micro calcifications (Fig. 3).¹²⁻¹⁵ Ultrasound examination of GM shows irregular, inhomogeneous and hypoechogenic masses, which are also signs of ductal carcinoma.^{13,14,16} In some GM cases breast abscesses without caverns are found. Doppler indicates an increased vascularity of the lesions and the surrounding tissue.^{15,17} On MRI, both carcinoma and GM appear as ill-defined heterogeneous masses. Even on dynamic contrast-enhanced MRI they are undistinguishable, based on increased vascularity in the malignant and inflammatory setting.^{13,18}

Since imaging is not able to exclude or prove these various causes of breast lumps, biopsy should be performed. Histopathological examination can exclude malignancy and may reveal breast granulomas. The histological findings may include epithelioid granulomas, Langhans giant cells and lymphocyte aggregates.⁵ When caused by TB, caseation and necrosis is often observed, and sometimes AFB can be demonstrated.⁵ However, AFB staining suffers a low sensitivity, as well as culturing *M. tuberculosis*. They both have a low positivity rate and therefore TB infection is difficult to diagnose.⁷ In our patient we were not able to demonstrate TB infection neither with direct staining nor with culture. Another possibility is to perform a T-spot TB test, which is not influenced by prior BCG vaccination in contrast to the tuberculin skin test.⁷ The highest sensitivity and specificity can be achieved by performing PCR on specific gene targets, where atypical forms of

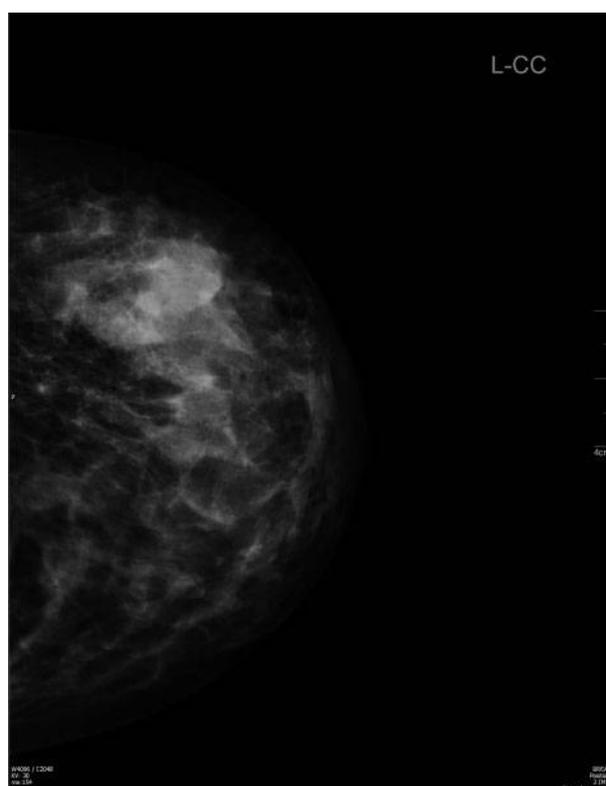


Figure 3 Mammographic image (left breast, cranio-caudal) showing an ill-defined dense heterogeneous parenchyma, associated with two speculated focal masses, without micro calcifications.

mycobacteria can also be revealed.¹⁹ Via the latter two we were able to prove the patients TB infection.

Besides her lump, our patient developed systemic symptoms like high grade fever, erythema nodosum on both legs, and arthralgia. Erythema nodosum on the lower legs in a breast TB case was described only once by Kao *et al.*, indicating the rarity of cutaneous involvement.⁵ Besides TB, systemic symptoms often occurs in association with other granulomatous diseases, like sarcoidosis, Wegener's disease, or IGM.

Breast sarcoidosis is rarely found and in the majority of cases, patients have a history with sarcoidosis.²⁰⁻²² It presents clinically as a firm mass and at mammography both well-defined round lesions, as well as irregular spiculated lesions mimicking carcinoma, have been found.¹² They mostly present in women in 2nd till 4th decade, which also applies for breast TB.^{5,6,12,21} In active disease, about 90% of patients have an abnormal chest X-ray at some time during the course of the disease.²³ This should always be checked when finding GM. Furthermore, lymphadenopathies are very common.²⁴ Histopathology shows epithelioid granulomas with Langhans giant cells, without caseous necrosis, calcification, or fat necrosis.¹² Extra-pulmonary sarcoidosis can be anticipated by compatible clinics, imaging, histopathology, and relative exclusion of other diagnoses (Table 2). In sarcoidosis, lesions will

Table 2 General diagnostics in case of suspected granulomatous disease

	Tuberculosis	Sarcoidosis	Wegener (GPA)	IGM
Clinics	Respiratory symptoms	Respiratory symptoms	ENT manifestations	Fever, poly arthralgia, erythema nodosum associated with lactation Lymphadenopathy
	Fever, malaise Weight loss Erythema nodosum Lymphadenopathy	Skin lesions Uveitis Arthritis Lymphadenopathy	Vasculitis, purpura Muscle or joint pain Glomerulonephritis	
Laboratory	Mantoux ESR, CRP T-spot PCR	ACE, ESR Eosinophilia Calciuria	cANCA/anti-PR3 Creatinine ESR, CRP, anaemia Proteinuria, haematuria	Sometimes inflammatory
Chest X-ray	Bilateral hilar LN Infiltration	Bilateral hilar LN Interstitial anomalies	Bilateral hilar LN Parenchymal lung nodes Diffuse interstitial anomalies Vasculitis	Normal
Histology	Necrotizing granulomas AFS and culture	Non-necrotizing granulomas, however some central necrosis is possible. Occasionally asteroid or schaumann bodies	Granulomatous inflammation, seldom nice formed granulomas without central necrosis	Non-necrotising inflammatory granulomas

Note: ACE: angiotensin converting enzyme; ANCA: anti-neutrophil cytoplasmic antibody; ENT: ear nose throat; ESR: erythrocyte sedimentation rate; GPA: granulomatosis with polyangiitis; IGM: idiopathic granulomatous mastitis, LN: lymph nodes.

usually resolve spontaneously, in contrast to breast TB. However, treatment with prednisolone is sometimes indicated.²⁵

Wegener's granulomatosis is a necrotizing granulomatous vasculitis affecting various organs, especially lung and kidney.²⁶ Breast involvement is uncommon, and primary breast Wegener's is even more exceptional.^{8,27,28} It clinically mimics mammary carcinoma, although breast tumours in Wegener's disease are usually tender. Additionally, mammography reveals a dense lesion with irregular of stellate borders resembling carcinoma.¹² Again, histopathology shows GM. However, when biopsy is not able to demonstrate vasculitis, in addition to absence of classic pulmonary and renal symptoms, Wegener's is often late- or misdiagnosed.^{8,27} When finding GM, it is important to check for presence of ANCA, nasal or oral inflammation, abnormal chest X-ray, and microhaematuria (Table 2).²⁹ It is generally treated with corticosteroids and cyclophosphamide.²⁷ In our patient there was absence of lung lesions and she tested negative for ANCA and haematuria, so we rejected this diagnosis.

IGM may present as a firm breast mass, sometimes with nipple retraction, pain, skin inflammation, or enlarged lymph nodes.^{30,31} Several cases presented with additional symptoms like fever, polyarthralgia, and erythema nodosum.³² It generally occurs two to six years after pregnancy, and is associated with lactation.³¹ Histopathological analyses show noncaseating, nonvasculitic granulomatous inflammatory reaction centred on lobules.¹² Most of these features where compatible with our case. However, IGM remains an exclusion diagnosis. Depending on the course of the disease, it can be treated with observation, immunosuppressants or surgery.³⁰⁻³²

Treatment strategies

The treatment of breast TB consists of ATT and at specific indication surgery is performed.⁵ Although ATT is the core treatment, there are no guidelines available for breast TB. Usually all extra-pulmonary TB, except for tubercular meningitis, are treated with the same four-drug combination regimen as pulmonary TB.^{4,9,11} Complete resolution is obtained in most patients. However, there are special schemes in case of resistance or slow clinical response.^{5,9} After 3 weeks of ATT, our patient showed obvious clinical response.

ATT is the treatment of choice; however, it is to a greater or lesser extent combined with surgery. Afridi *et al* describe a case series of 30 breast TB patients, where despite ATT, 70% required surgical management.^{14,33} Contrarily, Sakr *et al* report a need for surgical excision of the mass in 30%.^{14,33} Similar outcomes were demonstrated in two other case series, where ATT in combination with removal of infected breast tissue seemed to be the treatment of choice.^{34,35} Often incisional or excisional biopsy is performed for diagnostics, however surgery may also be required for drainage of abscesses, or removal of residual lumps after ATT.^{4,9} When large lumpectomies are performed, recovery is not obvious. Active infection inhibits the healing process and new lesions can arise. This was the case with our patient, as she arrived from Morocco with large abscedation at the level of her surgical wound and adjacent lesions. Therefore, every surgical intervention should be covered by ATT. Lastly, simple mastectomy is performed in case of extensive disease, causing a large painful ulcerated mass involving the entire breast.^{4,9}

Also during pregnancy there should be proper treatment for breast TB. All four first line drugs have

an excellent safety record in pregnancy and are not associated with fetal malformations.³⁶ However, there should be close follow up on adherence to treatment, since pregnant women are often repulsive for taking any medication or suffer from pregnancy-related nausea, which may impede the intake. Pyridoxine (vitamin B6) should be added to isoniazid containing ATT in all pregnant women.³⁶

Conclusion

Tuberculosis of the breast is a rare entity, and often confused with many other breast disorders, leading to delayed treatment and needless surgery. It is important to realize that not every breast lump consists of carcinoma, and that these rare disorders should be treated in specialized breast clinics. When finding granulomas on histopathology, all differential diagnoses should be explored since misdiagnosis may lead to high morbidity. However, it may be difficult to prove TB infection, because of low sensitivity of direct staining and culture. Thorough history questioning in combination with the tuberculin skin test, the T-spot test and PCR can confirm the diagnosis. Breast TB is treated with ATT and surgery is indicated in some cases.

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