

Breast tuberculosis: a case series

Mounir Moukit^{1*}, Youssef Bougrini², Mohammed Rahmoune¹,
Ismail Allilou¹, Abdellah Babahabib¹

¹Department of Gynecology, Military Hospital of Meknes, Meknes, Morocco

²Department of Pneumology, Military Hospital Moulay Ismail, Meknes, Morocco

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***Correspondence:**

Dr. Mounir Moukit,

E-mail: moukitmounir@yahoo.com

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ABSTRACT

Tuberculosis is one of the leading infectious and contagious diseases, caused by bacteria belonging to the Mycobacterium family. Breast involvement ranks last among the extrapulmonary manifestations of tuberculosis but remains an important clinical condition that may present clinical and radiological similarities with breast cancer, thus requiring a thorough diagnostic approach including histological and/or bacteriological confirmation. This is a retrospective study conducted at the department of Gynecology and Obstetrics of the Military Hospital Moulay Ismail - Meknes, over a period of 4 years. A total of 6 cases of breast tuberculosis were observed, resulting in an incidence rate of 6 cases per 7600 women-years. The mean age of patients was 39 years. Signs of tuberculosis impregnation were found in 33% of cases. The clinical forms encountered, in descending order of frequency, were: diffuse form (50% of cases), nodular form (33% of cases), and sclerotic form (16% of cases). The radiological findings were almost always suggestive of a suspicious lesion. Diagnosis was primarily based on the histopathological study of breast biopsy. All our patients received a standard regimen of anti-tubercular treatment including: 4 months of Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol followed by 2 months of Rifampicin and Isoniazid with favorable outcomes. Only one patient experienced a recurrence due to under dosing of Rifampicin, which was managed with a total of 9 months of treatment. One patient underwent additional surgical drainage. Early and thorough diagnosis of breast tuberculosis is crucial as it helps avoid mutilating surgery in often young women.

Keywords: Breast, Koch's Bacillus, Granuloma, Caseous necrosis, Antitubercular agents

INTRODUCTION

Tuberculosis is an infectious disease caused by bacteria belonging to the Mycobacterium family or Koch's bacillus (BK). According to the World Health Organization (WHO), it remains a major public health problem, causing approximately 1.4 million deaths annually worldwide.¹ Breast tuberculosis ranks last among extrapulmonary manifestations and represents approximately 0.1% of all cases.² Increasingly frequent cases are reported in industrialized countries, particularly with the emergence of human immunodeficiency virus (HIV) infection.^{3,4} It is crucial to differentiate breast tuberculosis from other breast conditions, especially cancers, due to their clinical and radiological similarities. In reality, breast tuberculosis

is often mistaken for malignancy, and only histopathological and/or bacteriological analysis can confirm the diagnosis. Treatment mainly relies on antituberculous medications; however, surgical intervention may sometimes be necessary. The prognosis under treatment is often favorable, with the outcome depending on other tuberculosis manifestations. In this paper, we present a series of six cases of breast tuberculosis, collected within the obstetrics and gynecology department of the Moulay Ismail Military Hospital in Meknes, Morocco, over a four-year period. Based on our findings and literature review, we emphasize the epidemiological, clinical, radiological, and therapeutic characteristics of breast tuberculosis. We also highlight the challenges encountered in differential diagnosis with other

breast diseases, particularly neoplastic ones, aiming to avoid mutilating surgeries in predominantly young patients.

CASE SERIES

Case 1

A 47-year-old multiparous woman, with no significant medical history, particularly no history of tuberculosis exposure. Referred for management of a right breast nodule discovered by self-palpation three months ago, without any associated symptoms. The breast examination revealed a nodule in the upper-inner quadrant, measuring 1.5 cm in diameter, soft and painless, mobile in both planes, without skin or nipple-areolar changes. The axillary and supraclavicular lymph nodes were normal, the left breast and the rest of the physical examination were unremarkable. Mammography showed a stellate opacity in the upper-inner quadrant, without microcalcification foci or skin or nipple-areolar abnormalities (Figure 1). Breast ultrasound revealed a hypoechoic, heterogeneous, poorly defined area without posterior enhancement in the right breast, suggesting mastitis that needed to be confirmed by magnetic resonance imaging (MRI) (Figure 2). MRI suggested a poorly defined lesion in the upper-inner quadrant, measuring 24 mm, with heterogeneous signal and contrast enhancement, along with another lesion in the lower-inner quadrant showing similar characteristics; both lesions were classified as breast imaging-reporting and data system (BI-RADS) V (Figure 3). Histological analysis of the material obtained by biopsy from both lesions revealed epithelioid granulomatous mastitis with caseous necrosis and no histological signs of malignancy. Further investigation for other tuberculosis locations, particularly pulmonary, was negative. The patient was treated with antitubercular drugs for six months, resulting in the disappearance of both nodules without sequelae.

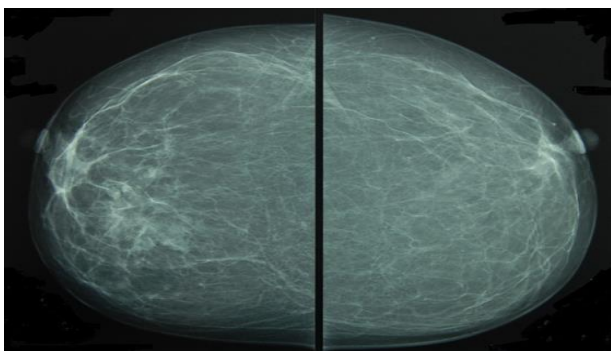


Figure 1: Mammogram (frontal view) revealing a stellate opacity in the upper-inner quadrant of the right breast.

Case 2

This concerns Mrs. M. I., 55 years old, of Gabonese origin, with no significant medical history, particularly no family history of neoplasia. Admitted to our department for left

breast induration without associated symptoms. Clinical examination revealed breast asymmetry with multiple left breast ulcers suggestive of granulomatous mastitis (Figures 4 and 5), with presence of mobile centimeter-sized axillary lymph nodes. The supraclavicular chain and the contralateral breast were unremarkable. Breast ultrasound and mammography were performed, revealing multiple confluent opacities in the left breast with skin infiltration and ipsilateral axillary lymphadenopathy. Additional biopsy of the skin ulceration and underlying induration showed epithelioid granulomatous inflammation with caseous necrosis. The patient was treated with anti-tubercular drugs (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol for 2 months and Rifampicin, Isoniazid for 4 months) with favorable outcome.



Figure 2: Breast ultrasound showing a poorly defined, hypoechoic, heterogeneous lesion without posterior acoustic enhancement in the right breast.



Figure 3: Breast MRI revealing two suspected lesions classified BI-RADS V.



Figure 4: Clinical view objectifying the asymmetrical aspect of breasts.



Figure 5: Side view revealing multiple left breast ulcers.

Case 3

This concerns Mrs. Z. A., 45 years old, nulligravida, widowed, with no significant medical history, particularly no family history of neoplasia. Admitted for right breast induration with a reported weight loss of 15 kg over two months. Clinical examination revealed a painless ulceration in the axillary extension of the right breast (Figure 6) with mobile centimeter-sized axillary lymph nodes. The supraclavicular chain and the left breast were unremarkable. Breast ultrasound and mammography were performed, showing a 6 cm irregularly bordered opacity in the upper-outer quadrant (UOQ) of the right breast with skin retraction and benign-looking axillary lymph nodes. Additional biopsy of the skin ulceration and underlying induration revealed epithelioid granulomatous inflammation without caseous necrosis. In consultation with the pathologists, a tuberculosis workup was requested. The thoracic Computed tomography scan was normal; however, the QuantiFERON-TB Gold test revealed a tuberculous infection. The patient was treated with anti-tubercular drugs (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol for 2 months and Rifampicin, Isoniazid for 4 months) with a favorable outcome. Follow-up showed good clinical progress over a one-year period.



Figure 6: Ulceration in the axillary extension of the right breast.

Case 4

A 30-year-old primiparous, with a history of pulmonary tuberculosis at the age of 22, treated and declared cured.

She has been using copper intrauterine contraception for 2 years and presents with a mass in the lower-inner quadrant (LIQ) of the right breast. In interrogation, signs of tuberculosis such as anorexia and weight loss were noted. Breast examination revealed induration of the entire LIQ of the right breast without identifiable nodules. Examination of the axillary and supraclavicular lymph nodes as well as the left breast was normal. Breast ultrasound and mammography revealed a lobulated, hypoechoic, heterogeneous, and vascularized formation in the LIQ of the right breast, measuring 40×20 mm and classified BI-RADS 4. Given the patient's young age, history of pulmonary tuberculosis, signs of tuberculosis exposure, and the radiologic findings, breast tuberculosis was suspected initially, followed by benign or even malignant breast disease. Histopathological examination of a biopsy from the induration revealed mammary tissue dissected by a granulomatous inflammatory infiltrate containing epithelioid and giant-cell granulomas but without central caseous necrosis, concluding granulomatous mastitis. Ziehl-Neelsen staining was negative. Thoracic computed tomography scan and QuantiFERON-TB gold test were normal. In consultation with pulmonologists and pathologists and given the strong suspicion of breast tuberculosis, a second biopsy followed by histopathological examination was performed, confirming the diagnosis this time by the presence of caseous necrosis foci. The patient received standard anti-tubercular treatment, with favorable evolution and no recurrence over a period of 2 years.

Case 5

This concerns Mrs. Z. E., 26 years old, primiparous, with no particular medical history, who underwent surgery by a private gynecologist for an abscess in the left breast (incision and drainage of the abscess with biopsy of the pockets). Culture of the abscess was negative, and histopathological examination of the biopsy suggested inflammatory changes. She was prescribed Amoxicillin. Three months after the procedure, the patient reported a recurrence of the same initial symptoms, but this time in another quadrant, prompting her consultation at our facility. During interrogation, she mentioned weight loss, along with weakness and night sweats. Clinical examination of the left breast revealed a radial scar in the upper-outer quadrant corresponding to the initial procedure, with palpation of a soft, warm, and painful structure with shiny skin in the lower-outer quadrant, measuring 4 x 5 cm and suggesting abscess. Given the size of the abscess, the decision was made to admit the patient to the operating room for new drainage and biopsy of the pockets. Bacteriological study of the purulent sample was requested, emphasizing the search of BK. The results consistent with a tuberculous infection, confirmed by positive culture of BK and histopathological examination revealing epithelioid granulomas with caseous necrosis. Chest X-ray was normal, and no other tuberculous site was identified. The patient received anti-tubercular treatment: Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol for

2 months, followed by Rifampicin and Isoniazid for 4 months. Follow-up revealed a recurrence in the form of a small subcutaneous breast collection of 1 cm in the fifth month of treatment, confirmed by ultrasound. Under-dosing of anti-tubercular treatment was suspected. After blood levels of anti-tubercular drugs were measured, the diagnosis of under-dosing of Rifampicin was confirmed. In consultation with pulmonologists, an increase in both dosage and duration of treatment was decided, totaling 9 months of treatment. The outcome was favorable, with complete resolution of breast symptoms and weight gain. The patient was declared cured. She is currently pregnant in 16 weeks with normal obstetrical follow-up.

Case 6

A 36-year-old multiparous, with no particular medical history, especially no family history of malignancy or tuberculosis exposure, presented to our department with right breast mastodynia that had appeared two months prior. Clinical examination revealed an orange peel skin appearance of the right breast associated with painless lower areolar ulceration (Figure 7), with the presence of ipsilateral axillary lymph nodes suggestive of locally advanced breast cancer (T_{4d} N₁ M_x); the left breast was unremarkable, as was the rest of the clinical examination. Ultrasound and mammography showed diffuse skin thickening of the right breast without nodular lesions or microcalcifications, associated with multiple hypoechoic axillary lymph nodes, the largest measuring 20 mm.

Biopsy of the areolar ulceration revealed epithelioid granulomas with caseous necrosis, confirming the diagnosis of breast tuberculosis mastitis. The patient was referred to the department of pneumology where a therapeutic regimen consisting of Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol for 2 months followed by Rifampicin and Isoniazid for 4 months was initiated, totaling 6 months of treatment. The course was marked by the resolution of inflammatory signs and ipsilateral axillary lymph nodes. It is noteworthy that the patient is currently pregnant at 27 weeks of gestation.



Figure 7: Orange peel appearance of the right breast associated with a lower areolar ulceration.

DISCUSSION

According to the WHO, tuberculosis is the thirteenth leading cause of mortality worldwide and the second leading cause of death due to an infectious disease, behind COVID-19 and ahead of HIV.⁵ Morocco is among the countries affected by tuberculosis. In 2021, the number of recorded cases was 29,327, including 240 cases with HIV co-infection.^{6,7} Breast tuberculosis was first described by Sir Astley Cooper in 1829 in London, under the term "cold tumor of the breast".⁸ Subsequently, the histopathological evidence of breast tuberculosis was discovered by Richet in 1880 and the bacteriological evidence by Ohnaker in 1883.^{9,10} In 1939, Webster noted that among 34 patients who died in the context of miliary tuberculosis, the only organ ever affected was the breast, highlighting the exceptional localization of this organ.¹¹ The frequency of breast localization of tuberculosis varies according to countries. In a study of 215 cases, Asia ranked highest with 45.2%, followed by Sub-Saharan Africa (27.4%), North Africa (17.2%), Europe (16.2%), and finally the Americas (4%).¹² In India, in 2015, the incidence of breast localization ranged between 3 and 4.5% of surgically treated breast diseases, whereas in the West, the incidence ranged from 0.06 to 1.78%.^{13,14} In Morocco, over an 8-year period from 2001 to 2008, Zekri et al found an incidence of breast tuberculosis of 0.4%, similar to those noted in studies conducted in North Africa.¹⁵ As for our study, over a period of 4 years, 6 cases of breast tuberculosis were collected out of a total of 1900 breast conditions, resulting in an incidence rate of 6 cases per 7600 women-years. Pathophysiologically, breast tuberculosis involvement can be either primary, where the infection appears to be strictly limited to the breast (60% of cases), or secondary to another tuberculous localization (pulmonary, and lymph nodes).^{16,17} Breast tuberculosis primarily affects females.¹⁸ In a study of 809 cases of male breast masses, Lilleng et al. found no cases of breast tuberculosis.¹⁹ However, Darré and colleagues reported two cases of breast tuberculosis in men in a series of 28 patients.²⁰ In our series, all patients were females, and until now, no cases of breast tuberculosis have been reported in males. The parameter "age" varies according to regions. In regions with high tuberculosis endemicity, the disease seems to affect young women, whereas in developed countries, it primarily affects elderly women. Mukerjee and Khaiz reported an average age of 58 years in America.¹² However, Cohen noted an age of 34 years in Africa, and Ben Hassouna reported an average age of 36 years in North Africa.^{12,21} Extreme ages are not spared. Webster reported a case of a 6-month-old male infant, and Goldman reported a case in an 84-year-old woman.^{3,22} In our series, the average age of patients was 39 years, which is consistent with that described in other series from the same region. The risk factors for breast infection by *Mycobacterium tuberculosis* classically reported in the literature are: pregnancy, lactation, history of pulmonary or extrapulmonary tuberculosis, history of breast trauma, and immunosuppression.¹² In our study, there was only one patient with a history of pulmonary tuberculosis treated

and cured. Breast tuberculosis is mastitis with an insidious and nonspecific onset. Delayed consultation is frequently observed. Indeed, patients consult after a variable delay ranging from one week to 5 years, which reflects the chronicity of the condition.¹² According to Morgan, the consultation delay ranged from a few weeks to more than 10 years, while for Wilson it was between 1 and 4 months only.^{13,14} In our study, the consultation delay ranged from 1 to 12 months, with an average of 3 months. The diagnosis of this disease remains difficult as it can mimic a large number of much more common conditions, especially breast cancer, which remains the main concern. In fact, the pseudo-neoplastic aspects revealed in the literature illustrate this difficulty well. However, some clinical criteria appear useful in drawing attention to a tuberculous etiology, namely: the recurrent nature of a breast abscess after surgical drainage and conventional antibiotic therapy, as in case 5, and the fistulizing nature of an axillary lymph node or breast nodule.

Breast tuberculosis can manifest in various ways: breast swelling, mastodynia, and bloody or purulent nipple discharge. According to Darré et al clinical signs at admission were: a nodule in 84.1% of cases, an abscess in 63.6%, and swelling with skin fistulization in 59.1% of cases.²⁰ In our patients at admission, four had breast swelling, one had mastodynia, and only one case presented with a breast abscess. General symptoms such as weakness, anorexia, weight loss, and fever are rare and have no diagnostic value.¹⁴ Breast involvement is unilateral in the vast majority of cases and bilateral involvement is rare and estimated at 3% in the series by Salem et al.²³ In our series, none of the patients had bilateral involvement. On breast examination, the skin is either normal or already affected by inflammatory processes, giving the appearance of "orange peel" skin, as was in case 6, initially suggestive of inflammatory breast cancer. Cutaneous or even axillary breast fistulas may be observed. The nipple is rarely affected, and it may present with eczematous lesions or nipple retraction, as seen in case 6. Tuberculous lesions primarily affect the upper-outer quadrant (UOQ), but all quadrants can be affected. In our series, involvement of the UOQ accounted for 33% of cases. Clinical scenarios such as concomitant breast carcinoma and breast tuberculosis, breast carcinoma with tuberculous axillary adenitis, or both, can occur. There appears to be no link between breast tuberculosis and breast cancer, and there is no evidence that tuberculosis is carcinogenic. The simultaneous appearance of carcinoma and tuberculosis can lead to numerous diagnostic and therapeutic challenges.

Five anatomico-clinical forms have been described.

Nodular form

This is the most common form and represents 76.8% of cases.²¹ It clinically presents as a well-defined swelling. This lesion evolves by forming caseation and may eventually open, causing chronic discharge.

Diffuse form

Occurs in cases of untreated nodular form and represents 11.2% of cases.²⁴

Sclerosing form

Represents 1.4% of breast tuberculosis cases and mainly affects elderly women.²⁵ It is characterized by a tuberculous sclerosis appearance; suppuration is very rare.

Obliterating form

Forms a tuberculous galactophoritis, manifested as a poorly defined periareolar nodule associated with early nipple retraction.

Acute milary mastitis

Rare and results from hematogenous infection of the breast. It is most often identified during autopsies of women who died from fulminant tuberculosis.

On radiological imaging, breast tuberculosis can present with various mammographic appearances. The nodular aspect may manifest as: a single, well-defined opacity, mimicking an adenofibroma or a cyst; and alternatively, an opacity with irregular contours, accompanied by a peritumoral halo and associated skin thickening with or without microcalcifications, mimicking malignancy.

In our study, mammography was performed in five patients. The reason for its non-performance in case 5 was the young age of the woman (dense breasts) on a breast operated few weeks before. On ultrasound, breast tuberculosis often appears as a hypoechoic, heterogeneous, ill-defined image with posterior enhancement, posing, as with mammography, the challenge of differential diagnosis with breast cancer.^{8,23} It should be noted that the combination of mammography and breast ultrasound increases the sensitivity and specificity of both examinations. In our series, five women underwent breast ultrasound. The clear clinical diagnosis of breast abscess was the reason for its non-performance in case 5. On breast MRI, the signs are not specific, and like ultrasound and mammography, the features can be misdiagnosed as a malignant lesion, as was in case 1 where both breast lesions were classified as BI-RADS V. Table 1 summarized the clinical and radiological characteristics of our patients. Chest X-ray is routinely performed in cases of breast tuberculosis to search for any associated active or old pulmonary localization. The tuberculin skin test has no direct value in the diagnosis of this tuberculous localization. It is often positive in patients living in endemic areas, and its negativity does not rule out the diagnosis of breast tuberculosis. Biopsy sampling for histopathological analysis plays a crucial role in diagnosis. It can be performed in various ways: surgical excision, biopsy with a tru-cut needle, or curettage of the fistulous tract. Histological examination reveals, in approximately

95% of cases, the presence of epithelioid granulomas and giant cells with central caseous necrosis, which is highly indicative of a tuberculous lesion.^{27,28} In Ben Hassouna's study, frozen section histopathological examination performed in 62 patients allowed the diagnosis of breast tuberculosis in 60 cases, with a success rate of 97%.²¹ In the remaining two cases, the diagnosis was established on definitive examination. In our study, histological examination of breast samples obtained from the six patients revealed the presence of giant-cell granulomas surrounding caseous necrosis in only three cases, while the other cases showed granulomatous mastitis without necrosis, necessitating further examinations. The

likelihood of detecting BK by direct examination or culture in the fluid obtained from fine needle aspiration or abscess is rare, as the tuberculous bacillus is found in only 25% of cases.¹³ Additionally, culture requires a delay of three to four weeks. The QuantiFERON-TB Gold test is a blood test based on the detection of interferon-gamma produced by T lymphocytes in response to specific antigens. These antigens are: highly specific to the tuberculosis complex; absent in all vaccine strains, eliminating the possibility of cross-reactions in vaccinated patients; and absent in non-tuberculous Mycobacteria, except for *M. Kansasii*, *M. Szulgai*, and *M. Marinum*.

Table 1: Summary of the clinical and radiological characteristics of patients.

Case	Age	Risk factors	Clinical form	Radiologic appearance
1	47	-	Nodular	BI-RADS V
2	55	-	Diffuse	BI-RADS IV
3	45	-	Sclerosing	BI-RADS V
4	30	Pulmonary tuberculosis	Nodular	BI-RADS IV
5	26	-	Diffuse	-
6	36	-	Diffuse	BI-RADS IV

However, QuantiFERON-TB does not distinguish between latent and active infection, so it is often used in combination with other tests to make the diagnosis. In our series, QuantiFERON-TB gold test was prescribed for two patients, and it came back positive in one, supporting the diagnosis of mammary tuberculosis. The treatment of mammary tuberculosis is based on anti-tubercular drugs, which have radically changed its prognosis. This treatment is only initiated after bacteriological or histological proof. Regarding the treatment regimen, it varies according to published series. Some authors prefer a 9-month regimen (consisting of 2 months of Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol, followed by 7 months of Isoniazid and Rifampicin) due to its generally lower relapse rate.²⁹ However, in most studies, a 6-month therapy with the same combination has been sufficient for the cure of all patients.^{30,31} In our series, the 6-month regimen was adopted in consultation with pneumologists. However, one patient (case 5) required an extension of treatment (an additional 3 months) due to under-dosing of Rifampicin. It is important to mention that multidrug-resistant tuberculosis is a significant concern. In such cases, a therapeutic approach combining first-line and second-line drugs is necessary, including Kanamycin, Ofloxacin, Ethionamide, Para-amino salicylic acid, Pyrazinamide and Isoniazid, as suggested by some studies.³² With the introduction of tru-cut biopsy into daily practice, surgery is increasingly being abandoned in the management of breast tuberculosis. However, in the case of an abscess collection (especially if there are multiple septa or deep-seated locations not accessible to ultrasound-guided aspiration), surgical drainage with destruction of the locules and tissue sampling is recommended. As a therapeutic modality, surgery is recommended as a second-line option, mainly when the initial medical treatment response is inadequate or for mastectomy with

breast reconstruction when the breast is severely damaged and perforated by multiple fistulas.³³ Finally, it is important to emphasize that local recurrences can occur, especially in the ipsilateral breast, axillary lymph nodes, or even contralateral breast, in case of inadequate anti-tubercular treatment or poor therapeutic compliance (as was in case 5). It is therefore essential to closely monitor the evolution of the disease under treatment and to implement appropriate management based on the clinical situation of each patient

CONCLUSION

Breast tuberculosis is a rare condition, even in endemic countries. It primarily affects women of reproductive age. Clinical presentation and imaging do not exhibit specific characteristics, posing a challenge for differential diagnosis with breast malignancy. Therefore, histological and/or bacteriological studies are necessary to establish an accurate diagnosis. Treatment mainly relies on medical management with anti-tubercular agents, leading to favourable outcomes. Currently, surgical interventions are reserved to specific situations.

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