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Various presentations of breast tuberculosis and tuberculous lymphadenopathy: A case series of surgical rarity

Meme tüberkülozu ve tüberküloz lenfadenopatinin değişik belirtileri: Seyrek görülen bir cerrahi olgu serisi

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ABSTRACT

Tuberculosis (TB) is a common granulomatous disease especially in endemic regions. The rarity is further accentuated if the pathology arises primarily from the breast. The diagnosis is arduous even upon complete triple assessment. These conditions often give a diagnostic dilemma mimicking malignancy which ultimately requires surgical intervention. We report a series of six cases of TB-related breast pathology with a variety of unusual presentations, our management strategies and review of the literature.

Keywords: *Extra-pulmonary, breast tuberculosis, breast lump, chronic sinuses*

ÖZ

Tüberküloz özellikle endemik bölgelerde sık görülen granülomatöz bir hastalıktır. Meme kaynaklı tüberküloz nadirdir. Tanı 3'lü komplet değerlendirmeye rağmen zorludur. Bu durum sonuç olarak cerrahi müdahale gerektiren maligniteyi taklit ederek tanısal bir dilemma yaratır. Farklı ve beklenmedik prezentasyon gösteren 6 adet meme tüberkülozu vakasını, yönetim stratejimiz ve literatür eşliğinde sunduk.

Anahtar kelimeler: *Ekstra pulmoner, meme tüberkülozu, göğüs yumrusu, kronik sinüsler*

INTRODUCTION

Tuberculosis (TB) is a common granulomatous disease caused by *Mycobacterium tuberculosis*. It is a major health problem worldwide, especially in developing countries. In Malaysia, TB was the second most common communicable disease in the year 2001[1]. About 24% of TB cases are contributed by the immigrant population, particularly due to the massive influx of immigrants from neighboring countries as well as the increasing number of immunocompromised patients[2]. The incidence is increasing year by year. The majority of TB cases are pulmonary in origin, with extra-pulmonary involvement consisting of only 11% of all cases[1]. The commonest extra-pulmonary manifestation is tuberculous lymphadenitis, followed by spinal TB[1].

The incidence of primary breast TB has been reported to be between 0.1 and 0.52% worldwide, displaying its extreme rarity[3]. This condition commonly presents as a swelling or lump, occasionally manifesting as chronic sinuses, ulcerations and breast abscesses. Many benign breast pathologies such as fibroadenomas, chronic granulomatous mastitis (CGM) and duct ectasia also present with breast lumps, and as such, TB should always be considered especially in endemic areas. However, if a lump is associated with

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axillary or cervical lymphadenopathy, carcinoma should foremost be the primary suspect.

The disease is often overlooked and misdiagnosed since it easily mimics both benign and malignant conditions. This will result in diagnostic dilemma both clinically and radiologically. As such, surgical intervention is often required for accurate diagnosis. Establishment of an accurate diagnosis is essential as medical therapy is the main, and the only treatment modality for breast TB which also prevents unnecessary surgery. Surgical intervention instead should only be reserved for patients who are refractory to medical therapy. Hereby, we present 6 cases of breast TB with various clinical presentations and our experiences to handle such unique entities.

CASE 1

A 40-year-old female patient had a lump in her left breast since 2008. There were no skin changes or ulceration, neither change in size of the breast nor nipple discharge. She had no constitutional symptoms as fever, night sweats, loss of weight or appetite. She had no family history of breast cancer or any TB contact. Clinically, a single lump measuring 2x1 cm was felt at the left upper outer quadrant of her left breast and there was no axillary or cervical lymphadenopathy. An ultrasound revealed multiple benign looking, well-defined hypoechoic lesions in the left breast (measuring 33x15x23 mm at 1 o'clock and 17x9x25 mm at 3 o'clock position) and in the right breast (measuring 9x5x9 mm at 9 o'clock position). She was subsequently managed for breast fibroadenomas. Annual radiological imaging was similar until 2014 whereby the lesions were reclassified into BIRADS IV-V. The 1 o'clock lesion in the left breast displayed malignant characteristics with ipsilateral axillary lymphadenopathy suspicious of lymph node metastases. The remaining lesions were unchanged.

Fine needle aspiration cytology (FNAC) showed proliferative lesion with atypia, suspicious of malignancy while axillary lymph node revealed suppurative granulomatous lymphadenitis. However, breast core biopsy only revealed fibroepithelial lesion. Due to conflicting pathological reports and the underlying possibility of malignancy, patient subsequently underwent left breast wide excision biopsy and axillary dissection. Histopathological examination (HPE) exhibited the presence of left breast fibroadenoma and tuberculous lymphadenitis. Patient subsequently was referred to Infectious Disease Team and started on fixed-dose combinations of anti-TB medication, ie. Akurit-4 which consists of ethambutol, isoniazid, rifampicin and pyrazinamide. She was given Akurit-4 for 9 months and subsequently recovered well without any surgical complications or anti-TB side effects.

CASE 2

A 23-year-old female patient complained of progressively worsening left mastalgia with discharge of pus from the breast associated with keloid formation and vague palpable mass for the past 1 month. She denied traumatic event or insect bite. There were no constitutional symptoms. However, she revealed previous pulmonary TB contact from family members with treated pulmonary TB who had already completed treatment. Clinically, there were multiple keloids at lower pole of the left breast with the biggest measuring 3x1 cm at 4-5 o'clock position (Figure 1a). There was a barely palpable mass at 8 o'clock position but no axillary lymph node was felt. Subsequent sonography showed a sinus tract arising from the keloid scar leading to a heterogeneous collection at 8 o'clock, measuring 3.3x1.1 mm in size.

Her sinus tract was incised, drained, and excised. HPE revealed the presence of a chronic granulomatous inflammation consistent with TB. Patient was later started on treatment with Akurit-4 which is a combination of ethambutol, isoniazid, rifampicin and pyrazinamide. It was given for 12 months without any recurrence of the sinus inflammation or abscess during follow-up period.

Figure 1a. Multiple keloids at lower pole of the left breast with the biggest measuring 3x1 cm from 4-5 o'clock position.
1b. A lump measuring 2x1cm on the nipple areolar complex at 9 o'clock position.
1c. Multiple sinuses with pus discharge before initiation of anti-TB treatment.
1d. After completion of anti-TB treatment.

CASE 3

A 64-year-old female patient was referred after accidentally found left breast lump with an enlarged left cervical and axillary lymph node during medical check-up. The breast lesion was painless without any associated nipple discharge. She denied constitutional or metastatic symptoms. She had not any symptoms of TB, but history of a pulmonary TB contact was revealed. Mammography revealed fatty breast with two nodules in the left upper outer quadrant. Complimentary ultrasound showed two hypoechoic nodules measuring 1.2x0.8 mm and 0.5x0.5 mm, respectively. The imaging was consistent with BIRADS-IV category.

FNAC of cervical lymph node revealed chronic granulomatous inflammation and only reactive changes in the left axillary lymph node. Core biopsy of the breast lump exhibited benign fibrofatty tissue. Patient then underwent wide local excision of the left breast and axillary dissection because of multifocality of the lesion. HPE of both specimens were consistent with breast tuberculosis and lymphadenopathy. Patient was started on oral treatment with Akurit-4-a combination of ethambutol, isoniazid, rifampicin and pyrazinamide-, and maintained for 12 months. She is currently in good health.

CASE 4

A 41-year-old female patient presented initially with right axillary swelling for 1 year which was progressively increasing in size, without constitutional or metastatic symptoms. FNAC and core biopsy confirmed metastatic invasive ductal cancer. Mammogram showed BIRADS-V lesion of the right breast. She then underwent right breast mastectomy and axillary dissection. Final HPE was consistent with grade 2 ductal carcinoma without any special type, and clear margin with positive lymphovascular invasion (Figure 4a). TNM score was T2N3Mx. Hormonal status revealed oestrogen & progesterone receptor negativity (ER- and PR-). HER-2 status was equivocal (2+). D-DISH

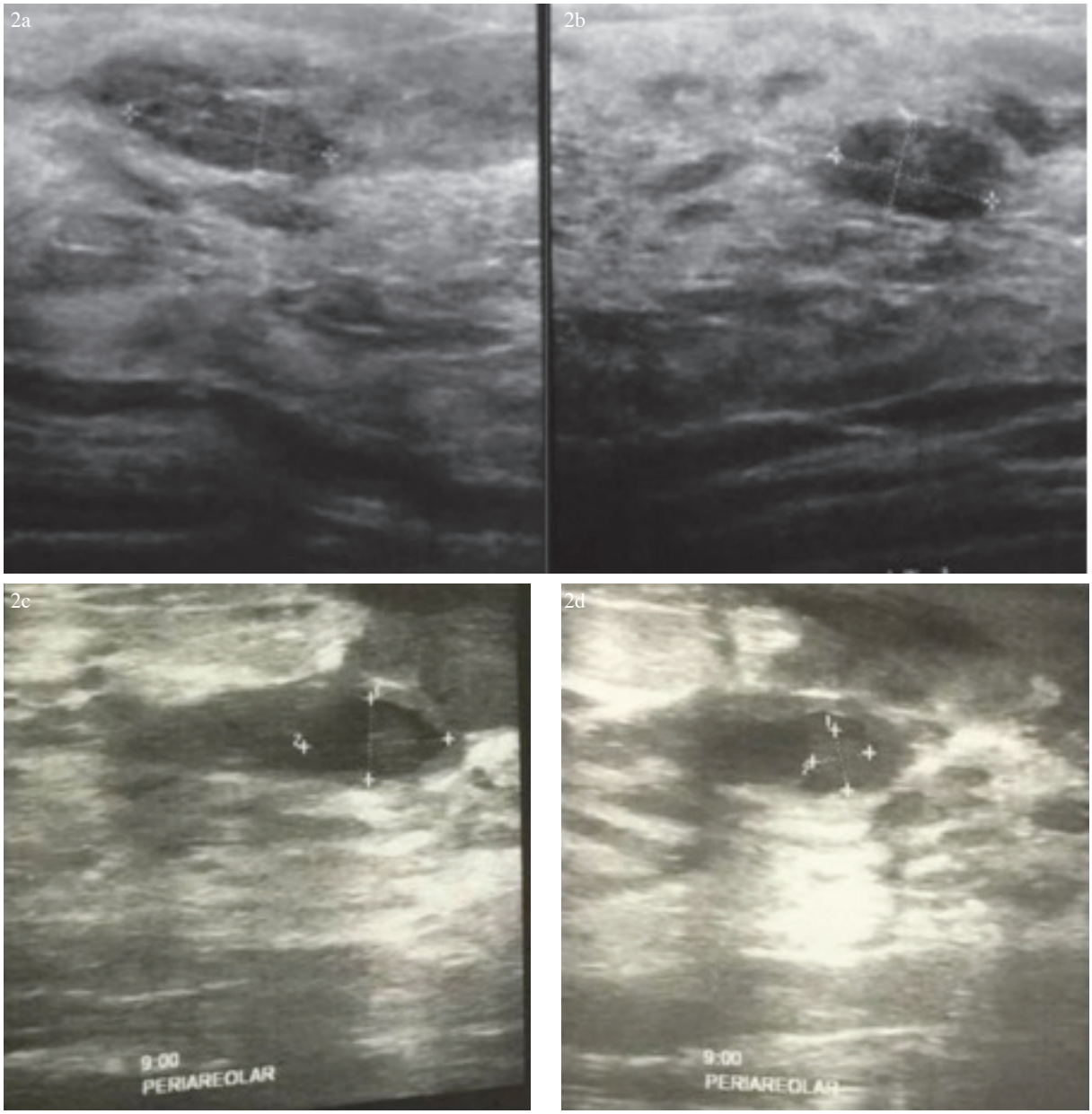
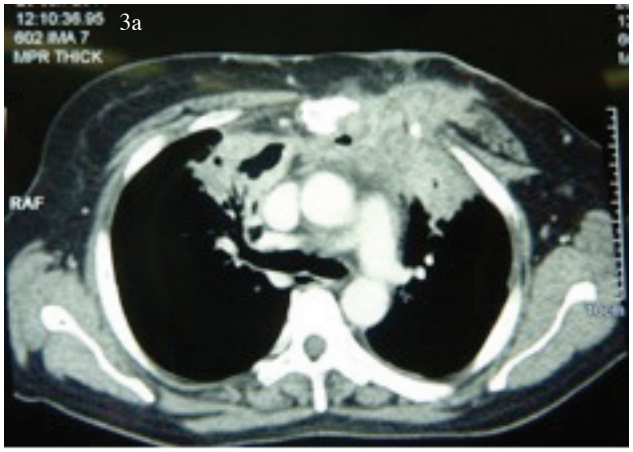


Figure 2a and 2b. Two ill-defined lesions at upper outer quadrant of left breast.
2c and 2d. A thick wall hypoechoic lesion measuring 0.6x1.1 cm containing a hyperechoic endoluminal lesion measuring 0.4x0.4 cm at 9 o'clock position located at periareolar region.

was amplified. She received 6 cycles of chemotherapy (FEC), 15 fractions of radiotherapy and 17 cycles of trastuzumab (Herceptin).

One year later, imaging surveillance showed two ill-defined lesions at upper outer quadrant of the left breast measuring 0.9x0.5 cm and 1.2x0.4 cm respectively (Figure 2a and 2b). They were classified as BIRADS-IV lesions. Hook wire localization and wide excision of the lesions revealed the presence of a fibroadenoma.

One year following the excision, she complained of left breast mastalgia without any palpable lump. Ultrasonography showed a cystic lesion containing avascular debris, representing an inflamed cyst. She was treated conservatively with strict radiologic follow-up. However, the lesion was still persistent. In view of



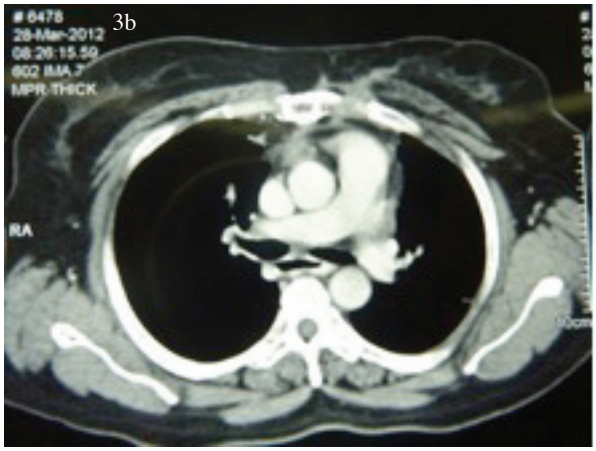


Figure 3a. Mass involving the left breast, anterior mediastinum, and lung with destruction of the adjacent ribs and sternum. 3b. CT scan picture after 12 months of anti-TB treatment revealed a significant reduction in size of the lesion.

inconclusive FNAC yield, she underwent core biopsy. The HPE revealed a suture granuloma evidenced by presence of inflammatory infiltrate with vague granulomatous aggregates of epitheloid histiocytes and giant cells and polarisable refractile foreign material. She was then treated conservatively and serial ultrasonographic examinations were planned to monitor the lesion. Nevertheless, she presented again 2 months later with a ruptured abscess from the previously diagnosed suture granuloma. The cavity was excised entirely and HPE was consistent with breast TB. Akurit-4 tablet which is composed ofethambutol, isoniazid, rifampicin and pyrazinamide was given for 12 months. She is well at the moment without any disease recurrence.

CASE 5

A 47-year-old female patient presented with recurrent formation of multiple sinuses from her left breast and anterior chest wall which was associated with pus discharge without septic complication for 8 years. She neither had TB symptoms nor TB contact. Clinically, there were multiple ulcerations at upper inner quadrant of the left breast extending up to the left upper chest wall (Figure 1c). Her mammogram showed thickening of the skin and anterior chest wall muscle. CT scan of the thorax and abdomen showed features suggestive of advanced breast carcinoma with extension into the mediastinum, ribs, lung with liver metastasis (Figure 3a). However, biopsy of the sinus tract was consistent with granulomatous inflammation secondary to TB. Anti-TB medication was given for 12 months and she responded well with the treatment both clinically and radiologically (Figures 1d and 3b).

CASE 6

A 31-year-old pregnant woman at 28 gestational weeks, presented with recurrent right breast abscess since one month. She had a similar swelling 6 months ago but spontaneously resolved. Initially, it was associated with pus discharge without septic complication. Clinically, there was a lump at 9 o'clock position on the nipple-areolar complex which measured 2x1 cm without evidence of surrounding infection (Figure 1b) Breast ultrasound showed a thick -walled hypoechoic lesion measuring 0.6x1.1cm and containing a hyperechoic endoluminal lesion measuring 0.4x0.4cm at 9 o'clock position located at periareolar region (Figures 2c, and 2d). FNAC and aspiration of pus revealed granulomatous inflammation and smear- positive acid-fast bacilli, respectively. Standard anti-TB medication, Akurit-4 which consists of ethambutol, isoniazid, rifampicin and pyrazinamide was initiated. She will receive Akurit-4 medication for 12 months as well. She is currently under our surveillance so as to monitor anti-TB response.

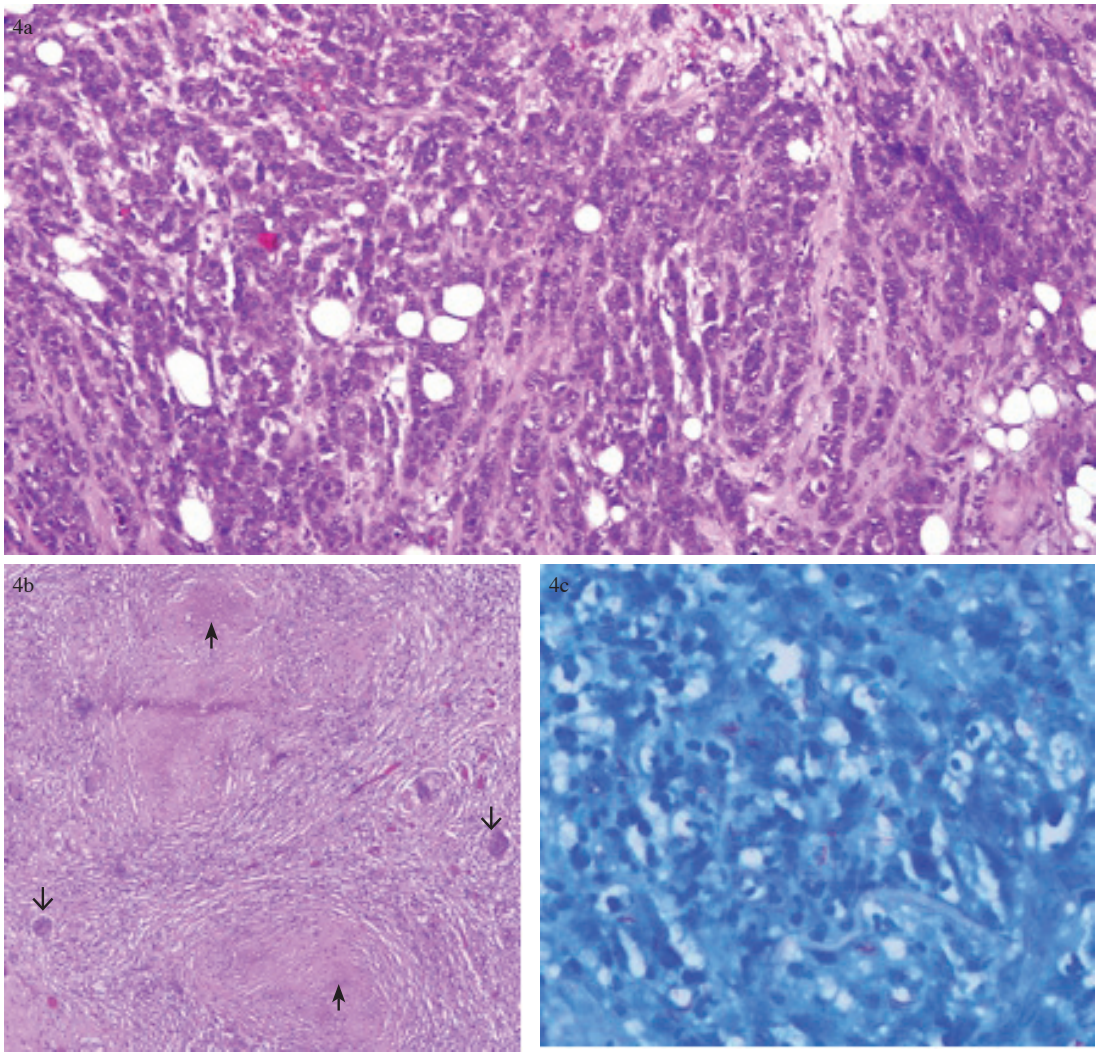


Figure 4a. Histopathological features of ductal carcinoma of no special type.
4b. Histopathology of breast TB showing caseating granuloma (upward black head arrow) with Langhan's giant cells (downward white head arrow).
4c. Scattered acid-fast bacilli highlighted by Ziehl-Neelsen stain.

DISCUSSION

Breast TB was firstly described by Sir Astley Cooper in 1829 as, "scrofulous swelling in the bosom of young women"[4]. It is an extremely rare entity, because breast tissue is remarkably resistant to tuberculosis. Similar to skeletal muscle and spleen, it provides a barren environment for the survival and multiplication of tubercle bacilli[5].

Primary breast TB is postulated to develop due to direct inoculation of the breast through skin abrasions or lacrimal duct openings in the nipple. It mostly develops in pregnant and lactating breasts due to an increased blood flow and dilated ducts. These physiological changes allow them to be more vulnerable to ascending infection. This condition happens in Case 6 as she was pregnant at the time of diagnosis. Breast TB is labelled as secondary type if the source of infection is identifiable. It is more common in comparison to the primary counterpart. Commonly it spreads through hematogenous, lymphatic or even direct pathway from the lungs or pleural spaces. Case 5 shows an example of secondary breast TB

since her breast was infected directly from the lung, pleura and mediastinal lymph nodes as evidenced by the CT scan.

Breast TB is classified into 3 categories namely nodular, diffuse/confluent and sclerosing tubercular mastitis[5]. The nodular type is considered to be the most common presentation of breast TB. It is slow growing, well circumscribed lesion and typically oval in shape. Such characteristics mimic fibroadenoma, however in an extremely worst scenario, it may even simulate malignancy. Yet, biopsy alone is not adequate for definitive diagnosis, hence surgical resection is needed. This category has been delineated by cases 1 and 3 in this manuscript. The diffuse/confluent type is characterized by multiple lesions associated with discharging sinuses, even seldom with keloid formation. This might be misinterpreted as breast abscess. Cases 2 and 4 display characteristics suggestive of this type. Occasionally, it can also present as a huge mass mimicking chronic granulomatous mastitis and unfortunately it can be misdiagnosed as inflammatory breast cancer[6]. The final type namely sclerosing tubercular mastitis is seen in elderly women and is characterized by an excessive fibrotic process. None of our cases depicted a similar presentation of this form.

Any breast pathology should normally be approached with standard triple assessment. They include history and physical examination, radiological assessment using mammography and complimentary ultrasonography, and lastly cytological and histological examination. The final diagnosis can safely be established if these steps are followed. In view of diagnostic ambiguity, the case should always be managed in tertiary center with the presence of breast and endocrine surgeon. Multidisciplinary team discussion is essential as variety of specialized field members are able to offer their expert opinions in co-managing this granulomatous infection, hence appropriate management can wholly be delivered.

Even mammography is part of a triple assessment, it is of limited value in breast TB. It does not aid in the diagnosis especially in young women in view of high density of the breast tissue. In nodular tubercular mastitis, it may reveal a dense round area with indistinct margins seen without the classic halo sign or popcorn calcification in fibroadenoma[7]. In diffuse/confluent type, mammography may show dense breast tissue with thickened skin in which it mimics inflammatory breast carcinoma[7]. Findings of a homogenous dense mass with fibrous septae and nipple retraction may be seen in sclerosing tubercular mastitis[7]. Besides, CT scan seldom adds to the diagnostic yields other than in defining the involvement of thoracic wall and in the assessment of treatment response. In fact, it may demonstrate radiologic features which are indistinguishable from advanced breast carcinoma as is seen in Case 5.

Definitive diagnosis of breast TB can be established via bacteriological, histopathological and molecular tests. The aspirated pus can be cultured in a special medium namely Lowenstein-Jensen (LJ) or BACTEC culture media. Presence of growth is essential for a confirmatory diagnosis. However, in reality, the culture is often time-consuming. The mean detection period for Mycobacterium tuberculosis by using Lowenstein-Jensen medium culture is 24 days and 12 days for BACTEC culture[8]. Culture media also has its own pitfall as the possibility of false-negative results in pauci-bacillary samples. These will lead to inevitable delay in obtaining the final result.

Microscopic evidence of caseating granuloma with Langhan's giant cells in the histopathological specimen is evocative of breast TB (Figure 4b). Presence of acid-fast bacilli highlighted by Ziehl-Neelsen stain is always pathognomonic (Figure 4c). However, its existence is not always available especially in partially treatable TB, low yield biopsy specimens and formalin-fixed tissue sections. In CGM, specimen reveals predominantly lobular granulomas and lack of caseous necrosis, while breast TB usually centers on the ducts rather than lobules[7]. Foreign body granuloma almost always masks the diagnosis of TB. The granuloma formation is often identical between these two, but the treatment is obviously discrete. Such

sequence of events has been highlighted in case 4.

Molecular method has a sensitivity of 75.9% for the diagnosis of breast TB[8]. TB-polymerase chain reaction (TB-PCR) is reliable with a rapid turnaround time of less than one day relative to mycobacterial cultures[8]. It is recommended in cases of negative culture results or for differential diagnosis of CGM[5]. By yielding faster test results, it obviates the need for mutilating surgery and anti-TB therapy can be initiated instead without delay. However, it is technology dependent, costly and not readily available in every center. None of our cases used TB-PCR as method of diagnosis in view of the deficiency of the relevant services.

The most recent technique aimed to improve molecular detection is culture-enhanced PCR especially in extra-pulmonary specimens. It has sensitivity, specificity, positive predictive value, and negative predictive values of 88.6%, 100%, 100%, and 97.9%, respectively[9]. Other newer diagnostic platform that can be used is The Xpert MTB/RIF assay, which is an automated, closed system that performs real-time PCR10. This enables rapid diagnosis of TB with minimal technical expertise. This method has been endorsed by the WHO in December 2010 as a replacement for sputum smear microscopy[10]. Up to date, many researches have been performed to evaluate the diagnostic accuracy of Xpert MTB/RIF assay[11,12].

Anti-TB medication is the first line treatment. Four drugs used as anti-TB medications include ethambutol 800 mg/day, rifampicin 450 mg/day, isoniazid 300 mg/day and pyrazinamide 1500 mg/day (EHRZ)[13]. For newly-diagnosed breast TB, the standard treatment is a minimum of 6-month regimen consisting of daily doses of EHRZ for two (intensive phase), then daily doses of HR (isoniazid and rifampicin) for 4 months (maintenance phase)[13]. Even the guideline has suggested for a minimum of 6-month period, we tend to initiate anti-TB drugs for 9, and 12 months for lymph node and breast TB respectively. Since separate dosages tend to cause non-compliance, the initiation of fixed dosage has improved its delivery. The introduction of Akurit-4 which consists of ethambutol 275 mg, isoniazid 75 mg, rifampicin 150 mg and pyrazinamide 400 mg, has reduced the risk of non-compliance by 17% and consequently improves effectiveness of therapy[14]. The recommended daily dosages of Akurit-4 are based on the body weight of the patients (30-37 kg, 2 tablets , 38-54 kg, 3 tablets, 55-70 kg 4 tablets daily, and for ≥ 70 kg, 5 tablets).

Nevertheless, surgical intervention is only needed in a patient histopathologically unresponsive to anti-TB therapy. Breast conserving surgery or mastectomy with or without axillary dissection is reserved for cases masquerading malignancy, extensive disease causing a large ulceration, persistently discharging sinuses or unsightly appearance of a keloid.

CONCLUSION

Breast TB represents a rare entity considering its breast pathology. It gives a perplexing dilemma for a definitive diagnosis. Yet, standard triple assessment should never be neglected. A combination of bacteriological, histopathological and molecular methods can enhance diagnostic accuracy, thus treatment strategy can be initiated early. Breast TB should always be considered in a patient with poorly responsive breast pathology especially in the endemic region.

DISCLOSURE

The authors have no conflict of interests regarding the publication of this article. Written informed consent was obtained from the patient for publication of this case report and its accompanying images.

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