

Tuberculosis of the Female Breast and Reproductive Organs: A Diagnostic Dilemma

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Abstract

Background: Tuberculosis is prevalent in developing countries and extra-pulmonary involvement is now a frequent manifestation. However, involvement of the breast and reproductive organs in females is a cause of diagnostic confusion due to the non-specific nature of presenting symptoms which may simulate malignant disease processes.

Materials and methods: All females with histological confirmation of tuberculosis involving the breast and reproductive organs were analyzed over a 16 year period. Tissue biopsies were fixed in formalin, processed in paraffin and stained with haematoxylin & eosin and Ziehl Neelsen stain to identify the acid fast bacilli of mycobacterium tuberculosis.

Results: 28 females are presented and their ages ranged from 14 to 52 years with a mean age of 29.3. Presenting symptoms were varied and included abdominal/pelvic pain, abdominal swelling, post coital bleeding, vaginal bleeding and discharge, amenorrhoea and infertility while four females presented with breast mass and pain. Duration of symptoms was from one month to 5 years. Clinical diagnosis included dermoid cyst, tubo-ovarian abscess, leaking ectopic gestation, malignant ovarian tumour, fibroadenoma and breast cancer. Eighteen of the females had laparotomy, four had endometrial curettage, another four had excision biopsy/lumpectomy and two had cervical punch biopsy. Only the four females with breast lesions had fine needle aspiration biopsy prior to tissue biopsy. Also, one female was HIV positive and on anti-retroviral drugs. Microscopy of tissue biopsies from the breast, ovary, fallopian tubes, endometrium and cervix revealed granulomata, multinucleated langhan type giant cells and extensive caseation.

Conclusion: Tuberculosis may mimic malignant lesions of the breast, ovary and cervix due to the absence of specific diagnostic symptoms and should be a differential diagnosis in breast and gynaecological diseases in reproductive age females. In resource limited setting, early diagnosis by fine needle aspiration technique and tissue histology may reduce attendant morbidity, irreversible sterility and also prevent unnecessary surgery in patients.

Keywords: Tuberculosis; Breast; Ovary; Cancer; Infertility; Reproductive age

Introduction

Tuberculosis affects one third of the world's population and Africa contributes 3% to 4% cases annually to the global epidemic [1-4]. It is primarily a pulmonary disease treated by multidrug therapy. The advent of multidrug resistant strains and HIV infection is steadily increasing its extra-pulmonary manifestation in developing countries and in predominant migrant populations in developed countries [5-7].

The female breast is structurally complex and undergoes varying morphologic changes from adolescence to menopause [8,9]. These changes are subject to hormonal control which may result in varying pathologic conditions ranging from benign fibrocystic changes to cancer. However, infection by tuberculosis is uncommon in the breast due to the resistance of breast tissue to the tubercle bacillus survival and multiplication [10-14]. Genital tuberculosis, though uncommon, occurs during the reproductive years and results from haematogenous spread involving the fallopian tubes and extends to the endometrium, cervix uteri and ovaries [15]. The annual incidence of genital tuberculosis is estimated at 0.036 per 100,000 women of child bearing age while its incidence in the breast ranges from 0.1% to 3.59% and includes lactating females [12,13,16-18].

There is no specific symptom or clinical presentation associated with tuberculosis of the breast and genital organs and thus a source of diagnostic difficulty from neoplastic gynaecological and breast diseases in reproductive age females.

Materials and Methods

Twenty eight female patients with histological diagnosis of tuberculosis involving the breast and reproductive organs were studied in the Department of Pathology, Ahmadu Bello University Teaching Hospital over a 16 years period (January 1997 to December 2012). Tissue biopsies of these patients were fixed in 10% formalin and processed in paraffin wax. Histology slides stained with Haematoxylin and Eosin (H&E) were viewed. Ziehl Neelsen stain was used to demonstrate the presence of acid fast bacilli (AFB) of mycobacterium tuberculosis. Clinical information and bio-data of patients were extracted from case files.

Results

Two hundred and forty seven patients (247) had histological diagnosis of tuberculosis during the study period. There were 133 males

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Received July 30, 2013; **Accepted** September 02, 2013; **Published** September 05, 2013

Citation: Samaila MO, adesiyun AG, Mohammed TT, Adewuyi SA, Usman B (2013) Tuberculosis of the Female Breast and Reproductive Organs: A Diagnostic Dilemma. J Trop Dis 1: 116. doi:10.4172/2329-891X.1000116

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| S/No | Age (years) | Symptoms / Clinical presentation | Duration of symptoms (months) | Sites of tissue Specimen for Histology | Clinical Diagnosis |
|------|-------------|---|-------------------------------|---|---|
| 1 | 33 | Vaginal bleeding, discharge | 7 | Endometrium Cervix | CIN 1 |
| 2 | 35 | Profuse vaginal discharge, ulcerated friable cervix and vulva | 8 | Cervix u/vulva | Cancer cervix |
| 3 | 30 | Vaginal bleeding following Amenorrhoea, | 4 | Endometrium | Product of conception |
| 4 | 21 | Abdomino-pelvic swelling | 6 | Ovary | Serous ovarian cyst |
| 5 | 25 | Abdomino-pelvic swelling, weight loss, amenorrhoea | 6 | Tube & Ovary | Neoplastic ovarian tumour |
| 6 | 20 | Vaginal discharge & bleeding | 4 | Cervix | Chronic PID |
| 7 | 25 | Vaginal bleeding & discharge, pelvic pain | 3 | Ovary | Tubo-ovarian abscess |
| 8 | 28 | Abdomino-pelvic mass, weight loss | 6 | Ovary | Malignant ovarian cyst |
| 9 | 28 | Amenorrhoea, vomiting, fever | 2 | Tube & ovary | Leaking Ectopic gestation |
| 10 | 19 | Amenorrhoea, fever, vomiting | 2 | Tube | Leaking ectopic gestation |
| 11 | 17 | Abdomino-pelvic mass, pain, | 10 | Tube & Ovary | Chronic Ectopic gestation |
| 12 | 52 | Abdomino-pelvic pain, Pelvic mass-22wks, vaginal bleeding | 12 | Ovary, Tubes, Uterus | Malignant ovarian tumour stage IIIc |
| 13 | 26 | Lower abdominal pains | 2 | Tube & Ovary | PID, Oophritis |
| 14 | 32 | Amenorrhoea | 60 | Endometrium | Secondary infertility |
| 15 | 29 | Breast mass, peau d' orange, tenderness | 14 | Breast | Mastitis/Breast cancer |
| 16 | 35 | Abdominal swelling, abnormal menstruation | 60 | Tube & Ovary | Ovarian cyst |
| 17 | 28 | Breast pain and lump | 4 | Breast | Fibroadenoma |
| 18 | 17 | Abdominal swelling | 6.5 | Ovary | Dermoid cyst |
| 19* | 25 | Abdomino-pelvic swelling | 8 | Ovary | Tuberculous Oophritis |
| 20 | 41 | Post coital bleeding | 60 | Cervix uteri | Cancer cervix |
| 21 | 19 | Lower abdominal pain & mass, vaginal discharge | 6 | Tubes & ovaries | Malignant Ovarian tumour/ Disseminated TB |
| 22** | 42 | Weight loss, fever, breast mass, paeu d'orange | 6 | Breast | Breast cancer |
| 23 | 14 | Amenorrhoea, abdominal swelling | 4- 12 | Ovary & Left Tube | Ovarian mass/ Cold abscess |
| 24 | 40 | Vaginal bleeding, abdominal swelling | 18 | Uterus, tubes, ovaries & peritoneal seedlings | CIN-III/Ca cervix |
| 25 | 45 | Lower abdominal mass, | 24 | ovary | Ovarian cyst |
| 26 | 35 | Fever, weight loss, breast lump, 6months pregnant | 12 | Breast | Breast cancer |
| 27 | 38 | Post coital bleeding, prolonged menstruation | 24 | Endometrium | Cervicitis/Abnormal Uterine bleeding |
| 28 | 22 | Lower abdominal swelling | 24 | Ovary | Ovarian Tumour |

*Known Tuberculosis patient

** Defaulted Retroviral positive patient

Table 1: Clinical Details, Presentations and Diagnoses of Patients.

and 114 females. Of the females, 28 had tuberculosis involving the breast, fallopian tube, ovary, endometrium and cervix uteri. Their ages ranged from 14 to 52 years with a mean age of 29.3. They presented with varying histories of breast pain, breast lump, abdominal swelling/mass, abdominal/pelvic pain, vaginal bleeding/discharge, post coital bleeding, amenorrhoea, weight loss, vomiting and fever. One female presented due to secondary infertility and one was a known tuberculosis case who defaulted on treatment. Of the four women with breast masses, one was a known HIV infected patient on HAART and one was six months pregnant. The presenting symptoms durations for all the cases varied from one month to 5 years (Table 1).

Clinical examination showed ulcerated and friable cervix uteri with lesions extending to the vaginal vault and vulva in one patient, another had bilateral tubo-ovarian masses, while a pelvic mass of 22 weeks gestation size was demonstrable in one. Ill defined to circumscribed nodular breast lumps were seen in four cases and two had associated peau d' orange. The range of clinical diagnoses and differentials included dermoid cyst, tubo-ovarian abscess, leaking tubal gestation, pelvic inflammatory disease, malignant ovarian tumour, fibroadenoma, cervical intra-epithelial neoplasia, cervical cancer and breast cancer (Table 1).

Eighteen patients had a laparotomy for suspected ectopic gestation, tubo-ovarian abscess and ovarian tumour, four had endometrial curettage for incomplete abortion, cervicitis and infertility while another two had a cervical punch biopsy. All four with breast lesions had fine needle aspiration cytology and subsequent excision biopsy. Of the eighteen that had laparotomy, two had total abdominal hysterectomy with bilateral salpingo-oophorectomy for suspected advanced malignant ovarian tumour and high grade cervical intra-epithelial neoplasia.

Tissue microscopy of biopsies from the breast, fallopian tubes, ovaries, endometrium and cervix uteri showed granulomata composed of epithelioid cells, lymphocytes, multinucleated langhan and foreign body giant cells and extensive areas of caseation (Figures 1-3). Other areas from the respective tissues showed residual breast tissue and fibrocystic change in one breast, expanded tubal wall, ovarian stroma and ectocervical epithelium. Ziehl Neelsen stains revealed acid fast bacilli of mycobacterium tuberculosis. All the patients received standard anti tuberculous drugs without further surgical intervention. The female with secondary infertility was yet to achieve pregnancy.

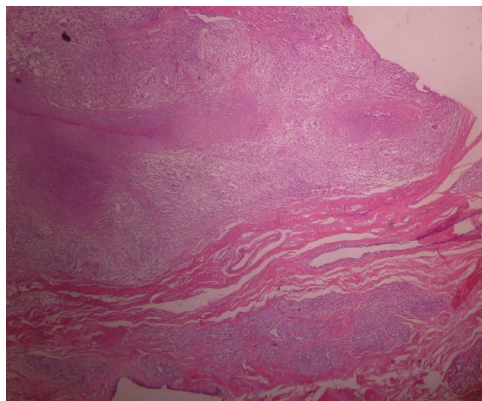


Figure 1: Breast Tissue showing granuloma, caesation and occasional acinus.

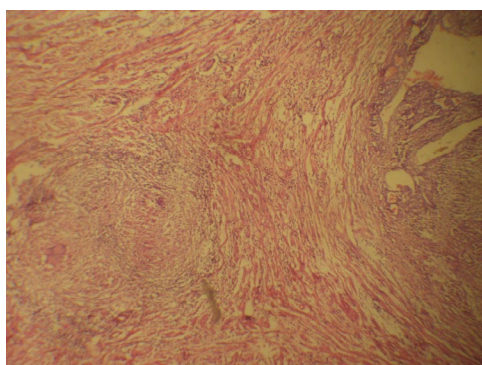


Figure 2: Expanded Tubal wall showing granuloma & fimbriae.

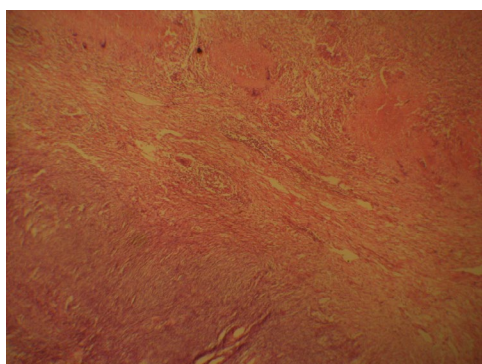


Figure 3: Residual ovarian stroma and granuloma.

Discussion

The resistance of the breast to tuberculosis infection is reduced during pregnancy and lactation due to increased blood flow and thus infection can be acquired through skin abrasions, ducts in the nipple or from a primary focus [19]. Presentation with peau d'orange and breast lump or mass can mimic breast cancer which is the commonest malignancy amongst females in our setting and a leading cause of death in women in developing countries. We had four women with breast tuberculosis, one was pregnant and another was a known retroviral case. Several reports of pregnancy exacerbating breast cancer have also been documented in literature. It is noteworthy that the occurrence

of breast lump during pregnancy may be tuberculosis as seen in our patient. HIV infection is also known to increase the propensity to tuberculosis in afflicted individuals [7,20,21].

The first case of tuberculous mastitis was described by Cooper [22] as "scrofulous swelling of the bosom" and McKeown and Wilkinson [23] first classified it into five pathological varieties of nodular, diffuse or disseminated, sclerosing, tuberculous mastitis obliterans and acute military tuberculous mastitis based on clinical manifestation. While, Tewari reclassified it into nodular, disseminated and abscess types [20]. The nodular variant is the commonest presentation in 60% of cases and thus may be misdiagnosed as a neoplastic lesion as also seen in our patients while, the abscess variant is often seen in young females and accounts for 30% of cases [20]. Diagnosis can be achieved with Fine Needle Aspiration Cytology (FNAC) though tissue biopsy is still advocated to differentiate from other causes of granulomatous diseases of the breast [24-26]. Granuloma centering round breast ducts and not lobules is diagnostic in tissue biopsy and the demonstration of acid fast bacilli is not mandatory [11].

Genital tuberculosis in females is prevalent during the reproductive years [8,27,28]. It is an uncommon manifestation of the disease and accounts for 0.7%-1% of gynaecologic admissions [29]. Over 90% of cases are diagnosed between 20-40 years [8]. The age range for our patients was from 14 years to 52 years with an average of 29.3 years. This range is expected because reproductive period is longer in our setting from early female marriages. Our finding is also comparable to similar studies [27,28].

The clinical manifestation of tuberculosis in this group of patients is variable and non specific thus posing a diagnostic difficulty from inflammatory and neoplastic gynaecological diseases. However, presenting symptoms often include pelvic pain, swelling and infertility in majority of cases though infertile patients rarely have symptoms [8,30,31]. We had one case of secondary infertility in a thirty-two years old woman who was desirous of pregnancy. The incidence of tuberculosis in infertile patients ranges from 5% to 16.4% [8,28]. In spite of adequate treatment with standard anti tuberculous drugs, many affected females like our patient will still not achieve pregnancy without other forms of medical interventions such as *in vitro* fertilization [32]. Other symptoms encountered in patients are abnormal uterine bleeding, amenorrhoea, pelvic swelling and vaginal discharge [33]. Fourteen (51.9%) of our patients had menstrual irregularity with vaginal discharge. Weight loss, malaise and temperature rise are often associated with tuberculosis though, these symptoms are non specific and may also be attributable to genital infection [33].

The ovary and fallopian tube were the frequent sites in this study with 16 and 9 cases respectively while 9 females had both organs involved. Other studies reported the ovary and endometrium as prevalent sites [27,33]. Only four had endometrial affectation in our study while one female had extensive vulva involvement. Vulval tuberculosis is rare and accounts for 0.2% of cases [34]. Pathogenetically, tuberculosis spreads haematogenously from the fallopian tubes to the endometrium, ovaries and cervix uteri in decreasing frequency order [8,28,30].

Breast and genital tuberculosis cannot be differentiated from the myriad of breast and gynaecological lesions such as fibroadenoma, fibrocystic changes, inflammatory diseases of the pelvis, ovarian tumours, uterine and breast malignancies on clinical features alone [30,33,35-37]. A combination of FNA for palpable masses, laparoscopy and tissue biopsy is the best approach to diagnosis in reproductive age women as well as a high index of suspicion especially in susceptible

population [33]. Diagnosis can also be achieved with Polymerase Chain Reaction (PCR) for the detection of mycobacterium DNA [38], this is however unavailable in most developing settings. Tissue microscopy showing granuloma, giant cells (Langhans or foreign body), lymphocytes and plasma cells with or without caseation is diagnostic [39]. The presence of AFB in the lesion can be confirmed with the Zeihl Neelsen stain though its presence is not necessary and AFB positivity is higher in untreated patients and HIV positive cases [24,40]. Standard anti-tuberculous drugs treatment can achieve complete resolution as in our cases and all the first line drugs of Isoniazid, Rifampicin, Ethambutol and Pyrazinamide are well tolerated in pregnancy without untoward fetal outcome [36,37,41,42].

Accurate diagnosis will forestall delayed treatment, unnecessary surgeries and reduce attendant morbidity such as sterility which is common in approximately 50% of patients [8].

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