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Fine-Needle Aspiration in Suspected Inflammatory Breast Cancer: Case Series with Emphasis on Approach to Specimen Adequacy

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Key Words

Fine-needle aspiration · Inflammatory breast cancer · Cytology · Pitfalls · Mastitis · Diffuse enlargement · Breast · East Africa

Abstract

Objectives: To highlight the utility of a tangential approach in the fine-needle aspiration (FNA) technique for obtaining cellular material adequate for a conclusive diagnosis in diffusely enlarged breast without a discrete lump. ***Study Design:*** FNA was performed on 5 women clinically suspected to have inflammatory breast cancer (IBC). All had unilateral diffusely enlarged breasts with peau d'orange changes of the skin. No distinct lump was palpable. The procedure was performed using a 10 cm^3 syringe with a tangential approach of a 23-gauge needle in all 4 quadrants with extra passes in the antigravity areas. Rapid on-site evaluation for adequacy was done. ***Results:*** All women were of African descent within the age range of 34–57 years. One case had a recent history of lactation. FNA smears showed low-to-moderate cellularity. One case was suspicious and 4 were positive for ductal carcinoma. Core biopsy confirmed IBC in 3 cases. Two cases had a mastectomy; 1 of these cases had preoperative neoadjuvant chemotherapy. ***Conclusion:*** The approach of FNA used in these cases helped to establish the diagnosis of IBC in 4 women presenting with a diffusely enlarged and tender breast, resulting in the timely initiation of appropriate management. The technique needs to be assessed in a larger cohort of women with diffusely enlarged breast to evaluate its diagnostic utility.

Introduction

Inflammatory breast cancer (IBC) is a rare type of aggressive cancer which presents as a diffusely enlarged, tender, and swollen breast without a discrete lump. The patient is put on antibiotics due to the mistaken diagnosis of mastitis, and the disease continues to progress [1].

In such patients, a rapid and correct diagnosis is of paramount importance to urgently initiate appropriate neoadjuvant chemotherapy.

Fine-needle aspiration (FNA) cytology can be of great value in rapid tissue diagnosis. However, a clinical breast examination, mammogram, and other imaging modalities are not helpful in guiding the FNA target [2, 3]. This poses a unique challenge for the cytopathologist who has to obtain adequate material on blind FNA to ensure that

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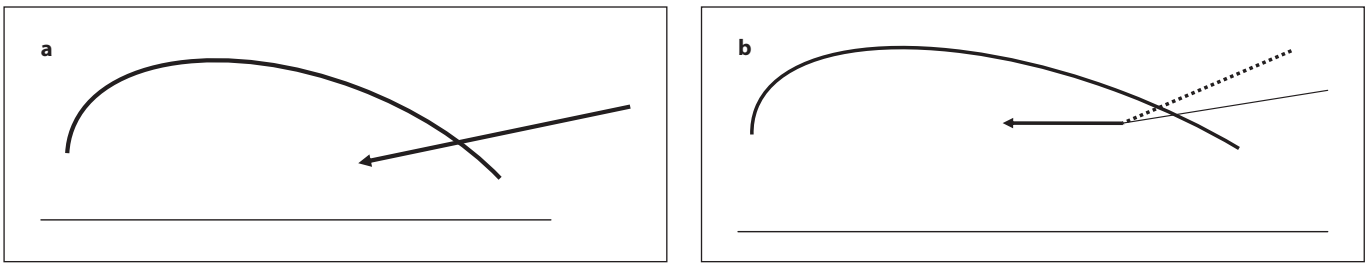

Fig. 1. a, **b** Line diagrams showing the tangential approach of the needle during FNA. After piercing the skin (**a**), the direction of the needle is changed to face upwards towards thickened skin with syringe becoming parallel to the horizontal plane (**b**).

the diagnosis of malignancy is not missed and differentiate it from benign lesions which can mimic IBC.

We report our experience with FNA in 5 cases of IBC to highlight the critical steps and precautions that should be taken to procure material that is sufficient for a conclusive diagnosis. This can be beneficial in resource-limited settings with a high incidence of breast cancer, such as Nairobi, where FNA is preferred over core biopsy as a first-line diagnostic approach. To the best of our knowledge, only 2 case reports exist documenting the diagnosis of IBC by FNA [4, 5].

Materials and Methods

Breast aspiration was performed in 5 cases of clinically suspected IBC over a 1-year period (September 2009 to August 2010). In case 1, random sampling yielded inadequate material on the first attempt. The FNA procedure was repeated by the consulting cytopathologist (N.K.) at our hospital. To improve the diagnostic yield, a standard protocol was formulated and adopted for subsequent cases.

FNA was performed with a disposable 23-gauge needle and a 10-ml syringe using a technique that employed a tangential approach of the needle in all 4 quadrants (fig. 1a, b). In addition, antigravity areas were targeted and extra passes done compared to heavily edematous lower quadrants of the breast. Overall, 6–8 passes were performed. Smears from each quadrant were labeled separately. Rapid onsite evaluation for sample adequacy was done using Diff-Quick staining. The remaining smears were wet fixed in 95% alcohol and stained using the Papanicolaou technique. Skin core biopsies were done in 3 patients. Two had mastectomies.

Results

All cases were women of African descent ranging in age from 34 to 57 years. Two patients were above 50 years of age. Table 1 provides clinicopathological details of the 5 cases. All patients fulfilled at least 3 clinical criteria for the suspicion of IBC; these comprised diffuse enlargement of the breast, erythema or increased warmth of the overlying skin, and edematous skin or peau d'orange. All cases presented with unilateral breast enlargement of up to 3 months. Only 1 patient (case 2) had a recent history of lactation.

Upon examination, the breast was tender and diffusely engorged, and the overlying skin was warm although redness was difficult to appreciate due to the natural dark pigmentation of the skin. The overlying skin was thickened, firm, and associated with marked peau d'orange (fig. 2a). Two cases (1 and 3) also had axillary node enlargement and subtle left upper limb swelling. The mammogram showed skin thickening but no masses in the breast and enlarged axillary nodes on the same side. Two women (cases 4 and 5) had nipple retraction and purulent discharge from the nipple. Case 4 also had skin ulceration in one area measuring 0.8 × 0.6 cm (fig. 2b).

Clinical differential diagnoses included acute mastitis, fat necrosis, inflammatory carcinoma, and lymphoma.

Cytology Findings

FNA smears showed low-to-moderate cellularity. The epithelial cells were predominantly distributed in tight, 3-dimensional, small clusters and dissociated singly. There was mild-to-moderate pleomorphism. Four cases were diagnosed positive for malignancy based on adequate cellularity, pleomorphism, nuclear irregularity, and an increased nuclear-to-cytoplasmic ratio. In case 2, a definitive diagnosis of malignancy was deferred for histologic confirmation considering the recent history of lactation although the suspicion of malignancy was raised. Two cases (4 and 5) also showed some neutrophils and lymphocytes surrounding malignant cells scattered in the dirty proteinaceous background (fig. 3a–c).

Table 1. Clinical, radiological, cytological, and histological findings

	Clinical data			Radiological evaluation	Cytological diagnosis	Follow-up and histological findings
	age, side of the breast, and lactation history	duration	other changes in addition to diffuse enlargement			
Case 1	34 years, left breast, not pregnant or lactating	1 month	Erythematous, hardened skin with peau d'orange. Nipple retraction but no nipple discharge. Subtle left upper limb swelling.	Ultrasound and mammogram showed skin thickening but no masses and 2 enlarged left axillary nodes.	Ductal carcinoma, nuclear grade 2 with inflammatory cells in a dirty background.	Core biopsy: invasive ductal carcinoma, grade 2. Negative for ER, PR and Her 2 receptors.
Case 2	37 years, left breast, stopped lactation 1 month before	2 months	No milk discharge. Erythematous skin with peau d'orange. Took antibiotics for 1 week.	Mammogram was normal.	Suspicious for carcinoma in view of the history of lactation in the recent past. Subsequently returned with an enlarged left axillary lymph node which was positive for carcinoma on FNA.	Received neoadjuvant chemotherapy 6 cycles after core biopsy in an outside facility followed by modified radical mastectomy at our hospital. Histology showed invasive ductal carcinoma, grade 2 with lymphovascular invasion. Positive for ER and PR and negative Her2 receptors. Prechemotherapy status not known.
Case 3	57 years, right breast	3 months	Thickened, hardened erythematous skin which is ulcerated in one area. Peau d'orange and associated right arm swelling and pain. No palpable axillary or supraclavicular lymph nodes.	Mammogram showed skin thickening at the breast and an enlarged right axillary node.	Positive for ductal carcinoma, nuclear grade 3.	Total mastectomy. Histology showed invasive ductal carcinoma, grade 3, with lymphovascular invasion. Negative for ER, PR, and Her2 receptors.
Case 4	44 years, left breast	6 weeks	Inverted nipple showing purulent discharge from multiple ducts. Thickened, hardened erythematous skin with peau d'orange.	Mammogram was not done.	Positive for ductal carcinoma, nuclear grade 3 with inflammatory cells in the background. Nipple discharge smears showed acute and chronic inflammation.	Core biopsy: ductal carcinoma grade 3. Positive for ER, PR, and negative Her2 receptors.
Case 5	54 years, left breast	2 months	Retracted nipple showing purulent discharge.	Mammogram was not done.	Positive for ductal carcinoma, nuclear grade 3 with acute and chronic inflammatory cells. Nipple discharge smears showed acute inflammation.	Core biopsy: invasive ductal carcinoma, grade 3 with lymphatic involvement. Negative for ER, PR, and Her2 receptors.

Her2 = Human epidermal growth factor receptor 2.

Histology

Subsequent skin core biopsies and mastectomy specimen revealed the characteristic tumor emboli plugging dermal lymphatics (fig. 3d). The histological diagnosis of invasive ductal carcinoma was rendered. Three cases (1, 3, and 5) were negative for estrogen (ER), progestron (PR), and Her2 receptors while 2 cases (2 and 4) were positive for ER and PR and negative for Her2 receptors (table 1).

Discussion

First described in 1924, IBC shows a geographic and ethnic variability in terms of incidence. It represents about less than 5% of all breast cancers in the developed world. This rate is high, comprising up to 20% of new cases in Tunisian and North African women, Egyptian women, and African American women in the United States and Western Europe [6–9]. No data is available from East Africa.

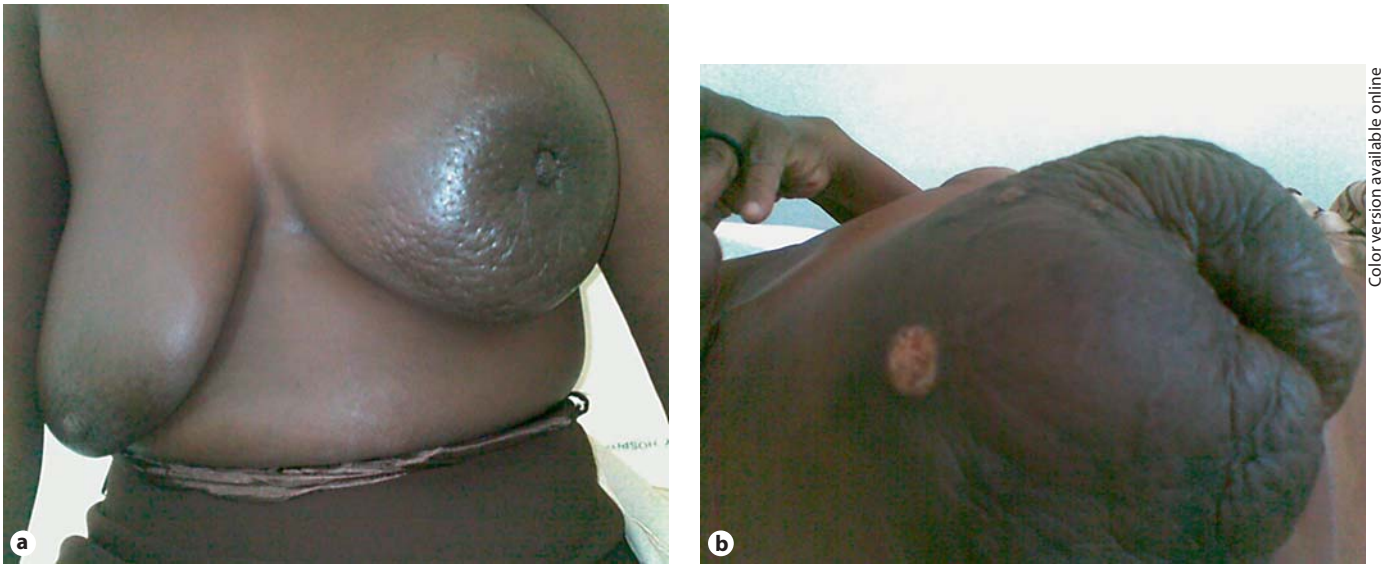

Fig. 2. a Clinical photograph of case 1 showing a diffusely enlarged left breast, peau d'orange, and a retracted nipple. **b** Clinical photograph of case 3 showing a diffusely enlarged right breast, an inverted nipple, ulceration, and peau d'orange.

The etiology and risk factors of IBC are not known. The Epstein-Barr virus and human herpes virus 8 are suspected culprits in view of the high incidence in North Africa. An association with obesity, a younger age at first childbirth, and a younger age at diagnosis has been noted in studies from North Africa [9]. Three of our patients are younger and premenopausal.

The earliest symptom is a color change (usually pink) in one breast; it becomes darker red and this change spreads over the entire breast. This feature is often missed in dark-colored skin such as that of our subjects. Patients usually do not have fever. The whole breast becomes rapidly enlarged over the next few weeks and the patient may feel a sensation of heat, tenderness, and heaviness. The usual history is of a rapid onset and a short duration of 3 months or less as was seen in our cases. Secondary changes such as itching, rash, nipple retraction, and nipple discharge can be present [1, 2, 10].

Clinically acute mastitis, duct ectasia producing subareolar mastitis, tuberculous mastitis, Mondor's disease (phlebitis of thoracoepigastric vein), and fat necrosis can mimic IBC but usually the involved area is well demarcated. Pyogenic infection usually subsides within 48 h of taking antibiotics. A history of trauma may or may not be elicited. Diagnosis is more challenging if women are younger, pregnant, or breastfeeding as was the case in 1 of our patients. Lactational mastitis is associated with localized tenderness, fever, and leukocytosis which may help to differentiate it from IBC [1].

The malignant lesions to be considered in the differential diagnoses include lymphoma and leukemic infiltration [1]. Peripheral blood examination can be useful for excluding leukemia. Adenocarcinoma metastatic to the breast presenting as inflammatory mastitis can mimic IBC [11].

Physical examination in IBC, unlike noninflammatory locally advanced cancer, often fails to reveal an underlying mass [12]. The patients are usually given antibiotics, and meanwhile the symptoms continue to worsen and the skin becomes progressively hard and thickened with peau d'orange changes; usually at this stage the patient is referred for FNA. A mammogram and ultrasound confirm skin thickening but do not show any mass [3]. Skin thickening involves the whole breast as was seen in 2 of our patients who had a mammogram. This finding helps in the differentiation of IBC from other inflammatory processes and from scirrhous carcinoma, which show local or segmental skin thickening [13]. Two of our patients had axillary lymphadenopathy which has been reported in 22–56% of IBC cases (mean 28%) [6].

The histological finding of tumor emboli in dermal lymph vessels is characteristic of IBC and is responsible for clinical symptoms. This finding without clinical symptoms is insufficient to be labeled as IBC. This may

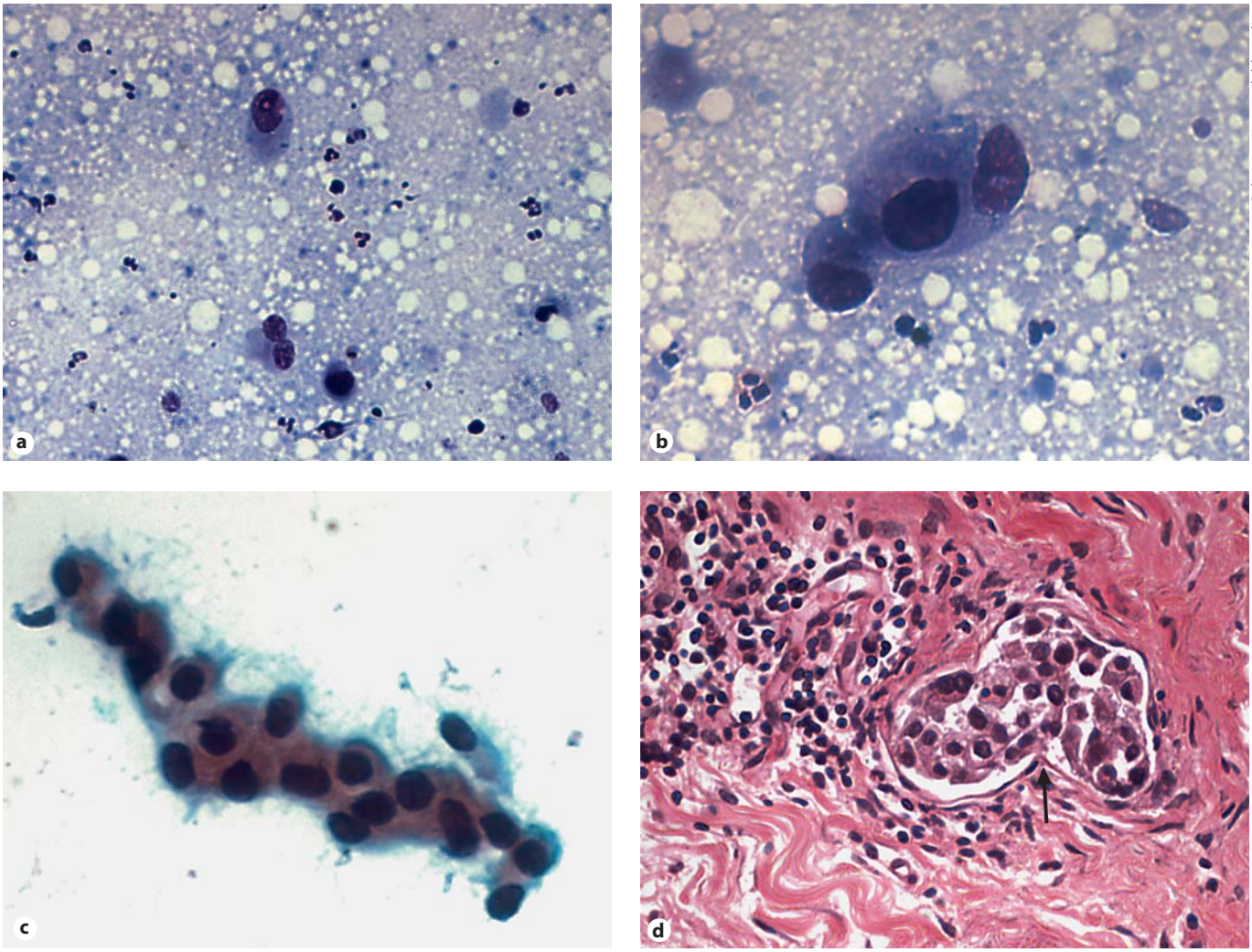

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Fig. 3. a FNA smear from case 1 showing few scattered atypical epithelial cells in a dirty background (Diff-Quick stain, ×20). **b** Repeat FNA smear from case 1 showing a small sheet of malignant epithelial cells in a dirty background (Diff-Quick stain, ×40). **c** FNA smear from case 3 showing a sheet of malignant epithelial cells in a dirty background (Papanicolaou stain, ×20). **d** Histological section showing tumor tissue fragments in dermal lymphatics (arrow) (H&E stain, ×20).

be absent due to a sampling problem in the biopsy. Dermal infiltration of lymphocytes is a nonspecific finding and is not responsible for clinical symptoms of IBC [14, 15].

FNA is often the first modality for establishing the initial tissue diagnosis of carcinoma in suspected IBC cases because of the low cost, rapidity, and convenience. The major problem is obtaining adequate material due to thick skin, edematous stroma, and lack of a discrete mass. Once the diagnosis of IBC is established in conjunction with clinical features, chemotherapy can be initiated quickly. FNA can be useful in follow-up after chemotherapy. FNA can also pinpoint the exact quadrant to be targeted for core biopsy depending upon the cellular material obtained from different quadrants in case a biopsy is deemed necessary. It can also procure material for molecular research in IBC. These are compelling reasons to explore various approaches of FNA and identify the best one to increase the chances of procuring adequate material.

The tangential approach described in our study increases the chances of aspirating tumor cell emboli in the dermal lymphatics. Using this approach, we were able to improve the cellularity adequate for a confident diagno-

sis; however, more large-scale studies are necessary to confirm the utility of our approach.

Neoadjuvant chemotherapy is used as the first line of treatment. Patients who respond well to chemotherapy are considered for definitive surgery. If the response to chemotherapy is poor, then radiotherapy is indicated. The 5-year median survival rate is approximately 40%; this is mainly due to delays in diagnosis, the lack of expertise in treating IBC, and its resistance to treatment with standard chemotherapy regimes [16].

IBC grows quickly and aggressively, and it has lymphotactic properties, high angiogenicity, and metastatic potential. It shows negative receptor status, increased expression of p53 (75%), and increased HER-2 amplification (40–45%) [17]. Three of our cases were negative for ER, PR, and Her2 receptors; 2 cases were positive for ER and PR and negative for Her2 receptors. A search for new molecular markers which may serve as potential targets for future therapeutic agents is underway [17].

We conclude that the diagnosis of IBC can be established by FNA using a tangential approach of the needle in all 4 quadrants with extra passes in antigravity areas. This can help in the timely initiation of chemotherapy. A learning curve exists to develop aspirator skills.

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