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Occult Male Breast Carcinoma, Non-Specific Type with Triple Negative Immunohistochemistry

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Abstract

Male breast cancer is a rare pathology with very low prevalence (<1%) of all breast cancers. Lymphadenopathy without a primary breast lesion is an atypical presentation both in men and women. Triple negative cancers, staining negative for the Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor-2 (HER2) are of relatively low prevalence i.e., 6 % in male and 13% in female. Here, we report the very rare case of 65 years old gentleman with Triple Negative Occult Male Breast Cancer (TNOMBC) diagnosed sequentially after a stepwise approach utilizing clinical examination, imaging, histopathology, and immunohistochemistry. The principal aim of this case report is to report a new unusual case, discuss its diagnostic approach, and emphasize the role of immunohistochemistry in Cancers of Unknown Primary (CUP).

Keywords: *Male breast cancer, Estrogen Receptor, Progesterone Receptor, Human Epidermal Growth Factor Receptor-2, Triple Negative Occult Male Breast Cancer, Cancer of Unknown Primary.*

Introduction

Male Breast Cancer (MBC) is a rare disease with a prevalence of less than 1% of both total breast cancer globally and all forms of cancer in males. Occult Breast Cancer (OBC) is a rare condition having metastatic axillary nodules without any clinically detectable primary breast lesion [1]. Most of the male breast cancers are hormone receptor positive (Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor-2 (HER2) negative [2]. Immunohistochemistry has a vital role in the diagnosis of cases of Cancer of Unknown Primary (CUP). We present a case of Triple Negative Occult Male Breast Cancer (TNOMBC) which was diagnosed by immunohistochemistry and is reportedly more aggressive with poor prognosis [3]. This case presented challenges in diagnosis and treatment. The motive of this study is to report and discuss the diagnosis, clinico-pathologic characteristics, and treatment of this rare and aggressive subtype of breast carcinoma.

Case Report

A 65 year old gentleman with a history of Type 2 DM for 4 years and mild asthma treated with medication came to our Medicine Out-Patient Department (OPD) for a diabetes consultation. Apart from the above chronic illnesses, he also had a past history of Tuberculosis 3 years ago for which he completed Anti-tubercular Therapy (ATT). The Patient is non-smoker and consumes alcohol occasionally. There is no history of cancer in his family.

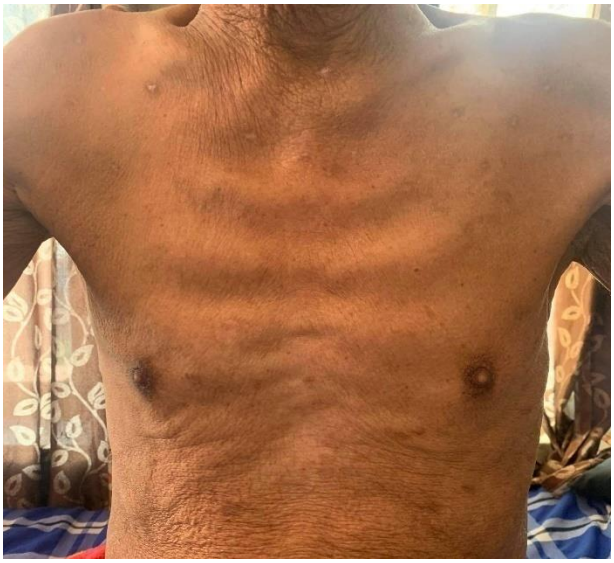


Figure: 1

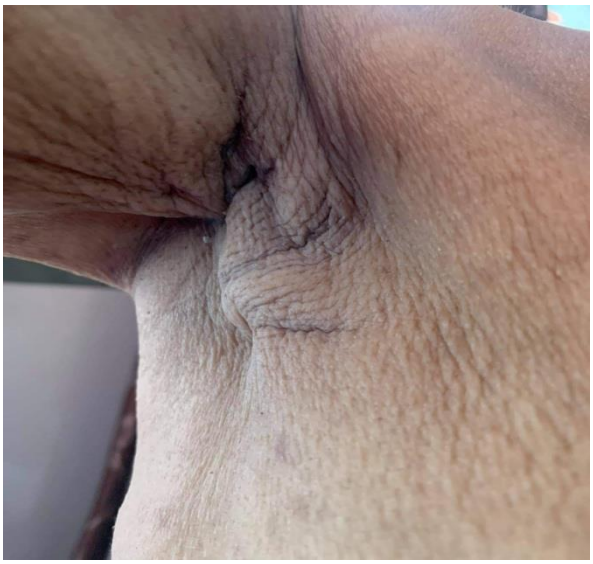


Figure: 2

Figure: 1, 2; Image showing the anterior chest wall and right axillary region with multiple palpable nodules.

On routine physical examination, he was averagely built (Figure: 1) and there were multiple palpable masses in the anterior right axilla (sub pectoral region). There were multiple, discrete, hard, fixed, non-tender nodules measuring approximately 5.5 cm in diameter (Figure: 2). Both the breast, contra-lateral axilla, chest and abdominal examination were normal. All of his hematological parameters were within normal limits. The patient tested negative for active tubercular infection. On ultrasonography (USG) of breast and axilla, no abnormal changes were identified in any of the breast and axilla other than a calcified mass in the right axilla.

He was then referred for Fine Needle Aspiration and Cytology (FNAC) of the right axillary lymph node which showed nuclear atypia, prominent nucleoli, nuclear polymorphism, and increased mitotic figures suggesting the possibility of metastatic carcinoma (Figure: 3).

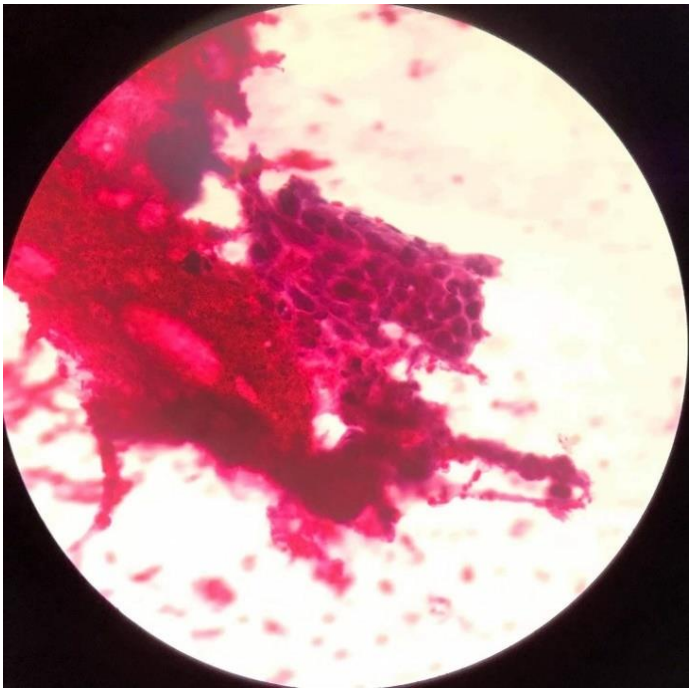


Figure: 3; Fine Needle Aspiration and Cytology of the right axillary lymph node showing atypical cells in clusters and papillary fragments with a dispersed pattern exhibiting moderate to marked nuclear pleomorphism with enlarged round to oval nuclei, coarse chromatin, and prominent nucleoli. Occasional mitotic figures are seen. Necrosed tumor cells are also present.

Computed Tomography (CT) scan was performed for further evaluation which showed a few heterogeneously enlarged right axillary and mediastinal (paratracheal and subcarinal) lymph nodes, tiny nodules in peripheral aspect of left lower lobe of lung and within right minor fissure, and a lytic lesion of left iliac bone (51x37x20 mm) (Figure: 4, 5, 6) which were all suggestive of a metastatic process but did not conclusively identify a primary site of origin.

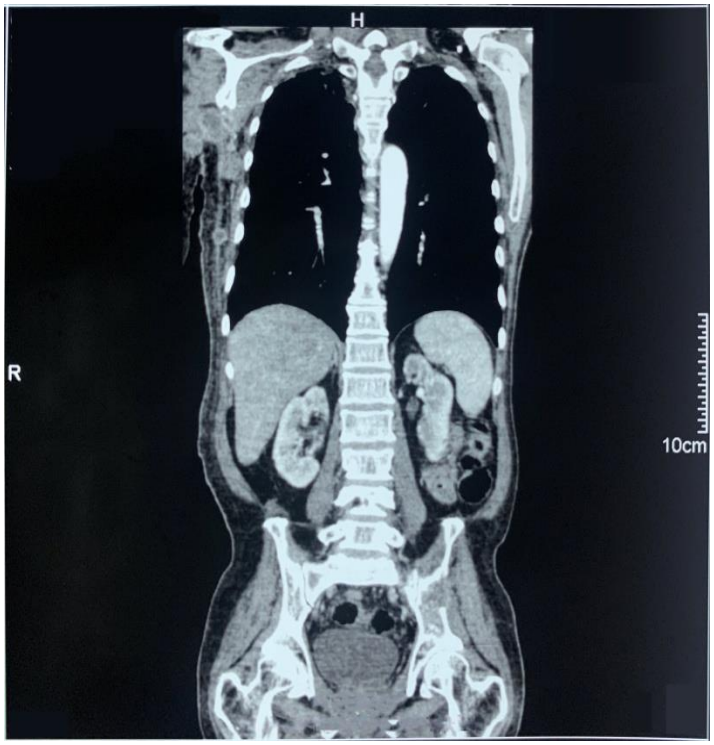


Figure 04

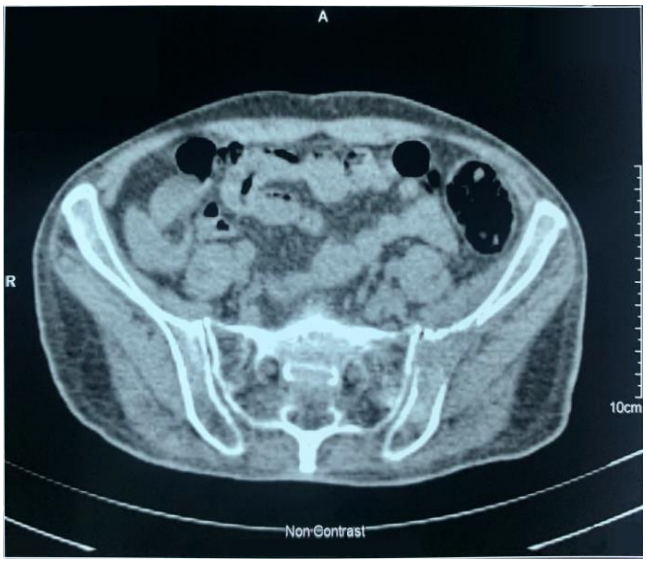


Figure 05

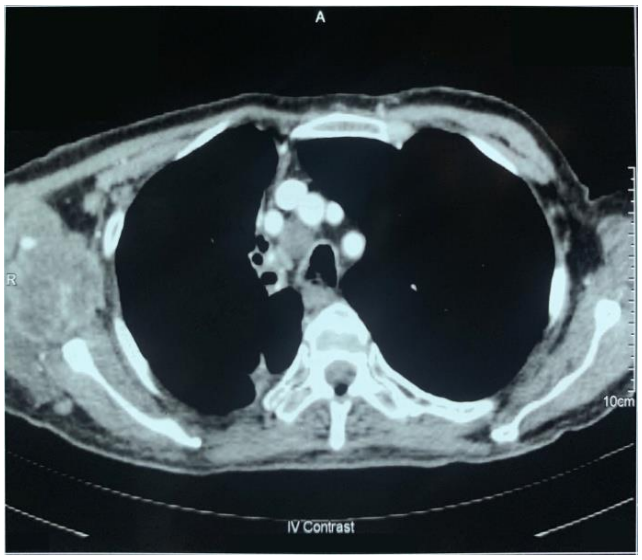


Figure 06

Figure: 4, 5, 6; CT-Scan (Non-Contrast CT and Contrast Enhanced CT) of chest, abdomen, and pelvis showing enlarged and heterogeneously enhancing right axillary lymph nodes and a lytic lesion with an enhancing solid component on left iliac bone.

Finally, the case was reported to the Department of Medical Oncology, ultrasound guided(USG) core needle biopsy (CNB) was advised and the specimen was sent for Histopathologic Examination (HPE). The microscopic features were suggestive of metastatic carcinoma (Figure: 7, 8). The immunohistochemistry (IHC) also revealed that the mass was Invasive Mammary Carcinoma, non-specific type (NST) metastatic to axillary lymph nodes (Nottingham Score: 8; Grade: 3) with a triple negative phenotype (ER: Negative, PR: Negative and HER2: Negative) (Figure: 9). It was a high grade carcinoma immunoreactive for Cytokeratin (CK), Cytokeratin 7 (CK7), GATA binding protein 3 (GATA3) (Figure: 10) while non-reactive for Cytokeratin 20 (CK20) and Thyroid transcription factor 1 (TTF1).

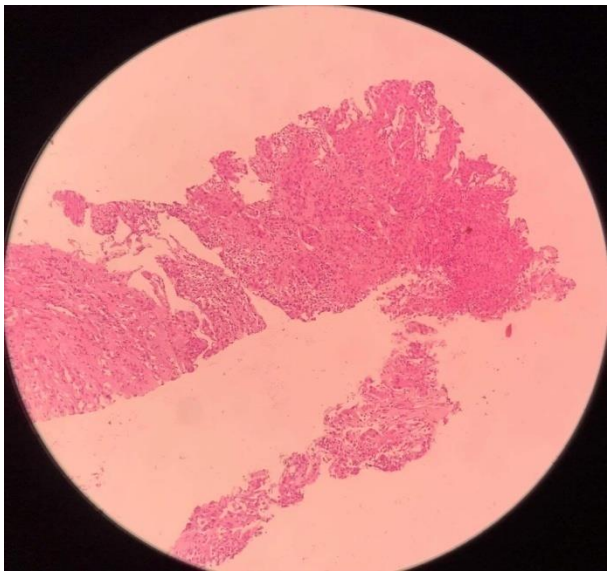


Figure: 7

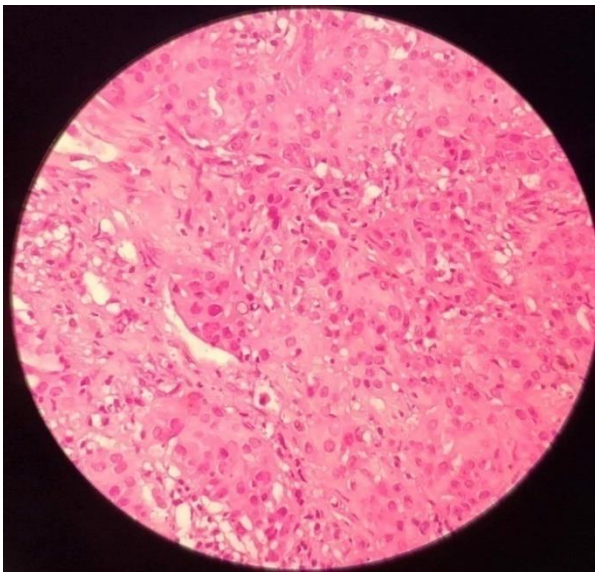


Figure: 8

Figure: 7, 8; Section shows features exhibiting infiltration by tumor arranged in nests, trabeculae, cords and a dispersed pattern. Occasional poorly formed gland-like structures are noted. The tumor cells exhibit moderate-marked nuclear pleomorphism with enlarged round to oval hyperchromatic nuclei, variably conspicuous nucleoli, and a moderate amount of eosinophilic cytoplasm.

As per the tumor board conclusion involving pathologist, radiologist, radio-oncologist, chemotherapy was stared on follow-up with Anthracycline-Cyclophosphamide followed by Taxane regimen (AC-T regimen) every 3 weeks for 4 cycles and was followed by a response evaluation with Contrast Enhanced Computed Tomography (CECT) chest, abdomen and pelvis.

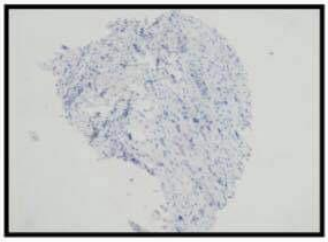
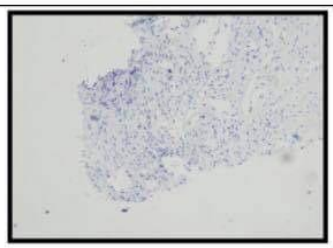
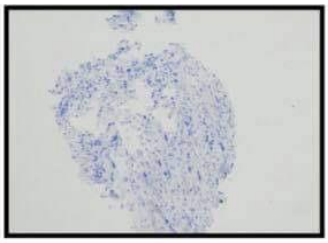
MARKERS (CLONES)	RESULTS		INTERPRETATION	IMAGE
ER (EP-1)	% of cells with nuclear staining in the invasive component of the tumor	0%	Negative	
PgR (EP-2)	% of cells with nuclear staining in the invasive component of the tumor	0%	Negative	
Her-2/neu (EP-3)	No staining seen in tumor cells	Score 0	Negative	

Figure: 9; Immunohistochemistry (IHC) for right axillary lymph node trucut biopsy showing hormone receptor negative (ER: Negative, PR: Negative and HER2: Negative).

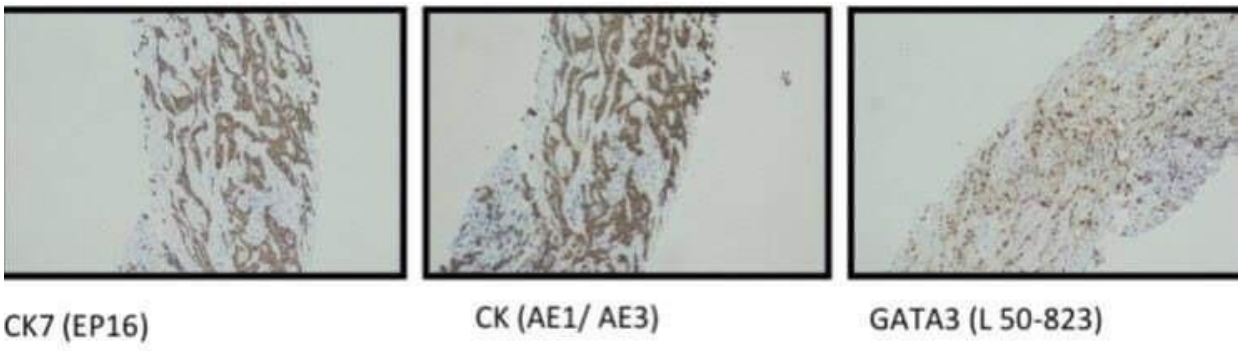


Figure: 10; Immunohistochemistry (IHC) for right axillary lymph node trucut biopsy showing CK stain and GATA marker.

Discussion

Occult Breast Cancer is a type of breast cancer having axillary metastatic nodules without any primary breast symptoms (lump, skin changes, excoriation and discharge) and without identifiable breast mass on confirmed radiologic examination such as mammography, USG and CT/MRI. Male breast cancer has a very low prevalence of below 1 % globally among total breast cancer and 1% of all male cancers. The highest prevalence of male breast cancer occurs between the ages of 52 and 71 years of age [1]. There are very few cases reporting Occult Male Breast Cancer (OBC) whereas the prevalence of OBC in females is reportedly about 0.2% to 0.9% [4]. Triple negative cancer exhibiting all ER, PR and HER2 negative accounts for 13% and 65% among females and males respectively and reported highest in non-Hispanic blacks and Hispanic patients (23.7% and 14.8%) [3].

Triple negative occult breast cancer isa very rare clinical condition reported in few papers, one of an 82 year old associated with dermatomycosis [5] and another of a 48 year old patient who only had a painless erythematous lesion on the lateral chest wall. Both of these cases presented with palpable axillary nodes [6].

Male Breast cancer has risk factors similar to female breast cancer which include; older age, positive family history of BRCA1/BRCA2 gene mutation, radiation exposure, temperate climate, obesity, hyperlipidemia, DM, liver damage, and estrogen intake. In addition, Klinefelter's Syndrome, bilateral orchiectomy, undescended testis and gynecomastia are additional risks in males [7]. Older age and Diabetes Mellitus were the only known risk factors found in our patient. Clinically, most patients with OBC present at a late age, more advanced stage, and are more likely to have >10 positive lymph nodes [8]. One of the case reports of Occult Male Breast Cancer (OMBC) was discovered in association with anemia, thrombocytopenia, and bone marrow metastasis which might be due to the lateness of presentation of the disease [9].

In our patient, there were no signs other than multiple palpable right axillary nodules. The radiologic findings could have been consistent with a lung or breast primary. Imaging was further confounded by his past tubercular infection with calcified axillary lymph nodes and enlarged mediastinal lymph nodes. CECT of chest, abdomen and pelvis findings of suspicious nodes in axillary region and the lytic lesion with enhancing solid component in the left iliac bone were highly suggestive of metastatic disease. Tissue biopsy for HPE and IHC were required to confirm the final diagnosis of Invasive Mammary Carcinoma

with triple negative breast carcinoma. The literature also reports that bone is the most common site for metastasis in breast cancer [10] and third most common site in lung cancer [11].

TNBC is a highly aggressive breast cancer and accounting for about 5.9% of the breast cancer in males, more in young ages (less than 30 years) and Hispanics in both the populations with Invasive Mammary carcinoma, NST being the most common histologic type. TNBCs were more likely to present with large size, fast progression, and higher nuclear grades than non-TNBCs and significantly less likely to have positive nodes [3]. IHC has a vital role in evaluation of CUP after unsuccessful clinical radiological and histopathological examination. The two most common CK stains used for CUP are CK7 and CK20, and the combination of CK7 and CK20 IHC profiling has been helpful to identify primary tumor sites. CK7 positive/CK20 negative phenotype is seen in a wide variety of carcinomas such as carcinoma of lung, breast, thyroid, pancreas, and female genital tract. In contrast, CK7 negative/CK20 positive phenotype is often associated with carcinomas of colorectal origin [12]. Similarly, GATA3 is a useful marker for identifying breast cancer, both ductal and lobular carcinoma, and urothelial cancer. More than 96% of metastatic invasive ductal carcinoma is positive for GATA3 [13]. Non-reactivity for TTF1 can be helpful in differentiating breast cancer for other primary sites. TTF1 is a reliable marker for metastatic lung adenocarcinoma (95%) and thyroid cancer but is typically non-reactive for breast cancer at only 3.1% [14].

According to American Cancer Society, TNBC treatment and prognosis depends upon the stage of the cancer. Surgery followed by adjuvant chemotherapy is the preferred treatment. Adjuvant radiotherapy is often recommended for lymph node positive cases. The ability to perform surgery depends on size of the tumor and the stage. Lymphedema can be a complication of surgery. In general, the five years survival rate for regional and distant metastasis in TNBC are 65% and 11%, respectively [15].

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