

## Nasopharyngeal carcinoma metastasis to the breast

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## ABSTRACT

إن ورم الثدي الناجم عن الأورام غير الثديية نادر الحدوث ، حيث يمثل حوالي 2 % من جميع الأورام الخبيثة في الثدي . أبلغنا عن حالة من ورم خبيث من سرطان البلعوم الأنفي (NPC) المنتشر إلى الثدي لدى مريضة تبلغ من العمر 43 عاماً اشتكت من كتلة بطيئة غير مؤلمة في ثديها الأيسر وتورم في منطقة إبطها الأيسر. تم إجراء خزعة موجهة بالموجات فوق الصوتية من كتلة الثدي والعقد الليمفاوية الإبطية ، وأظهر فحص الأنسجة من العقد الليمفاوية الإبطية والثديية نواة من الأنسجة الليفية مختزقة بالحبال وأوراق من خلايا الورم المضلع الأضخم المتوسعة مع النحافة إلى المعتدلة ، الحمضية السيترولازم والنوى المتضخمة ، متعددة الأشكال وتعد الأَشكال مع الأغشية النووية غير المنتظمة . كان الفحص المناعي الكيميائي (IHC) إيجابياً لـ an cytokeratin وسالِباً لـ leukocyte common antigen (LCA)، HMB45، CD 20، desmin، myogenin، gross cystic disease fluid protein 15 (GCFDP-15)، thyroid transcription factor (TTF-1)، villin، estrogen receptor (ER)، progesterone receptor (PR)، and HER2 ، حيث أن المريضة مشخصة مسبقاً بسرطان البلعوم الأنفي، واستناداً إلى نتائج الفحص المخبري والصبغات المناعية، تم تشخيص المريضة بسرطان الثدي المهاجر من سرطان البلعوم الأنفي . رفض المريض أي علاج آخر وتوفي بعد ثلاثة أشهر من التشخيص .

Breast metastases from extra-mammary neoplasms are rare, accounting for <2% of breast cancer cases. A 43-year-old female patient presented with a mass in her left breast and swelling in her left axillary region. A histopathological examination of the mass showed enlarged polygonal tumor cells with scant to moderate, eosinophilic to amphophilic cytoplasm and enlarged, hyperchromatic and pleomorphic nuclei with irregular nuclear membranes. An immunohistochemistry (IHC) examination was positive for pan cytokeratin and negative for CK7, CK20, S-100, LCA, HMB45, CD 20, desmin, myogenin, GCFDP-15, transcription factor-1, villin, estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2. As she was a known case of nasopharyngeal carcinoma, and based on the histopathology findings and IHC profile, the patient was diagnosed with breast metastasis from NPC. The patient was deceased 3 months after refusing the recommended medical intervention.

**Keywords:** nasopharyngeal carcinoma, metastasis, breast, Madinah, Saudi Arabia

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Metastasis to the breast is rare, accounts for <2% breast tumors, and most commonly arises from the primary tumors from the opposite breast or from extra-mammary primary tumors such as melanomas, lung, hematological, gynecological, and gastrointestinal cancers.<sup>1,2</sup> Metastasis to the breast from head and neck tumors is very rare, and primaries from nasopharyngeal carcinoma (NPC) are extremely rare.<sup>3</sup> Nasopharyngeal carcinoma differs from other head and neck carcinomas by its distinctive geographic location and relationship with the Epstein-Barr virus (EBV) infection. Metastatic sites are usually multifocal and involve the skeleton, lymph nodes, lungs, and liver.<sup>4</sup> Metastasis to the breast from NPC is a rare clinical finding and may pose a diagnostic challenge due to its clinical and radiographical similarities to primary breast tumors.<sup>5</sup>

An extensive search of English-language literature revealed very few previously published cases of breast metastasis from NPC, indicating the rarity of the lesion. Herein, we report a case of NPC with metastasis to the breast in a female Mauritanian patient from the Madinah region and highlight the importance of immunohistochemistry (IHC) in the differential diagnosis of this rare entity.

**Case Report. Patient information.** A 43-year-old Mauritanian female was presented to King Fahad Hospital, Madinah, Saudi Arabia, in February 2017 with

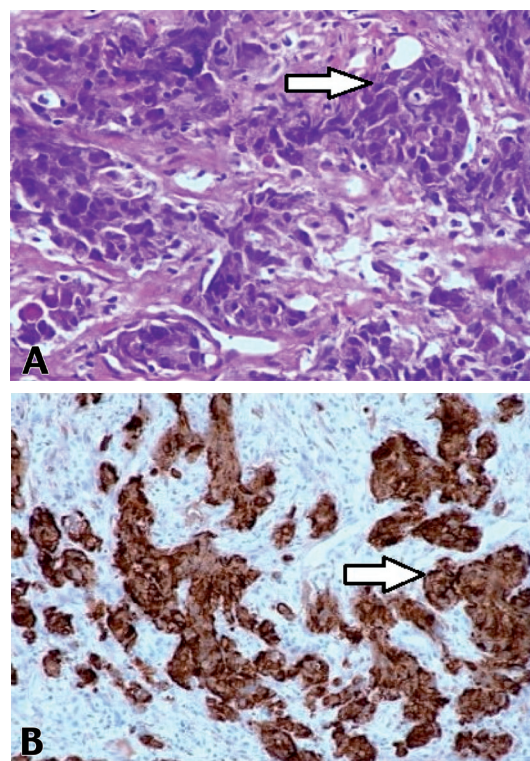
a 2-month history of headache, epistaxis, nasal discharge, nasal blocking, unilateral hearing impairment, and bilateral neck swelling. Physical examination revealed bilateral neck nodes enlargement with the largest measuring 3.5 cm × 5 cm in the left cervical region. On nasopharyngoscopy, a mass in the nasopharynx was identified and biopsied. Histopathology findings of the biopsied mass reported as an undifferentiated nasopharyngeal carcinoma (NPC) (World Health Organization type III). Computed tomography (CT) and magnetic resonance imaging (MRI) of the head and neck showed a large heterogeneous mass at the left Fossa of Rosenmuller (FOR) with direct extension into the paranasal sinuses. Enlarged lymph nodes in the left supra-clavicular fossa is also noted which is in favor of metastatic lymphadenopathy. A complete metastatic work-up including CT of chest and abdomen, and bone scan was performed and revealed no significant abnormalities. She was thus diagnosed to have a NPC stage III (T3N3M0), according to the American Joint Committee on Cancer Staging.<sup>6</sup> Three cycles of concurrent cisplatin (75 mg/m<sup>2</sup>) and radiation therapy (70 Gray) were administered to the patient in March 2017 and were finally completed in May 2017.

**Clinical findings.** Upon completing her treatment, she was in clinical remission and was disease-free for 21 months until she presented again with a mass in her left breast and swelling in her left axillary region. The physical examination revealed a firm, rubbery, non-tender, and mobile lump involving the upper outer quadrant of the left breast. The skin and nipple-areola complex were unremarkable. The left axillary lymph nodes were matted, measuring 3 cm × 3.5 cm. No significant abnormalities were identified in the contralateral breast or axillary area.

**Diagnostic assessment.** Mediolateral and craniocaudal mammograms showed a spherical mass lesion in the left breast with ill-defined speculated margins, measuring 4 cm × 3.5 cm × 4.5 cm. A subsequent CT scan and MRI of the chest and abdomen revealed no signs of lung or liver metastases. Similarly, a bone scan revealed no bone metastases. An ultrasound-guided biopsy of the breast lesion and axillary lymph nodes was performed, and a histopathological examination from the breast and axillary lymph nodes showed cores of fibrous tissue infiltrated with cords and sheets of

enlarged polygonal tumor cells with scant to moderate, eosinophilic to amphophilic cytoplasm and enlarged, hyperchromatic and pleomorphic nuclei with irregular nuclear membranes (**Figure 1**). An IHC examination was positive for pan cytokeratin (phosphoenolpyruvate carboxykinase, monoclonal, MNF 116, 1:300, Dako, Carpinteria, California, USA) and negative for CK7, CK20, S-100, leukocyte common antigen (LCA), HMB45, cluster of differentiation (CD) 20, desmin, myogenin, gross cystic disease fluid protein 15 (GCFDP-15), thyroid transcription factor (TTF-1), villin, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (**Figure 1**). As she was a known case of NPC, and based on the histopathology findings and IHC profile, the patient was diagnosed with metastatic NPC, undifferentiated type of the left breast and left axillary lymph nodes.

**Therapeutic intervention, follow-up, and outcomes** She refused any further treatment and died 3 months after diagnosis (**Figure 2**). The case report was conducted ethically in accordance with the World



**Figure 1** - Microphotography showing poorly differentiated A) malignant cells (hematoxylin-eosin at magnification x 40) and B) positive staining of tumor cells for PCK (Avidin Biotin at magnification x 40) (arrows indicate malignant cells).

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Medical Association Declaration of Helsinki. Informed consent was not obtained from the patient due to no communication.

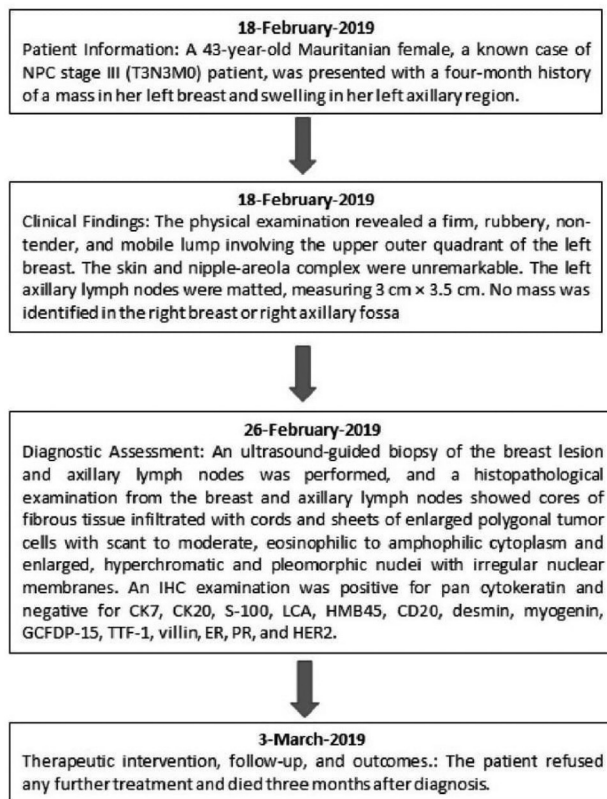
**Discussion.** The breast is an uncommon site for a metastatic tumor, with the incidence of metastatic breast tumors from other primaries having been reported in the range of 1.7-6.6% in an autopsy study, 1.2-2% in clinical reports, and 2.7% from fine needle aspiration cytology reports.<sup>5</sup> However, many other studies have reported a rate of 0.5-6%.<sup>7</sup> Moreover, breast metastases from NPC are extremely uncommon and usually occur as part of a disseminated disease. It has been observed that a metastatic breast lesion can be either the first evidence of recurrence or the first manifestation of a clinically occult malignancy.<sup>8</sup> The first case of NPC metastasizing in the breast was reported in 1991; since

then, only 12 cases of NPC metastasis in the breast have been described in the literature.<sup>9</sup> A majority of these cases have reported it in the unilateral side, and only 3 case reports have reported it in bilateral breasts.<sup>7-9</sup> Although metastatic NPC in the breast is seen mainly in female patients, 2 cases have been reported in males as well.<sup>3,10</sup>

The mechanism by which NPC metastasizes to the axillary lymph nodes is not completely understood and can be explained by the following ways: i) retrograde lymphatic drainage due to obstruction; when the large supraclavicular lymph nodes block the lymphatic ducts, as in our patient, metastasis can spread retrograde to the axillary lymph nodes;<sup>11</sup> ii) the destructive effect of radiotherapy during the first treatment, which cuts off blood supply to the tumor; this is unfavorable for tumor growth and causing it to relocate and occur far from the nasopharynx such as the axilla.<sup>12</sup>

The previous literature has reported the age range of the breast metastases from NPC in the fifth and sixth decades of the patients' lives; our patient was also in her fifth decade. Clinically, breast metastases from NPC are usually present as solitary, mobile, and well-circumscribed masses; however, Pai et al<sup>1</sup> and Leach et al<sup>5</sup> have reported multiple rubbery subcutaneous masses in their reports. In the present case, the tumor presented as a firm, rubbery, non-tender, and mobile mass. Following the primary NPC, the latency period from the initial diagnosis of NPC to the diagnosis of breast metastasis ranged between 6 and 42 months, with a median latency period of 27 months. It has been observed that a metastatic breast tumor could occur immediately after the first course of treatment or within 24 months of treatment completion.<sup>1,3</sup> In our case, the patient developed breast metastasis after 21 months of initial treatment for NPC. A comparison of the present case report with previous cases of NPC metastasizing to the breast is summarized in [Table 1](#).

Metastatic NPC can present a diagnostic challenge, which is mainly attributed to the rarity of this lesion. The distinction between metastatic NPC and primary breast tumors on clinical, histopathological, and radiological examination is challenging, as their characteristics are quite similar in the majority of cases.<sup>5</sup> Metastatic NPC may mimic lymphoepithelioma like carcinoma, medullary carcinoma, or an infiltrating ductal or lobular carcinoma with inflammatory stroma. This is further complicated by the absence of ER, PR, and HER2 immunostaining, a phenotype unique to patients with triple negative breast cancer. Hence, histopathological, IHC, and radiological findings, along with the patient's clinical history, must be considered in the



**Figure 2** - Timeline summary of the patient's current illness, clinical examinations, diagnostic evaluations, therapeutic management and follow-up. IHC: immunohistochemistry, LCA: leukocyte common antigen, cluster of differentiation: CD20, gross cystic disease fluid protein 15: GCFDP-15, thyroid transcription factor: TTF-1, ER: estrogen receptor, PR: progesterone receptor

**Table 1** - Comparison of present case report with the previously reported cases of nasopharyngeal carcinoma (NPC) metastasizing to the breast.

Author	Year	Age/ gender	Time to breast metastasis (months)	Site	Axillary lymph nodes	Other distant metastasis	Treatment	Survival
Driss et al <sup>8</sup>	2007	25/F	42	B/L	Present	Liver and bones	Palliative	N/R
Leach et al <sup>5</sup>	2013	49/F	39	Left breast	Present	Bone Iliac lymph nodes	Chemo + radiation	N/R
Liang et al <sup>10</sup>	2014	49/M	5	Right breast	Present	Cervical lymphadenopathy	Chemo + radiation	Surviving till the reporting of the case
Li et al <sup>4</sup>	2015	56/F	3	Left breast	Present	Absent	Refused	6 months
Xiao et al <sup>3</sup>	2015	41/F	6	Left breast	Absent	Liver	Refused	5 months
		46/M	9	Right breast	Absent	Absent	Chemo + mastectomy	>10 years
Vaishnav et al <sup>7</sup>	2015	28/F	2	B/L	Absent	Absent	Chemo	N/R
Pai et al <sup>1</sup>	2017	45/F	52	Right breast	Present	Supraclavicular and intraabdominal lymph nodes soft tissues	Chemo + radiation neck dissection	Surviving till the reporting of the case
Zhao et al <sup>9</sup>	2020	52/F	12	B/L	Present	Absent	Chemo	Surviving till the reporting of the case
Present case	2020	43/F	21	Left breast	Present	Absent	Refused	3 months

N/R: not reported B/L: bilateral

differentiation of metastatic NPC from primary breast cancer. Therefore, the correct diagnosis is of critical significance, as the treatment modalities of these 2 types of tumor is variedly different.<sup>13</sup> An in situ hybridization using an EBV encoded RNA probe is the most sensitive and specific diagnostic tool available in the literature.<sup>14</sup> Unfortunately, this technique is not available in our laboratory at present. However, we believe that the clinical history, histopathological findings, and IHC profile clearly confirm the diagnosis of NPC metastatic to the breast in our patient. The ideal treatment for metastatic NPC is chemotherapy and radiotherapy, and patients with solitary breast metastasis from NPC may gain long term survival, as observed by Xiao et al.<sup>3</sup>

In conclusion, this case highlights the rarity of the NPC lesion and importance of clinical, histopathological, and IHC examination, along with the patients' history, for appropriate diagnosis and treatment.

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