Egyptian Journal of Radiology and Nuclear Medicine

CASE REPORT Open Access

Metastatic non-muscle invasive transitional cell carcinoma of urinary bladder: a case report

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Abstract

Background: Axillary lymphadenopathy is a common clinical presentation of variety of benign and malignant diseases. However, majority of patients with unilateral axillary lymph node enlargement have an underlying malignancy in which association with breast carcinoma being the commonest one. In most of these patients there will be a discernible primary tumor, either clinically or radiologically. However, in axillary lymphadenopathy with negative mammogram is not very common, and in this case other malignant causes should also be considered in addition to occult breast cancer and these can be metastases from other primary tumors for, e.g., lung, genitourinary tract, gastrointestinal, ovarian, thyroid carcinomas and malignant melanoma.

Axillary node is an uncommon site of metastases from Transitional cell carcinoma (TCC) of urinary bladder even from its muscle invasive form, and distant metastasis from low grade superficial tumors without muscle invasion or regional metastasis is a very rare occurrence. Here we present a case of axillary nodal metastases from non-muscle invasive (superficial) bladder cancer without history of local recurrence and regional metastases.

Case presentation: We present a case of female patient who complaint of hard swelling in right axilla and right breast enlargement. Patient had past history of non-muscle invasive transitional cell carcinoma of urinary bladder (pTa, grade II A) which had been treated accordingly. No recurrence of bladder growth had been observed on serial check cystoscopies. On clinical examination of breast and axilla, right breast appears enlarged and there were palpable hard fixed axillary lymph nodes. Ultrasound showed enlarged malignant looking lymph nodes. Occult breast carcinoma with metastatic axillary lymph nodes was our initial impression; however, subsequent biopsy of axillary lymph nodes showed Transitional cell carcinoma.

Conclusions: This patient's case emphasizes the importance of having sound knowledge of natural behavior of primary tumor and common and uncommon sites of distant metastases. The causes of unilateral axillary lymphadenopathy include both benign and malignant disease.

Keywords: Superficial transitional cell carcinoma, Non-muscle invasive transitional cell carcinoma, Metastasis, Axillary lymphadenopathy, Case report

Background

Lymph nodes enlargement in the body anticipates the presence of important localized and systemic diseases. Axillary lymphadenopathy imparts broad differential diagnosis and can be present in both malignant and benign diseases [1]. Benign enlargement of axillary lymph nodes can be seen with benign reactive hyperplasia, infections (bacterial/fungal/tuberculosis), systemic inflammatory diseases, collagen vascular diseases, and several other causes. Most common malignant cause of axillary lymph node enlargement is breast cancer; however, with negative mammogram in addition to occult breast cancer, other malignant causes can be metastases

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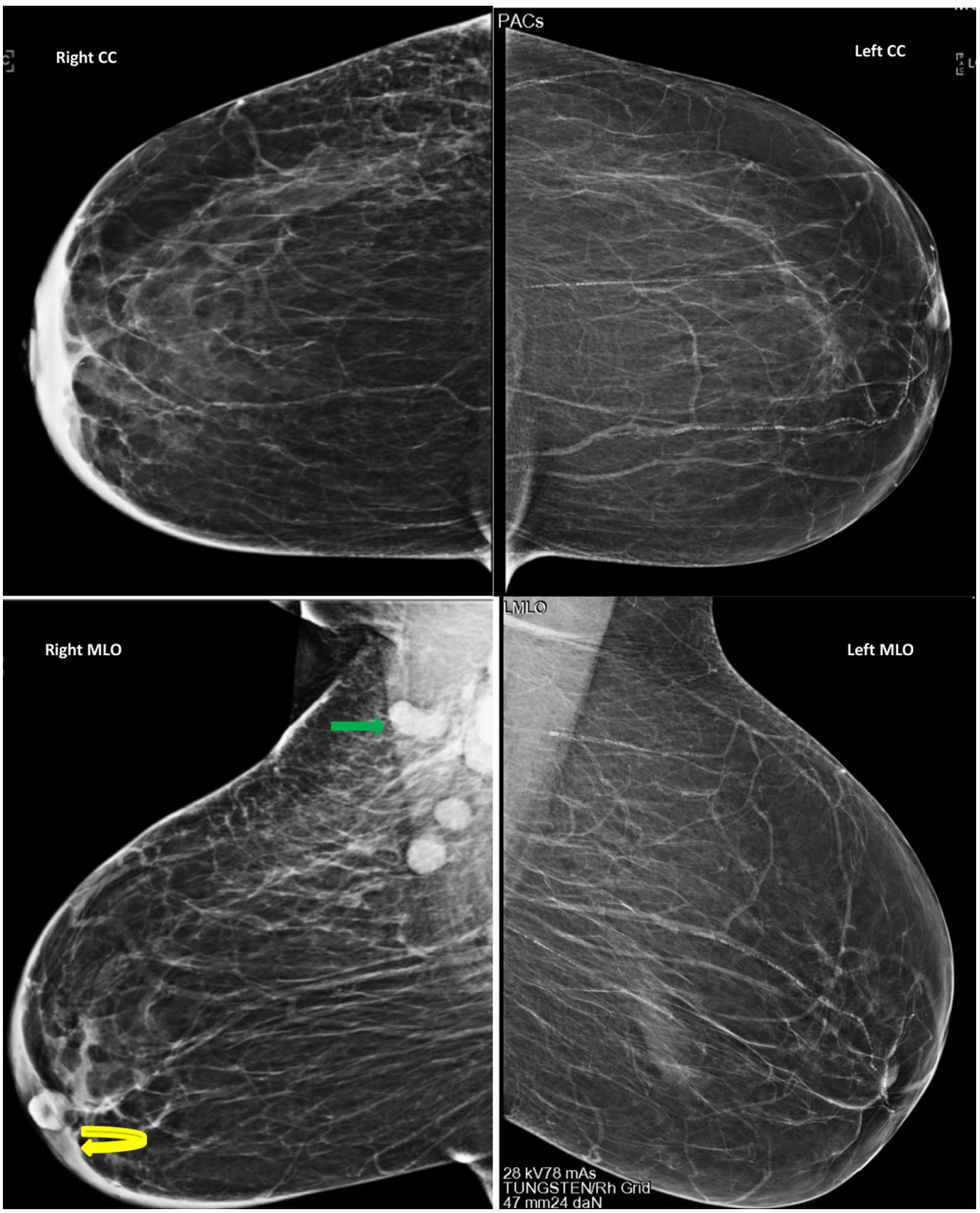

Fig. 1 Craniocaudal and Mediolateral oblique views of both breasts: Right breast shows slight increase in density when compared to the contralateral side. There is diffuse thickening of skin (yellow arrow). This is secondary to lymphatic obstruction because of enlarged ipsilateral axillary lymph nodes. Multiple enlarged malignant looking lymph nodes are seen in right axilla, round in shape with loss of fatty hilum (green arrow)

from other primary tumors (e.g., lymphoma, stomach, ovarian carcinomas lung malignant melanoma) [2].

Axillary node is an uncommon site of metastases from TCC of urinary bladder even from its muscle invasive form, and distant metastasis from low grade superficial tumors without muscle invasion or regional metastasis is a very rare occurrence. The most common sites of distant metastases of Transitional cell carcinoma (TCC) are lung, liver, mediastinum, adrenal gland and bone. It is also known to spread via regional lymphatics [3]. There is limited data about early metastasis from low grade superficial tumors in the literature.

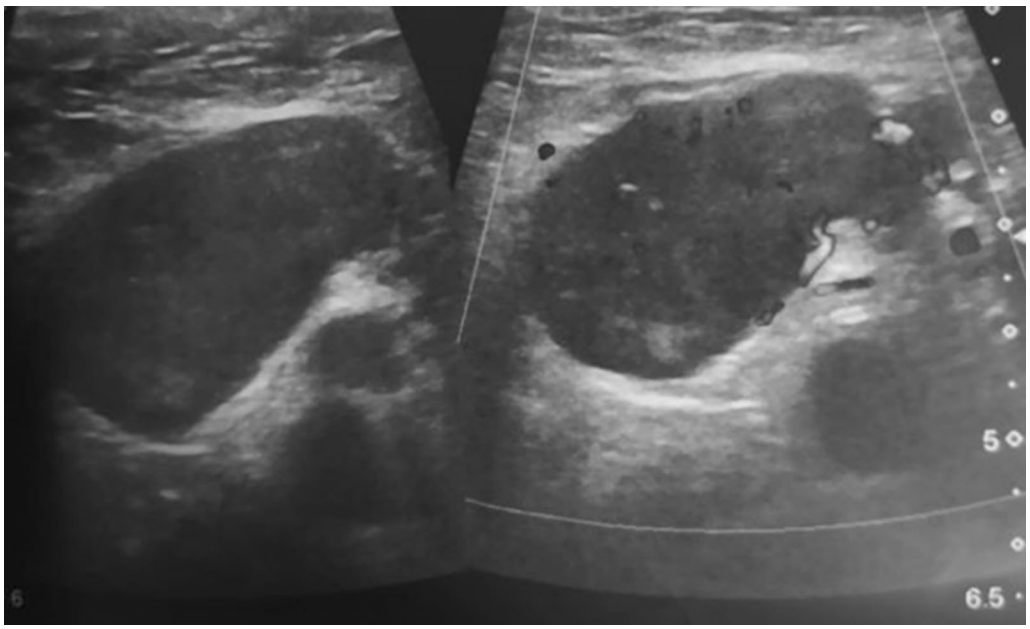

Fig. 2 Ultrasound of right axilla: Enlarged malignant looking lymph nodes in right axilla. Complete effacement of fatty hilum is seen in all the visualized lymph nodes. Doppler flow is seen in hilum as well as in the abnormally thickened cortex. Associated perinodal edematous changes also visualized

Case presentation

60 years old married female presented to us in breast clinic with complains of hard swelling in right axilla and right breast enlargement. There was no abdominal or urinary complains. Patient had past history of non-muscle invasive transitional cell carcinoma of urinary bladder (pTa, grade II A) which had been treated with complete resection followed by intravesical chemotherapy 5 years back. Ever since patient was on follow-up and multiple check cystoscopies were done periodically, that showed no recurrence of bladder growth. Last check cystoscopy and random biopsy was done one month back before presenting to us showed no recurrence of tumor.

On clinical examination of breast and axilla, right breast appears enlarged and skin showed Peau'd orange appearance. However, no discrete mass was clinically palpable in the breast. There were palpable hard fixed axillary lymph nodes. Ultrasound done in the clinic showed enlarged malignant looking round to oval lymph nodes with complete effacement of fatty hilum (Fig. 1). However, ultrasound breast showed edematous changes and underlying fine details were obscured. Keeping in mind patient's past history of transitional cell carcinoma, ultrasound of kidneys and urinary bladder was also done that showed that turned out to be normal. Afterward patient was referred for mammogram which showed increase in the size of right breast with global increase in breast density. Diffuse skin thickening was also seen, however, no malignant mass was noticed. There was no evidence of micro or macro calcifications on mammogram (Fig. 2). Inflammatory breast carcinoma was suspected. Because no breast mass was identified, axillary lymph node biopsy was advised.

Histopathology showed sheets and nests of atypical epithelial cells with intervening fibrous stroma. Atypical epithelial cells showed abundant eosinophilic cytoplasm, pleomorphic and hyperchromatic nuclei. Immunohistochemical marker Cytokeratin-7 (CK-7), Cytokeratin-20 (CK-20) and GATA-3 were diffusely positive in tumor cells. However, GCDFP, Estrogen receptors (ER), Progesterone receptor (PR), GCDFP-15 were negative in tumor cells (Fig. 3a–e). These morphological and immunohistochemical profile are of metastatic transitional cell carcinoma. Further workup done for urine microscopy, culture, and cytology, that was normal. Staging workup CT scan showed no metastatic disease elsewhere except right axillary lymphadenopathy. Urinary bladder was also normal (Fig. 4a, b).

Discussion

Axillary lymphadenopathy is not uncommon to see in day to day clinical practice. It has wide range of differential diagnosis and can be seen in various numbers of both benign and malignant diseases [2]. However, in approximately one third of patients with unilateral

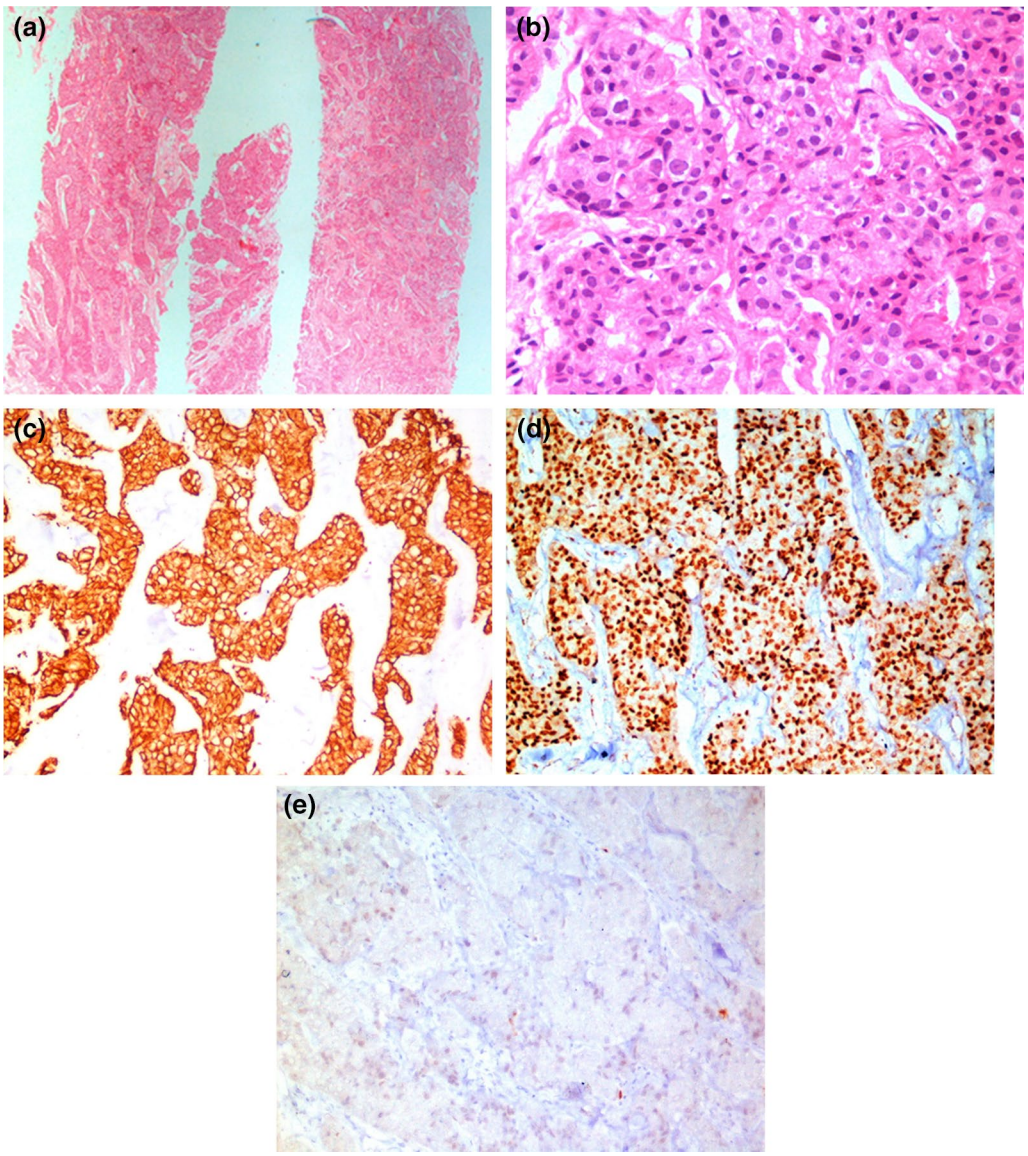

Fig. 3 **a** Low power magnification view of trucut axillary lymph node biopsy, showing nests of atypical epithelial cells with intervening fibrous stroma. No lymphoid tissue is seen. **b** High power magnification view, showing nests of atypical epithelial cells with abundant eosinophilic cytoplasm, pleomorphic, hyperchromatic nuclei and intervening fibrous stroma. **c** Immunohistochemical marker Cytokeratin-7 (CK-7) and Cytokeratin-20 (CK-20) showing diffuse cytoplasmic positivity in tumor cells. **d** Immunohistochemical marker GATA-3 showing diffuse nuclear positivity in tumor cells. **e** Immunohistochemical markers Estrogen receptors (ER), Progesterone receptor (PR), GCDFP-15 are negative in tumor cells.

axillary lymph node enlargement there is an underlying malignancy in which association with breast carcinoma being the commonest one. In most of these patients there will be a discernible primary tumor, either clinically or radiologically. It is uncommon to see occult breast cancer presenting with axillary adenopathy, accounting for less than 1% of cases. This can pose diagnostic difficulty as there are other metastatic causes of axillary adenopathy including, lung, genitourinary tract, gastrointestinal, ovarian, thyroid carcinomas and malignant melanoma [1].

It is unusual to have nodal metastasis with Non–muscle-invasive (superficial) bladder cancer (NMIBC) [4, 5].

An extensive PubMed search showed fifteen cases of distant metastases of superficial bladder cancer without local invasion or regional metastases. Approximately 80% of bladder TCC is NMIBC (Ta, T1 and TIS

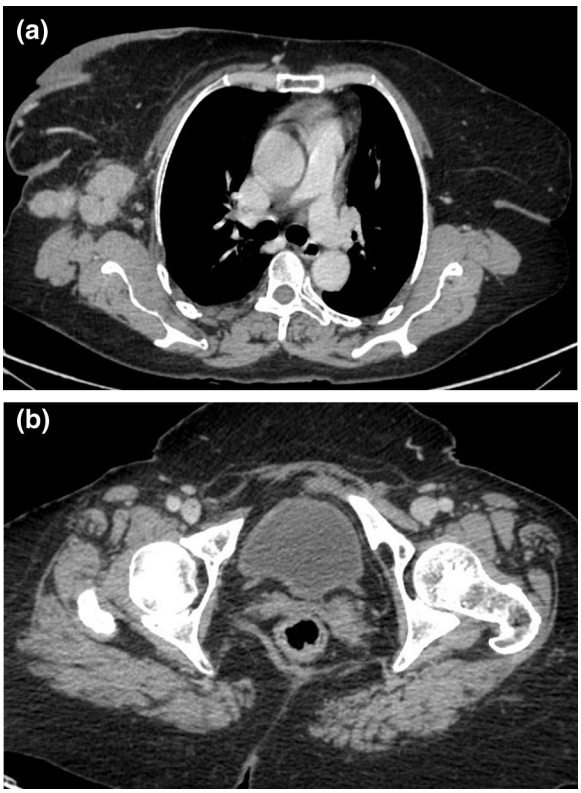

Fig. 4 **a** CT scan post contrast axial section: There are multiple enlarged lymph nodes in right axilla. Diffuse skin thickening is also visualized in the right breast. **b** CT scan post contrast axial section shows normal urinary bladder. No mass or wall thickening

tumors). As it is considered a low grade tumor, it has generally good prognosis and tend to remain localized. The most worrisome aspect of NMIBC is recurrence and not distant metastases. Close to 50–70% of superficial tumors show tendency to recur after resection [6]. Only 10–20% of cases progress to muscle invasion and/or metastasis [4]. As these are superficial tumors and are limited by basement membrane, they do not have approach to blood vessel and lymphatics [4, 5]. The interesting debate here could be about the route of spread of tumor cell and it would be worthwhile to discuss significance of micro-metastasis. It is suggested that long before display of clinical symptoms these tumor cells are shed into the blood stream from the primary tumor and creep into distant organs. The unpredictable and heterogeneous behavior of bladder cancer can be well explained by these circulating tumor cells (CTCs) which act as proxy for early metastatic spread of disease [7].

Conclusions

This patient's case emphasizes the importance of having sound knowledge of natural behavior of primary tumor and common and uncommon sites of distant metastases. The causes of unilateral axillary lymphadenopathy include both benign and malignant disease. Patients having axillary lymphadenopathy and negative mammogram should be considered having other primary site of malignancy aside from occult breast carcinoma. This case also highlights significance of having thorough and comprehensive understanding about the concept of micro-metastases and circulating tumor cells.

Abbreviations

TCC: Transitional cell carcinoma; GCDFP: Gross cystic disease fluid protein 15; GATA-3: (GATA Binding Protein 3); ER: Estrogen receptor; PR: Progesterone receptor; NMIBC: Non-muscle-invasive bladder cancer.

Acknowledgments

Not applicable.

Author contributions

All authors have read and approved the manuscript. SS (corresponding author) suggested and developed the idea. She did manuscript writing, revising, and editing. KA assisted in manuscript editing. SS and RR helped in histopathology descriptions and images.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit organizations.

Availability of data and materials

Data are available on request.

Declarations

Ethics approval and consent to participate

Ethical approval was waived from the Ethical Review Board of our Sindh Institute of Urology and Transplantation, Karachi, Pakistan. Written informed consent was obtained from the patient for assigning them to sample and using their data in research.

Consent for publication

Written informed consent to publish this information was obtained from study participant.

Competing interests

All the authors declare that they have no competing interest.

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Received: 28 September 2022 Accepted: 9 December 2022
Published online: 23 December 2022

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