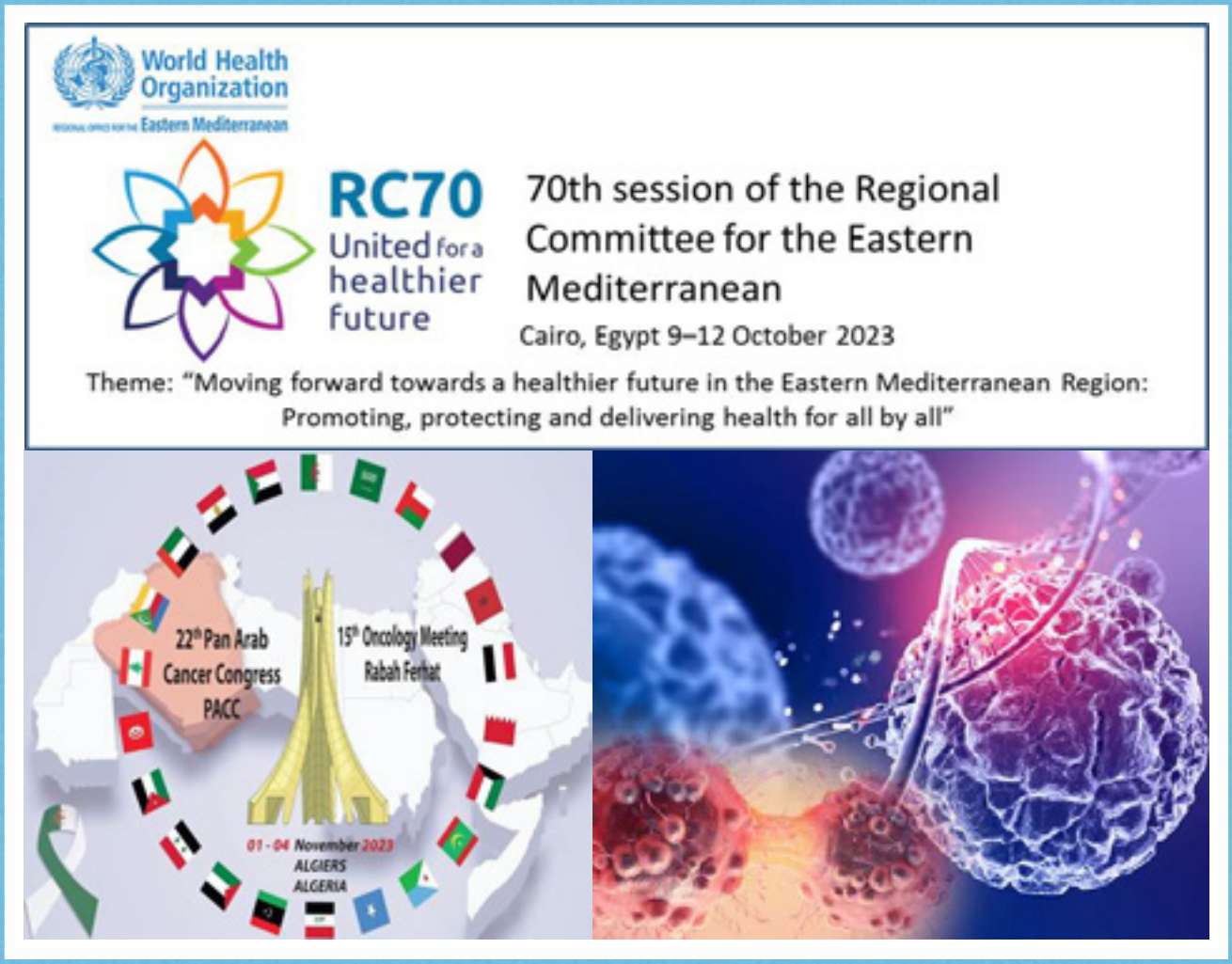
The Gulf Journal of Oncology

Indexed By PubMed and Medline Database

Issue 43, September 2023
ISSN No. 2078-2101



The Official Journal of the Gulf Federation For Cancer Control

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Scrotal Wall Metastasis from Adenocarcinoma of Unknown Origin, with Concurrent Extramammary Paget's Disease – a Case Report

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Abstract

Introduction: Scrotal cancer is a very rare disease, with the most common subtype being squamous cell carcinoma. Metastatic carcinoma to the scrotal wall is very rare. A histological finding of adenocarcinoma in a scrotal malignancy invariably suggests a metastasis from another primary cancer. We describe an enigmatic case of metastatic adenocarcinoma to the scrotum managed as metastatic adenocarcinoma of unknown origin. Attempts to identify a primary cancer were complicated by ambiguous diagnostic results. This is the first case in literature of metastatic cancer to the scrotum from an adenocarcinoma of unknown origin, and this was complicated by concurrent extramammary Paget's disease.

Case Presentation: A 70–year–old male presented with painless progressive scrotal skin swelling, which was shown on histology to be adenocarcinoma. Immunohistochemistry showed prostatic lineage markers. However, the argument for a prostatic primary was weakened by negative prostate transrectal ultrasound biopsy findings and negative radiological findings. The scrotal metastatic adenocarcinoma was managed as metastatic adenocarcinoma of unknown origin. A differential of occult poorly differentiated prostatic primary was considered in view of the clinical phenotype of an elderly male patient with extensive sclerotic bony metastases, immunohistochemistry results and relatively low PSA level in relation to systemic burden of disease. The patient was managed with palliative systemic chemotherapy (carboplatin/paclitaxel) with initial disease response, but eventually developed progressive disease.

Discussion and Conclusion: Finding of adenocarcinoma in scrotal skin malignancy indicates a metastasis and should prompt further work–up to identify a primary cancer, particularly of other genitourinary or lower gastrointestinal origin, so that treatment can be targeted at the underlying primary malignancy. However, attempts to identify a primary cancer might be complicated by ambiguous diagnostic results.

Keywords: Scrotal cancer, adenocarcinoma of unknown origin, prostatic metastases, extramammary Paget's disease, case report

Introduction

Scrotal cancer is a very rare disease. The most common subtype of scrotal cancer is squamous cell carcinoma. A histological finding of adenocarcinoma in a scrotal malignancy invariably suggests a metastasis from another primary cancer. Metastatic carcinoma

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to the scrotal wall is very rare, of which metastatic adenocarcinoma is a subtype.

We describe here an enigmatic case of metastatic adenocarcinoma to the scrotum managed as metastatic adenocarcinoma of unknown origin. A differential of possible occult poorly differentiated prostatic primary was considered in view of the clinical phenotype of an elderly male patient with extensive sclerotic bony metastases, immunohistochemistry (IHC) results and relatively low serum prostate–specific antigen (PSA) level in relation to the systemic burden of disease. However, the argument for a prostatic primary was weakened by negative prostate transrectal ultrasound (TRUS) biopsy findings and negative radiological findings. The patient was also found to have overlying extramammary Paget's disease (EMPD). To the best of our knowledge, this is the first case in literature of metastatic cancer to the scrotum from an adenocarcinoma of unknown origin.

Case Presentation

A 70–year–old gentleman, premorbidly well, was seen in the Urology clinic in December 2020 for a painless right scrotal swelling progressively enlarging over one year. There were no other significant clinical symptoms including bone pain. Other past medical history included hypertension, dyslipidaemia, impaired fasting glucose, mild renal impairment (creatinine clearance 45–55mL/minute) and a history of previous hepatitis B infection. He had a good (Eastern Cooperative Oncology Group (ECOG) performance status of 1. The patient had previously visited overseas commercial sex workers several times in the last few years. Physical examination revealed a warty right scrotal lesion measuring 4 x 4cm. (Refer to figure 1) The right testis was not well felt. There was no abnormality with the left testis

Figure 1: A 70–year–old gentleman presented with a progressively enlarging painless right scrotal swelling. Physical examination revealed a warty right scrotal lesion measuring 4 x 4cm. This image is published with the patient's consent.

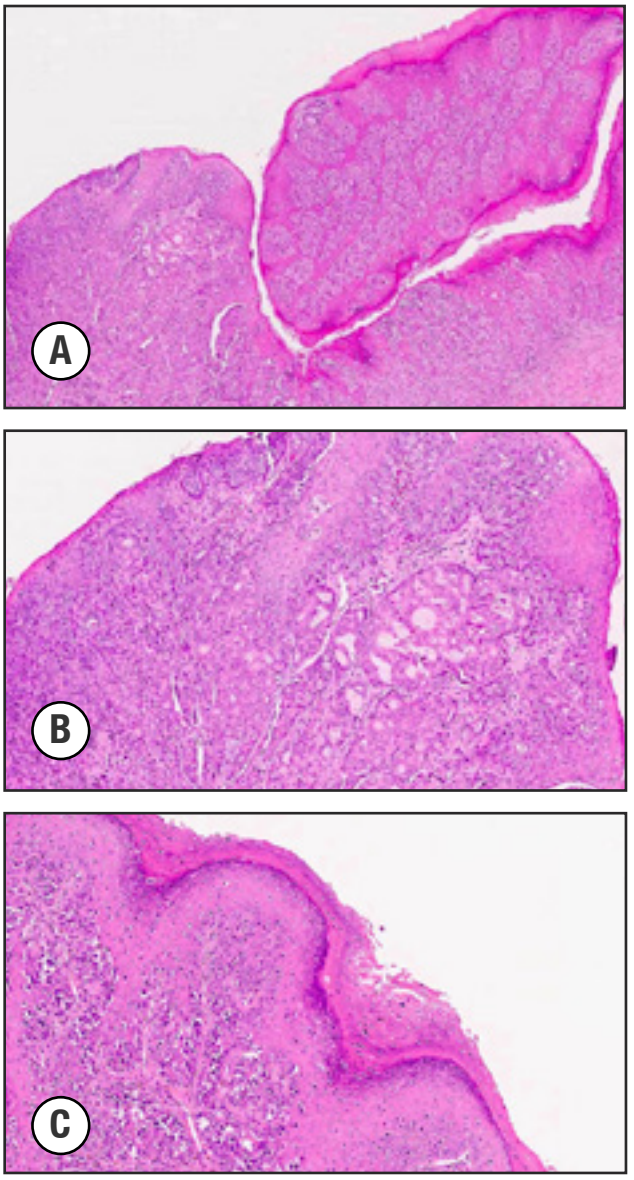

Figure 2: Histology of the scrotal skin excision demonstrating an adenocarcinoma composed of malignant glands invading the subepidermal stroma. Extramammary Paget's disease characterised by a proliferation of clusters of neoplastic cells along the overlying epidermis is also present. An adjacent coexisting condyloma acuminatum is seen in Figure 2A. (Figure 2A: Haematoxylin and Eosin stain, Original magnification, x40; Figure 2B: Haematoxylin and Eosin stain, Original magnification, x100). Figure 2C shows Extramammary Paget's disease featuring pagetoid growth of neoplastic cells into the adjacent condyloma acuminatum (Haematoxylin and Eosin stain, Original magnification, x100).

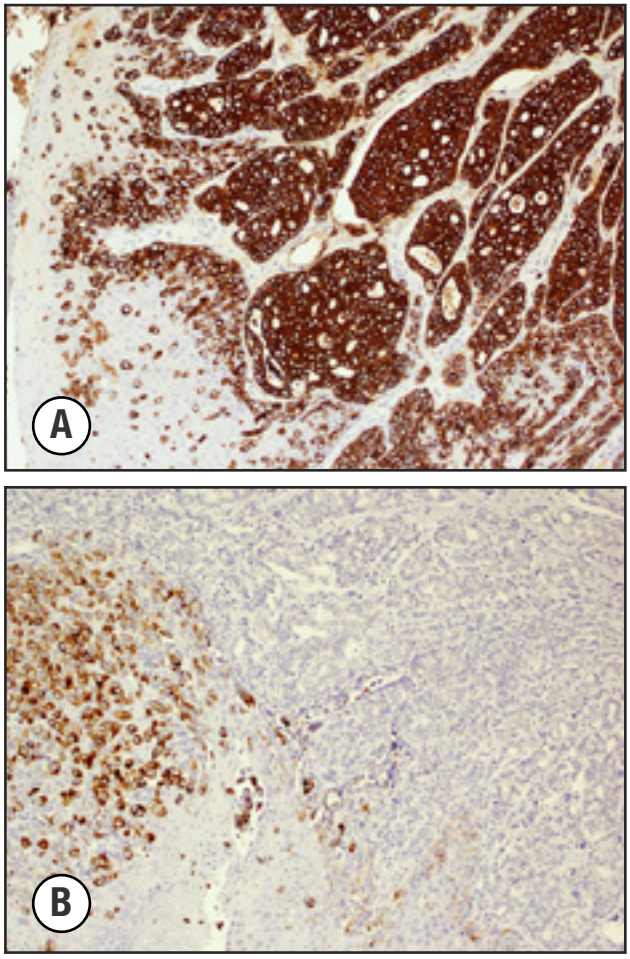

Figure 3: Immunohistochemical staining of the neoplastic cells showing diffuse positivity for Cytokeratin 7 (CK7) in Figure 3A, patchy positivity for Cytokeratin 20 (CK20) in Figure 3B. Figure 3A: CK7 immunohistohemical stain (Original magnification, x100). Figure 3B: CK20 immunohistohemical stain (Original magnification, x100).

nor the penis. There was no clinically apparent inguinal lymphadenopathy. Prostate specific antigen (PSA) level was 6.19ng/mL (normal range 0 – 4.00).

The patient underwent wide margin excision of the right scrotal lesion with biopsy. Intraoperatively, the right scrotal skin tumor was noted to be attached to another deep perineal mass measuring 6cm. The right testis was normal. During excision of the scrotal skin lesion, the stalk was broken off from the perineal mass. In view of the lack of prior imaging, decision was made not to proceed with deep perineum mass excision and to reconsider surgery if the mass was found to be excisable after dedicated imaging.

Histology of the scrotal skin excision specimen demonstrated an adenocarcinoma composed of cribriform nests and irregular, anastomosing glands lined by neoplastic epithelial cells displaying hyperchromatic, pleomorphic nuclei, nucleolar prominence and moderate amounts of eosinophilic cytoplasm. A coexisting condyloma acuminatum arising from the overlying epidermis was also identified. There was extensive invasion of the subepidermal tissue by the adenocarcinoma. In addition, extramammary Paget's disease featuring pagetoid growth of the neoplastic cells within the overlying epidermis and the condyloma was also observed (Figure 2). Perineural invasion and multiple foci of lymphovascular invasion were found. On IHC staining, the neoplastic cells displayed diffuse positivity for BER–EP4, cytokeratin 7 (CK7) and androgen receptor (AR), patchy positivity for monoclonal carcinoembryonic antigen (CEA), cytokeratin 20 (CK20), p16 and human epidermal growth factor receptor 2 (HER2), focal positivity for NKX3.1 and very focal staining for prostatic acid phosphatase (PSAP) (Figure 3). Stains for p40, Melan–A, SOX–10, CDX–2, TTF–1, PSA, synaptophysin and chromogranin were negative. HER2 fluorescence in–situ hybridisation (FISH) was negative. In view of these findings, metastasis from a visceral site had to be excluded. In particular, a prostatic primary had to be considered as this adenocarcinoma demonstrated expression of prostatic lineage markers NKX3.1 and PSAP, albeit focally.

Computed tomography scan of the thorax abdomen and pelvis (CT TAP) showed an ill–defined soft tissue mass at the base of the penis extending to the perineum corresponding to the perineal mass seen during the surgical excision. There were also small volume but enhancing right inguinal lymph nodes. Extensive sclerotic bony metastases in the axial and proximal appendicular skeleton were seen. The prostate was mildly enlarged. However, no obvious source of primary malignancy was detected on CT. A bone scan showed multiple bony metastases involving the cervical, thoracic and lumbar vertebrae, bilateral scapulae, bilateral clavicles, sternum, bilateral ribs, pelvis, bilateral proximal humeri and femora. Magnetic resonance imaging (MRI) scan of the prostate showed a 4.4cm ulcerating mass at the perineum invading the spermatic cords and corpus spongiosum. However, no primary prostatic malignancy was visualized on MRI. (Figure 4) Flexible cystoscopy showed the prostate to have enlarged and obstructing lateral lobes, but no intraluminal bladder or urethral tumor was visualized. TRUS 12–core biopsy of the prostate revealed prostatic tissue with no evidence of high grade prostatic intraepithelial neoplasia (PIN) or malignancy on histologic evaluation.

Oesophageal–gastro duodenoscopy (OGD) and colonoscopy were performed but no indication of gastrointestinal malignancy was found. OGD showed chronic gastritis, while colonoscopy showed tubular adenomas and hyperplastic polyps within the colon.

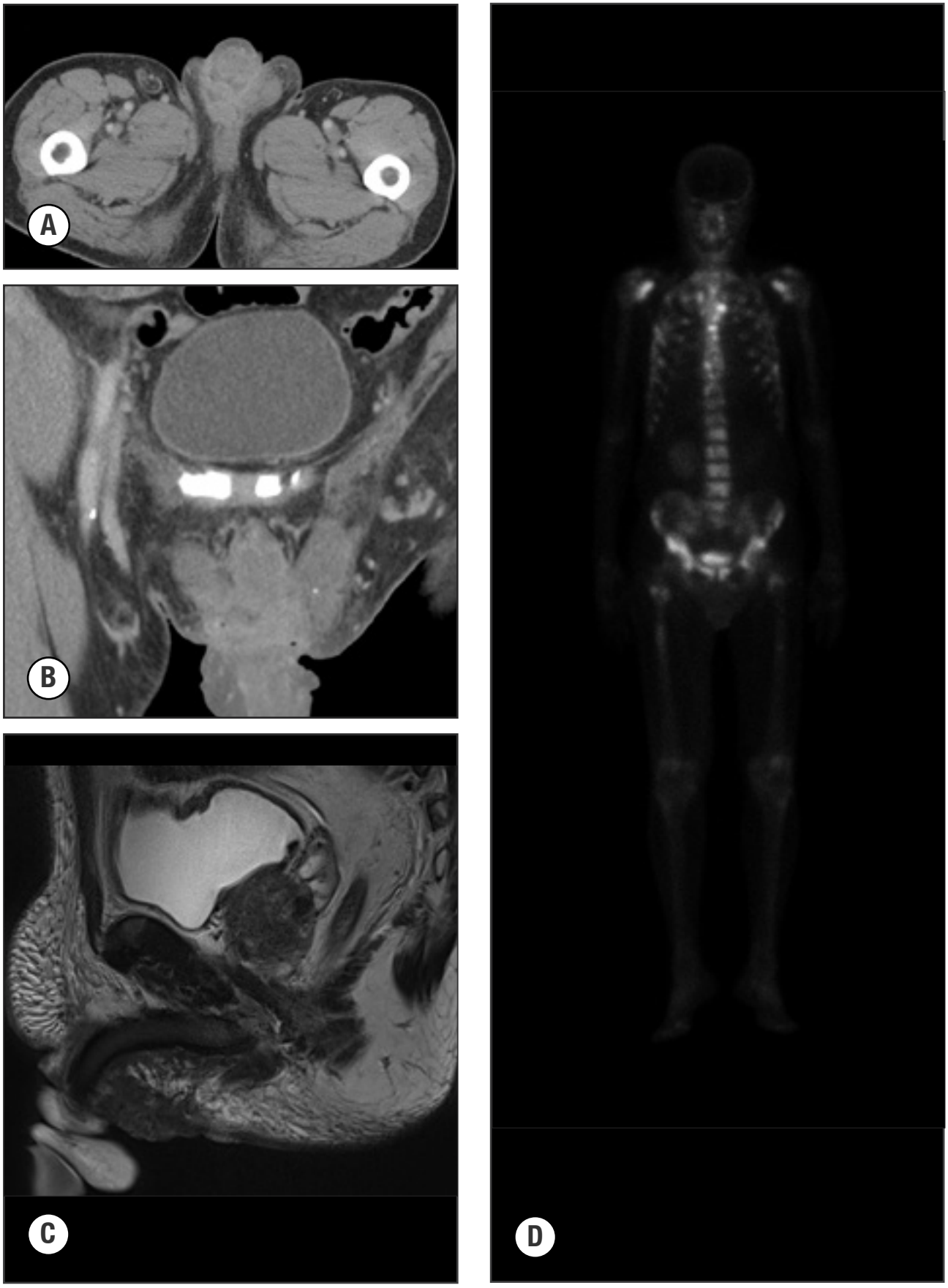

Figure 4: Initial imaging results of the metastatic lesion. CT contrast–enhanced axial (4A) and coronal (4B) images showed an ill–defined soft tissue mass at the base of the penis extending to the perineum. MRI T2–weighted sagittal images (4C) showed an ulcerated lobulated mass at the perineum posterior to the root of the penis. No primary prostatic malignancy was visualized. Bone scan (4D) showed extensive metastases in the axial and proximal appendicular skeleton.

This case was presented for discussion at a multidisciplinary genitourinary tumor board with consensus of a diagnosis of metastatic adenocarcinoma of unknown origin. A differential of occult poorly differentiated prostatic primary was considered in view of the clinical phenotype of an elderly male patient with extensive sclerotic bony metastases similar to those typically seen in prostate cancer, IHC results and relatively low PSA level in relation to burden of disease. The patient was treated as for metastatic adenocarcinoma of unknown primary and was started on palliative systemic chemotherapy with carboplatin AUC (area under the curve) 2 and paclitaxel 80mg/m^2 on days 1 and day 8 every 21 days in February 2021. He was also started on denosumab for prevention of skeletal–related events. CT imaging after 3 cycles of chemotherapy demonstrated reduction in size of the soft tissue mass in the base of the penis and improvement in thickening of the spermatic cord bilaterally. Restaging bone scan demonstrated increased uptake at the scapulae, ribs, pelvis and right femur. As the patient remained clinically well without symptoms of bone pain, and as alkaline phosphatase (ALP), a marker of bone turnover, had also decreased from 564 U/L pre–chemotherapy to 216 U/L, it was thought that the bone scan findings represented a flare response to treatment. The patient was continued on chemotherapy with carboplatin and paclitaxel.

After 6 cycles of chemotherapy, a repeat CT TAP in July 2021 showed continued improvement in the soft tissue mass at the base of the penis and inguinal lymphadenopathy, and bone scan showed stable findings apart from mild increased tracer uptake in the L2 vertebra and right iliac bone. ALP had decreased to 164 U/L and PSA had decreased from 6.19 to 4.85ng/mL. The patient was placed on a chemotherapy break. Repeat CT TAP and bone scan in September 2021 showed stable disease.

However, in November 2021, the patient was noted to have new onset anaemia and thrombocytopaenia, with haemoglobin of 7.5g/dL (baseline 11–12g/dL) and platelet count of 118 x 10^9/L (baseline 200–250 x 10^9/L). Bone marrow trephine biopsy showed extensive infiltration by an adenocarcinoma that was diffusely positive for AE1/3, with rare cells showing NKX3.1 expression, and a singly PSAP positive atypical cell seen. Bone marrow aspirate was not sent as it was a dry tap. CT TAP showed marginal increase in size of small bilateral pulmonary nodules, with otherwise stable findings in the abdomen and pelvis. Bone scan showed stable disease. PSA increased from 4.85 to 32.05ng/mL. Due to disease progression with bone marrow infiltration, the patient was restarted on palliative chemotherapy with weekly paclitaxel. In view of visceral crisis in the setting of a possible occult prostatic malignancy with diffuse AR–expression on previous scrotal skin biopsy, decision was undertaken for addition of androgen–deprivation therapy (ADT) with degarelix (gonadotropin–releasing hormone–antagonist) to chemotherapy for maximal palliative systemic therapy for disease control. Supportive management with packed red cell transfusions were also administered to keep hemoglobin levels above 7–8g/dL. After 3 months of chemotherapy and ADT, restaging CT TAP in March 2022 showed resolution or improvement in size of the pulmonary nodules, and bone scan showed mixed response with increased uptake in lesions in the frontal bone, skull base, both humeri and femurs, possible new lesion in the occipital bone and stable lesions in right hemi–mandible, sternum, ribs, vertebrae, pelvis and scapula. Hemoglobin and platelet levels stabilized at 7–8g/dL 100–120 x 10^9/L respectively. PSA had improved to 3.31ng/mL The patient was placed on a chemotherapy break. He continued on ADT and started on enzalutamide, an androgen receptor signaling inhibitor, in March 2022. He continues to have disease control on ADT and enzalutamide as of June 2022, and remains on active follow–up.

Discussion

The majority of para–testicular lesions are benign cystic lesions. Among solid extra–testicular lesion, lipomas and adenomatoid tumors are the most common common benign solid lesions. Primary solid neoplasms of para–testicular tissues are very rare, with incidence between 3%–16% of patients referred for ultrasound investigations.[1]

Scrotal skin cancer is a very rare disease, affecting approximately 1 per 1 million males per year. The most common subtype is squamous cell carcinoma (35%). Other subtypes include EMPD, sarcoma, basal cell carcinoma, melanoma and adnexal skin tumors.[2] A finding of adenocarcinoma in the histology of scrotal skin cancer would suggest a metastasis from another primary cancer. A scrotal skin metastasis usually presents as a painless scrotal swelling with a firm–to–hard mass.[3] A review of literature revealed only sporadic case reports about adenocarcinoma metastasis to the scrotal skin, which included gastric and colorectal adenocarcinoma[3–5], lung adenocarcinoma[6–7] and prostate adenocarcinoma (of which there have only been 3 case reports of primary prostate adenocarcinoma metastasizing to the scrotal wall).[7–9]

Cutaneous metastatic spread of prostate cancer is very rare and represents less than 1% of all cutaneous metastases.[9] The most common sites of metastasis for prostate cancer are the pelvic lymph nodes and bones.[10] It had been postulated that the spread of prostate cancer to cutaneous regions in the inguinal regions could be through the lymphatic system. Prostate cancer patients with cutaneous metastases usually have a poor prognosis.[9]

In our case, the primary cancer was assessed to be adenocarcinoma of unknown origin by a multi–disciplinary

tumor board due to the ambiguity of diagnostic investigations which precluded a conclusive diagnosis of prostatic primary (surgical histology of adenocarcinoma in the scrotal skin lesion with positivity for prostate lineage markers NKX3.1 and PSAP, but no indication of prostate cancer on CT, MRI prostate and TRUS prostate). NKX3.1 has a reported sensitivity of up to 98.6% and specificity of up to 99.7% for detecting metastatic prostatic adenocarcinoma,[11] while PSAP is less sensitive for detection of prostatic metastases (77%).[12]

In general, the prognosis for adenocarcinomas of unknown primary is poor, with a median overall survival of less than 1 year (6–10 months)[13].The patient was started on first line palliative chemotherapy with carboplatin and paclitaxel, a commonly used first line systemic therapy for carcinomas of unknown primary,[14,13] with initial disease response. However, there was subsequent disease progression.

EMPD is a rare malignancy mainly affecting areas of apocrine gland prevalence (such as the anogenital and axillary regions). It is believed to originate from undifferentiated pluripotent cells of the epidermis. Primary EMPD is an *in–situ* tumor derived from the epidermis or its appendages, while secondary EMPD involves direct expansion to the skin from another underlying neoplasm, usually from colorectal or urogenital neoplasm. Primary EMPD usually has a better prognosis because of slow growth and confinement of the lesion to the epidermis. [15]

This case report provides an example of the diagnostic dilemma clinicians may encounter in determining the primary cancer site for patients presenting with metastatic adenocarcinoma of unknown origin, for which details of the contradicting diagnostic results and the rationale for the management plan were provided. As this is to our knowledge the first reported case of a metastatic adenocarcinoma of unknown primary to the scrotal wall, our experiences would be useful for clinicians who might encounter similar cases. Longer follow–up and analysis of treatment and outcomes of more patients will be useful to determine the optimum management of patients with similar presentations.

Conclusion

Scrotal skin malignancies are not well studied due to the rarity of such cases. Finding of adenocarcinoma in scrotal skin malignancy suggests that this is a metastasis and should prompt further work–up to identify a primary cancer in another location. However, attempts to identify a primary cancer might be complicated by ambiguous diagnostic results as evidenced in our case. Our case also illustrates that patients with a metastatic scrotal skin malignancy could have concurrent EMPD. Further investigations for a primary tumor origin is needed if there is suspicion of secondary EMPD.

Acknowledgement:

Nil

Ethical approval:

This paper did not require approval from our institution's Institutional Review Board (IRB) as it was a case report involving only one patient. The patient's identifying details were excluded from this paper to maintain his anonymity.

Funding and Conflict of Interest:

Nil

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