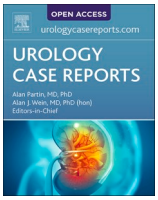
Urology Case Reports 57 (2024) 102875

Contents lists available at ScienceDirect

Urology Case Reports

journal homepage: www.elsevier.com/locate/eucr



Oncology

The diagnostic challenges of differentiating metastatic extramammary Paget disease and prostatic adenocarcinoma: A case report and review of the literature

Gregory Palmateer [a], Edouard H. Nicaise [a], Jatin Gandhi [c], Taylor Goodstein [a], Michelle Sheng [a], Kenneth Ogan [a], Omer Kucuk [b,e], Melinda Yushak [b,e], Martin G. Sanda [a,b], Keith A. Delman [b,d], Viraj Master [a,b,*]

[a] Department of Urology, Emory University School of Medicine, Atlanta, GA, USA
[b] Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA, USA
[c] Department of Pathology, Emory University School of Medicine, Atlanta, GA, USA
[d] Department of Surgery, Emory University School of Medicine, Atlanta, GA, USA
[e] Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA, USA

ARTICLE INFO

Keywords:
Extramammary paget disease
PSA
NKX3.1
Prostate cancer

ABSTRACT

Extramammary Paget disease (EMPD) is a rare dermatologic malignancy with a high rate of recurrence and increased risk for developing secondary malignancies. We present a 74-year-old male with previously resected primary EMPD who presented with widespread PSMA-avid lesions without prostatic uptake, an elevated PSA >100, and a negative prostate biopsy. Based on this and immunohistological staining, recurrent EMPD was suspected. However, after additional staining and reexamining their clinical presentation, metastatic prostate cancer without a detected primary lesion is more probable. This case highlights the diagnostic challenge variable expression of shared biomarkers found in EMPD and prostate cancer present to clinicians.

1. Introduction

Extramammary Paget disease (EMPD) is a rare dermatological malignancy involving regions of high apocrine sweat gland concentrations (i.e. vulva, penis, scrotum, perineum, and perianal region) that affects older men and women. Lesions are frequently ill-defined with erythematous, scaly, or ulcerated features. To differentiate it from similar appearing lesions, biopsy with immunohistological staining is required. On histology, Paget cells are atypically large cells with abundant pale cytoplasm and large pleomorphic nuclei.[1] EMPD is subdivided into primary–lesions that originate directly from the epidermis –and secondary–lesions that originate from an underlying carcinoma such as colorectal or urothelial.[2,3] Immunohistochemical (IHC) staining for a variety of site-specific markers, including those of apocrine differentiation, can help differentiate the primary from secondary lesions.[2,3]

Patients with primary EMPD, regardless of invasive status, are at increased risk for developing secondary malignancies. Up to 30 % of patients with EMPD will develop a secondary malignancy, most commonly colorectal carcinoma.[4] Historically, it was thought that the diagnosis of EMPD required exclusion of an underlying "primary" lesion to ensure that the cutaneous disease was not a metastatic site given its common association with other malignancies. An increased incidence of prostate cancer following primary EMPD has been described in several retrospective studies, however, whether this rate exceeds that of the general population remains uncertain.[4,5] Elevations in prostate-specific antigen (PSA) above 4.0 ng/mL, seen in 8.4 % of the general population, have been noted in up to one-third of patients with EMPD.[4,6] A minority of EMPD lesions express PSA; however, its expression has not yet been correlated with more invasive EMPD or underlying prostate cancer.[7] Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) scan has high sensitivity and specificity for identifying prostate cancer. PSMA, however, is not truly prostate specific. It has been observed in other cancers and plays an important role in extracellular matrix degradation and tumor-associated angiogenesis.[8] These features cumulatively can present diagnostic challenges for clinicians differentiating EMPD from prostate cancer. We present a case of a

* Corresponding author. Department of Urology, Emory University, 1365 Clifton Road NE, Building B, Suite 1400, Atlanta, GA, 30322, USA.
E-mail address: vmaster@emory.edu (V. Master).

https://doi.org/10.1016/j.eucr.2024.102875
Received 15 August 2024; Accepted 24 October 2024
Available online 24 October 2024

patient with a significantly elevated PSA without clear evidence of prostate cancer in the setting of a history of primary EMPD, highlighting these diagnostic challenges.

1.1. Case presentation

The patient is a 74-year-old white male who was undergoing skin checks every 6 months with a dermatologist because of their remote history of melanoma over 30 years prior. During one such visit in 2020, the patient was noted to have a scaly erythematous rash in the perianal region. Initially thought to be inverse psoriasis, the patient was prescribed topical steroids without notable improvement. A punch biopsy was obtained which demonstrated highly atypical epithelial cells within the epidermis that stained positive for CK7 and CAM5.2 and negative for CK20 and p63, strongly suggestive for noninvasive primary EMPD. The patient underwent wide local excision of a 15 × 4 cm region in the perianal skin including the base of the scrotum. They had positive margins without dermal invasion on final pathology but was started on surveillance without additional intervention.

Three years following their surgery, the patient presented to their family physician with a chief complaint of right flank pain. A renal ultrasound revealed moderate right-sided hydronephrosis. During evaluation, they was also noted to have a new 2 × 4 cm area of erythema located anterolaterally on the right side of their previous incision, as well as a 3 cm firm right inguinal lymph node. Concurrently during this time, they underwent routine PSA screening with their primary care physician (PCP), which was severely elevated at 179 ng/mL. The patient had no history of abnormal screening PSA; however, they had not been screened for over two years as a result of their former PCP retiring. A follow-up computed tomography (CT) scan showed mild hydronephrosis with evidence of ureteropelvic junction obstruction, multiple lytic lesions throughout the thoracolumbar spine without fracture, as well as pelvic, inguinal, and retroperitoneal lymphadenopathy. A fine needle aspiration (FNA) of the right inguinal lymph node was performed demonstrating metastatic adenocarcinoma with strong Cytokeratin-7 (CK7) and Gross Cystic Disease Fluid Protein (GCDFP-15) expression. As such, it was suspected that they had metastatic recurrence of their primary EMPD. Notably, the lesion at the site of the prior resection was not excised.

However, given the significantly elevated PSA, a prostate cancer workup was also initiated. An additional PSA was obtained and remained elevated at 200 ng/mL (Fig. 1). Although an MRI of the prostate was discussed, proceeding directly to systematic biopsy was deemed more appropriate, as MRI results would not likely alter the plan to biopsy. A standard ultrasound-guided 12-core prostate biopsy revealed benign prostate tissue without any evidence of malignancy. There was no evidence of prostatitis on urinalysis or urine culture, and a digital rectal exam did not reveal any suspicious abnormalities. Given that a high suspicion for prostate cancer remained, the decision was made to obtain a positron emission tomography (PET) prostate-specific membrane antigen (PSMA) scan. This demonstrated innumerable PSMA-avid lytic lesions throughout the axial and appendicular skeleton as well as uptake in abdominal and pelvic lymph nodes consistent with widespread metastasis (Fig. 2). There was, however, no abnormal PSMA radiotracer uptake in the prostate gland or the site of their prior EMPD resection. To better delineate if two primary cancers were present, a biopsy was obtained from a T8 lytic lesion and the previously biopsied right inguinal lymph node was completely excised. Histologically, both specimens were similar in appearance, demonstrating neoplastic cells with positive CK7 and GCDFP-15 expression. Thus, the lesions were suspected to represent one pathologic process. The PSA was rechecked a third time and was 807 ng/mL.

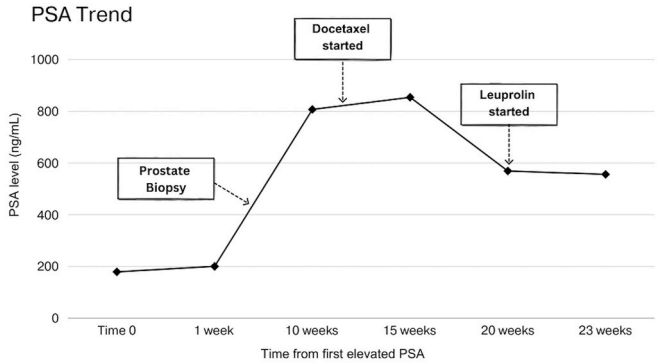


Fig. 1. PSA levels over the course of disease workup and treatment.

The patient's case was presented to our genitourinary tumor board. Without any histological evidence to support a diagnosis of prostate cancer, it was recommended they start treatment for suspected metastatic EMPD. They received a course of docetaxel which was complicated by mild thrombocytopenia (52,000/mcL) requiring modification of their chemotherapy regimen and suspension of active treatment. During this time, their PSA was rechecked and it continued to remain elevated (854 ng/mL). Molecular testing of the right inguinal node revealed negative HER2 expression and low tumor mutational burden. Androgen deprivation therapy (ADT) was initiated with leuprolide and their PSA measurements have since been trending downwards (most recently 556 ng/mL). They underwent an MRI of the brain, as part of a workup for headaches, which showed diffuse pachymeningeal thickening and enhancement. A subsequent lumbar puncture demonstrated rare atypical cells consistent with leptomeningeal spread of their malignancy, which is now being treated with whole brain radiation.

To examine if the PSMA-avid lesions were responsible for their significantly elevated PSA, pathological tissue blocks were retrieved and additional immunohistological staining was performed as summarized in Table 1. Notably, the primary EMPD lesion stained positive for androgen receptor (AR) and negative for PSA and NKX3.1 (Fig. 3). The vertebral lesion, conversely, stained positive for PSA, NKX3.1, AR, CK7, and GCDFP-15 (Fig. 4). The tissue that remained after molecular testing from the right inguinal lymph node was insufficient to perform additional staining. Given this new information, it is more likely that their metastatic disease is prostate cancer without an identifiable primary lesion, rather than recurrent EMPD.

2. Discussion

Considerable overlap in biomarkers exists between EMPD and prostate cancer which can make accurate diagnosis challenging. We present a case of a 74-year-old male diagnosed with primary EMPD who, after initial resection, developed widespread metastatic disease and a significantly elevated PSA. While their lesions were PSMA avid, a lack of PSMA uptake in the prostate, a negative prostate biopsy, and immunohistological stains more commonly seen with EMPD made prostate cancer seem less likely. Prostate MRI might have been helpful for identifying a primary lesion in the prostate that was not evident on PSMA-PET, but was not obtained because the metastases were more accessible for tissue acquisition. Further staining of the procured metastatic tissue enabled confirmation of the diagnosis of metastatic prostate cancer without requiring tissue acquisition from the suspected non-PSMA avid primary lesion. This case highlights the diagnostic challenges that result from the shared immunohistological markers of EMPD and prostate cancer and the importance of incorporating clinical features to aid in diagnosis.

2.1. A review of relevant biomarkers

Decreased PSA expression has been reported in up to 69.2 % of metastatic prostate cancers.[9] Conversely, PSA expression has been shown to be high in approximately 30 % of patients with EMPD.[7] Prostate specific antigen phosphatase (PSAP), an alternative marker to

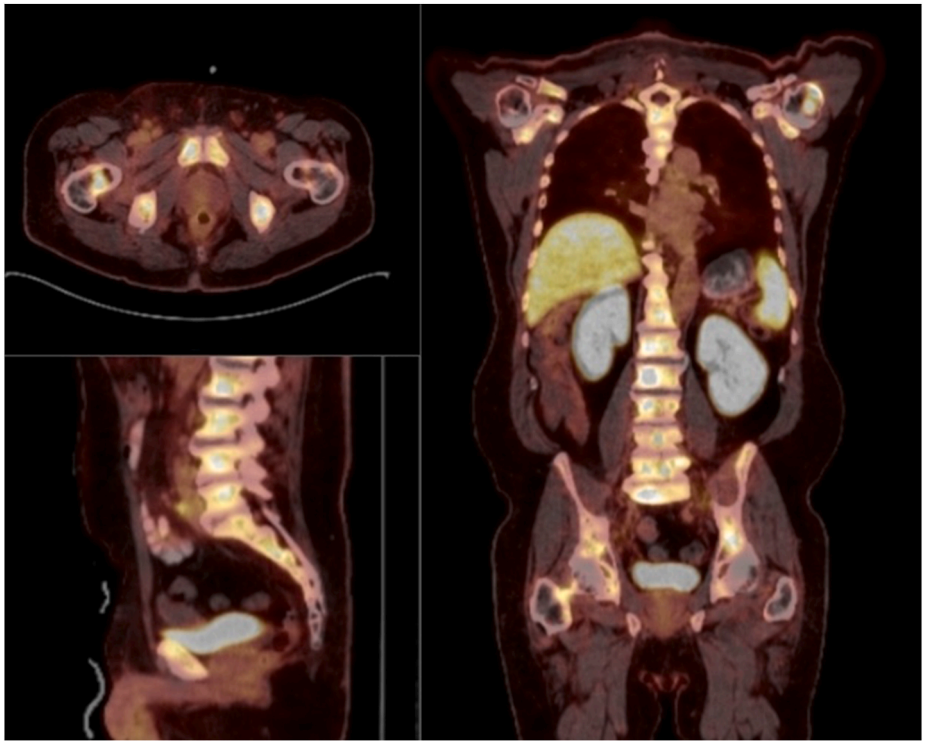


Fig. 2. Positron emission tomography (PET) of prostate specific membrane antigen (PSMA) with transverse (top left), sagittal (bottom left), and coronal (right) views.

Table 1
Summary of immunohistological stains performed.

Stains	Skin gluteal cleft biopsy	Primary perianal EMPD resection	FNA of right inguinal mass	Metastatic Bone Lesion + right inguinal lymph node
PSA		(−)		(+)
NKX3.1		(−)		(+)
AR		(+)		(+)
CK7	(+)		(+)	(+)
CK20	(−)			
CAM 5.2	(+)		(+)	
GCDFP-15			(+)	(+)
PSAP				(−)
HER2			**2+ (equivocal)**	
p63	(−)			
p40			(−)	
Melan-A	(−)			
SOX10			(−)	
Mucicarmine			(−)	

Abbreviations: Extramammary Paget Disease (EMPD), Fine needle aspiration (FNA), Prostate specific antigen (PSA), Androgen receptor (AR), cytokeratin (CK), gross cystic disease fluid protein (GCDFP), prostate specific antigen phosphatase (PSAP), human epidermal growth factor (HER).

PSA, has increased expression in metastatic prostate cancers compared to localized prostate cancer. PSAP expression in EMPD has not been sufficiently examined, however.[9] NKX3.1 is an androgen-regulated, prostate-specific transcription factor that functions as a tumor suppressor; its downregulation has been observed in more advanced prostate cancers.[9] NKX3.1 expression has also been observed in lobular and ductal breast carcinoma and up to 21 % of cases of EMPD.[10,11] Both prostate cancer and EMPD frequently demonstrate HER2 positivity which correlates with disease severity.[12,13]

With rare exceptions, primary EMPD stains CK7+/CK20-, while secondary EMPD stains CK7+/CK20+.[14] While most prostate adenocarcinomas stain negative for both CK7 and CK20, CK7-positive staining has been reported in up to 30 % of metastatic prostate cancer.[15] GCDFP-15, a marker for apocrine differentiation, is expressed in approximately 80 % of invasive primary EMPD and only rarely in secondary EMPD.[2] While not common, up to 10 % of prostate cancers have been observed to exhibit GCDFP-15 expression.[16] Both EMPD and prostate cancer frequently express mucin, and regularly stain positive for mucicarmine. However, mucin *inexpression* is much less common in EMPD than in prostate cancer.[17] Negative p63, p40, melanin-A, and SOX10 staining, as seen in our patient, rules out melanoma or Bowen disease, both of which can appear histologically similar to EMPD.[2]

2.2. A case for metastatic prostate cancer with undetected primary lesion

Cancer with unknown primary (CUP) has a historical incidence rate of 3–5%, which has decreased to 1–2% over the past decade.[18] Adenocarcinomas comprise the majority of CUP, however, the proportion of these that represent cancer of prostatic origin is not well defined. Expression of PSA and NKX3.1 as well as involvement of the axial skeleton and brain are features typically observed in metastatic prostate cancer. Moreover, prostate cancer generally exhibits a low tumor mutational burden as was seen on molecular testing in our patient.[19] While not common, there have been cases of prostate cancer staining positive for CK7 and GCDFP-15 and negative for PSAP.[15,16] Additionally, an estimated one-third of standard 12-core biopsies result in false negatives, so it is plausible that a small primary was missed.[20]

2.3. A case for new secondary or recurrent primary EMPD

During the initial diagnostic workup, it was believed their metastatic disease represented recurrent primary EMPD originating from the site of their previous resection, although the new skin lesion was never histologically examined. The initial histological stains combined with their history of primary EMPD supported this diagnosis. However, widespread metastasis is uncommon in primary EMPD. Moreover, PSMA

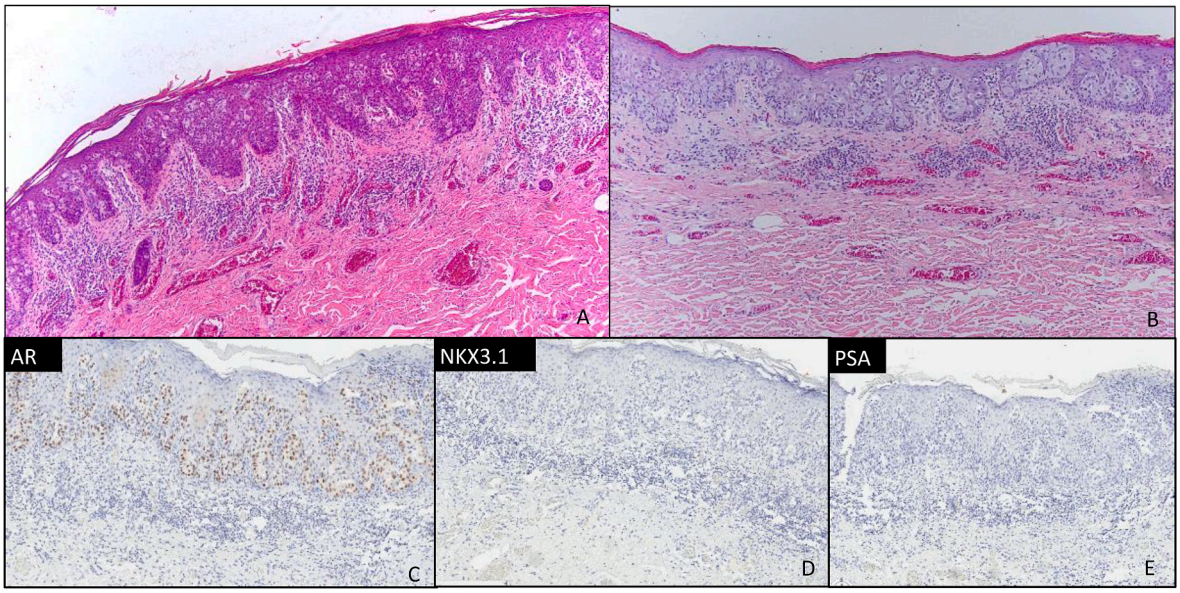


Fig. 3. H&E images from the primary EMPD resection showing intraepithelial clusters and single cells of adenocarcinoma growing as nests and single tumor cells with no invasion (Fig A and B); AR immunohistochemical stain highlights tumor cells within the epidermis (Fig C); NKX3.1 and PSA immunostain negative in the intraepidermal carcinoma cells (Fig D and F).

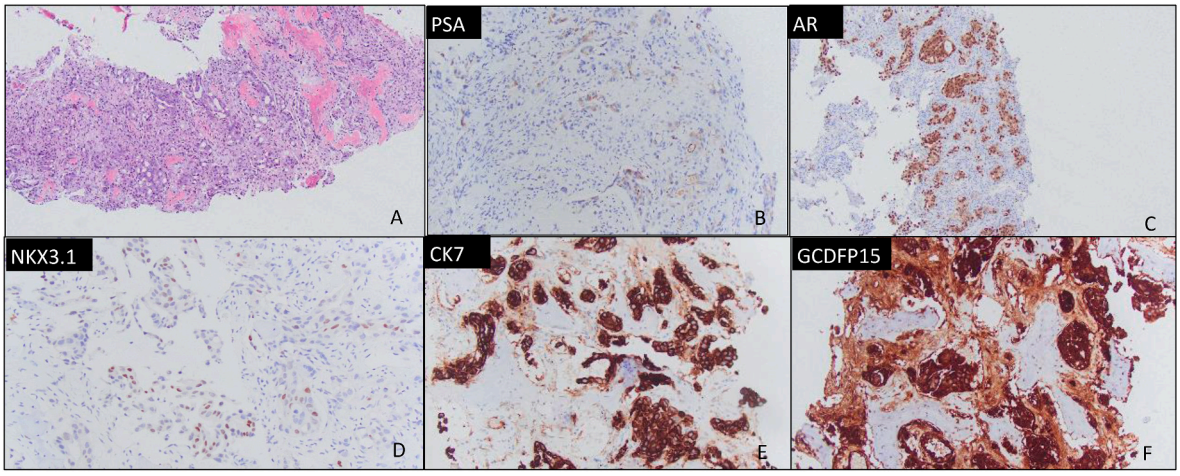


Fig. 4. H&E image of the vertebral lesion showing metastatic adenocarcinoma with glandular and cribriform growth patterns (Fig A); Immunostains for PSA, AR, NKX3.1, CK7 and GCDFP-15 are variably expressed in the metastatic adenocarcinoma cells (Figs B–F).

uptake would have been expected at the prior surgical bed. While PSA and NKX3.1 staining has been observed in EMPD, it is unclear if EMPD could produce an elevated PSA of this magnitude. Secondary EMPD arising from an underlying prostate cancer may better explain the significantly elevated PSA. However, the positive GCDFP-15 expression in these lesions make this diagnosis less likely. Additionally, the metastatic lesions lacked mucicarmine expression, which is rare for either primary or secondary EMPD. The preponderance of evidence indicates that while EMPD is plausible, metastatic prostate cancer is the more likely diagnosis.

3. Conclusion

The variable expression of shared biomarkers in EMPD and prostatic adenocarcinoma is a challenge that can impede accurate diagnosis. The case presented herein highlights this challenge and emphasizes the importance of obtaining comprehensive immunohistological staining and using clinical characteristics to aid in diagnosis. Patients with primary EMPD have a high risk for recurrence and subsequent development of secondary malignancies and require regular screening. Further research is needed to identify immunohistological markers with greater specificity to help differentiate EMPD and prostate cancer.

CRediT authorship contribution statement

Gregory Palmateer: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Edouard H. Nicaise:** Conceptualization, Writing – review & editing. **Jatin Gandhi:** Data curation, Visualization, Writing – review & editing. **Taylor Goodstein:** Writing – review & editing. **Michelle Sheng:** Writing – review & editing. **Kenneth Ogan:** Conceptualization, Writing – review & editing. **Omer Kucuk:** Writing – review & editing. **Melinda Yushak:** Writing – review & editing. **Martin G. Sanda:** Writing – review & editing. **Keith A. Delman:** Conceptualization, Supervision, Writing – review & editing. **Viraj Master:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Viraj Master reports financial support was provided by Crotts Initiative. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We gratefully acknowledge the financial support of the Crotts Initiative, which will help develop multicenter basic, translational, and clinical research projects focused on the management and treatment of extramammary Paget disease.

References

1. St Claire K, Hoover A, Ashack K, Khachemoune A. Extramammary Paget disease. *Dermatol Online J*. 2019;25(4). https://www.ncbi.nlm.nih.gov/pubmed/31046904.
2. Ishizuki S, Nakamura Y. Extramammary paget's disease: diagnosis, pathogenesis, and treatment with focus on recent developments. *Curr Oncol*. 2021;28(4):2969–2986.
3. Kibbi N, Owen JL, Worley B, et al. Evidence-Based clinical practice guidelines for extramammary Paget disease. *JAMA Oncol*. 2022;8(4):618–628.
4. Shi G, Ye DW, Yao X, et al. Extramammary Paget's diseases in men from the Shanghai area: its association with PSA level increase. *APMIS*. 2010;118(10):777–781.
5. Karam A, Dorigo O. Increased risk and pattern of secondary malignancies in patients with invasive extramammary Paget disease. *Br J Dermatol*. 2014;170(3):661–671.
6. Espaldon R, Kirby KA, Fung KZ, et al. Probability of an abnormal screening prostate-specific antigen result based on age, race, and prostate-specific antigen threshold. *Urology*. 2014;83(3):599–605.
7. Hammer A, Hager H, Steiniche T. Prostate-specific antigen-positive extramammary Paget's disease–association with prostate cancer. *APMIS*. 2008;116(1):81–88.
8. Lauri C, Chiurchioni L, Russo VM, Zannini L, Signore A. PSMA expression in solid tumors beyond the prostate gland: ready for theranostic applications? *J Clin Med Res*. 2022;11(21). https://doi.org/10.3390/jcm11216590.
9. Gurel B, Ali TZ, Montgomery EA, et al. NKX3.1 as a marker of prostatic origin in metastatic tumors. *Am J Surg Pathol*. 2010;34(8):1097–1105.
10. Gelmann EP, Bowen C, Bubendorf L. Expression of NKX3.1 in normal and malignant tissues. *Prostate*. 2003;55(2):111–117.
11. Chen CV, Francois RA, Mully TW, et al. Positive NKX3.1 as a diagnostic pitfall for prostate cancer in extramammary Paget's disease of genitourinary sites. *Histopathology*. 2024;84(3):565–569.
12. Masuguchi S, Jinnin M, Fukushima S, et al. The expression of HER-2 in extramammary Paget's disease. *Biosci Trends*. 2011;5(4):151–155.
13. Maillet D, Allioli N, Péron J, et al. Her2 expression in circulating tumor cells is associated with poor outcomes in patients with metastatic castration-resistant prostate cancer. *Cancers*. 2021;13(23). https://doi.org/10.3390/cancers13236014.
14. Ohnishi T, Watanabe S. The use of cytokeratins 7 and 20 in the diagnosis of primary and secondary extramammary Paget's disease. *Br J Dermatol*. 2000;142(2):243–247.
15. Tot T. Adenocarcinomas metastatic to the liver: the value of cytokeratins 20 and 7 in the search for unknown primary tumors. *Cancer*. 1999;85(1):171–177.
16. Wick MR, Lillemoe TJ, Copland GT, Swanson PE, Manivel JC, Kiang DT. Gross cystic disease fluid protein-15 as a marker for breast cancer: immunohistochemical analysis of 690 human neoplasms and comparison with alpha-lactalbumin. *Hum Pathol*. 1989;20(3):281–287.
17. Smith RF, Stern BH, Smith AA. Mucin immunohistochemistry in the diagnosis and mapping of extramammary Paget's disease. *J Cell Mol Med*. 2008;12(5A):1605–1610.
18. Rassy E, Pavlidis N. The currently declining incidence of cancer of unknown primary. *Cancer Epidemiol*. 2019;61:139–141.
19. Chung JH, Dewal N, Sokol E, et al. Prospective comprehensive genomic profiling of primary and metastatic prostate tumors. *JCO Precis Oncol*. 2019;(3):1–23.
20. Serefoglu EC, Altinova S, Ugras NS, Akincioglu E, Asil E, Balbay MD. How reliable is 12-core prostate biopsy procedure in the detection of prostate cancer? *Can Urol Assoc J*. 2013;7(5-6):E293–E298.