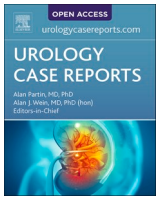
Urology Case Reports 60 (2025) 103034

Contents lists available at ScienceDirect

Urology Case Reports

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



Oncology

The diagnostic dilemma of squamous differentiation in prostate cancer: A case report

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A B S T R A C T

Squamous differentiation in prostate cancer is rare, presenting unique diagnostic and therapeutic challenges. We report a case of high-grade prostatic adenocarcinoma with focal squamous differentiation in a 73-year-old man without prior radiation or androgen deprivation. Immunohistochemistry confirmed the squamous component arose from the adenocarcinoma, not a separate malignancy. This case highlights the importance of morphological assessment and strategic immunohistochemical evaluation to distinguish prostate cancer variants. A biopsy capturing only the squamous component could have led to misdiagnosis and inappropriate treatment. To improve diagnostic accuracy and management, we propose the term 'adenocarcinoma with focal squamous differentiation' over adenosquamous carcinoma.

1. Introduction

Prostate cancer (PCa) is the second-leading cause of cancer-related death among U.S. men, with a mortality rate of 19 deaths per 100,000 men annually.[1,2] While approximately 95 % of PCa cases are classified as adenocarcinomas, the disease is known for its heterogeneity due to its variable molecular profiles and clinical behaviors.[3,4] The remaining 5 % include rare histological variants that develop either independently from distinct cellular origins or via transdifferentiating from prior prostatic adenocarcinoma.[5]

Among these variants, squamous differentiation in PCa refers to the pathological process whereby prostate cells, typically of adenocarcinoma origin, acquire squamous cell morphology and characteristics.[5] Proposed etiologies for this change include metaplastic transformation of adenocarcinoma cells, a collision-type tumor with the emergence of squamous elements from metaplastic foci, or differentiation driven by pluripotent stem cells.[6] Regardless of etiology, squamous differentiation in PCa is classified into two primary categories: adenosquamous carcinoma (ASC) and pure squamous cell carcinoma (SCC). The coexistence of squamous differentiation with adenocarcinoma is pathognomonic for ASC, while pure SCC is characterized by squamous differentiation without any glandular components.

Pure SCC is rare, constituting 0.6–1 % of all prostatic malignancies.[5] Approximately half of these cases follow prior radiation or hormonal therapy for adenocarcinoma, while others arise de novo.[5] Diagnosing pure SCC relies on Mott's five criteria, which include clearly malignant traits (disorganized growth, cellular anaplasia, invasion), evidence of squamous differentiation (keratinization, squamous pearls, intercellular bridges), absence of glandular/acinar components, no prior estrogen therapy, and exclusion of primary squamous cancer elsewhere.[7]

ASC, however, is distinguished by the coexistence of both glandular and squamous components. Based on incidence rates of ASC and all PCa cases over the same period, the estimated prevalence of ASC is approximately 0.002 % (or about 2 cases per 100,000 PCa diagnoses).[2,8] However, this is thought to be an underestimation due to diagnostic challenges.[9] Unlike pure SCC, ASC exhibits significant variability in the extent of squamous differentiation, ranging from as little as 5 % to as much as 95 %, with an average of approximately 40 %.[10] This variability extends to its spatial distribution within the prostate as well. Though ASC is described as the coexistence of glandular and squamous components, it can take different forms, including focal areas of differentiation or more complex patterns. Some reports note that the two often intermingle, which can make interpretations difficult to decipher.[10–13]

The variability in both histological composition and clinical behavior can make ASC feel like a catch-all category that encompasses a wide spectrum of cases. However, not all cases of PCa fit neatly into the existing terminology, highlighting the need for a more nuanced approach. This is a case report of a 73-year-old male with high-grade

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https://doi.org/10.1016/j.eucr.2025.103034
Received 22 March 2025; Accepted 4 April 2025
Available online 4 April 2025

prostate adenocarcinoma that underwent squamous differentiation in a localized area, notably without any prior history of hormonal or radiation therapy. Considering the unusual focal histologic trans-differentiation of this patient, we propose that there be a distinct classification for a type of ASC called "adenocarcinoma with focal squamous differentiation". This distinction is important because many of these cases may be missed, as a needle biopsy may catch only a squamous or adenocarcinoma component.[9]

2. Case presentation

A 73-year-old Caucasian male with a past medical history of smoking, hypertension, hyperlipidemia, and benign prostatic hyperplasia presented to the urology clinic with lower urinary tract symptoms (LUTS) and an elevated serum PSA at 12.79 ng/mL (reference range based on age: 0–6.5 ng/mL). Digital rectal examination revealed an enlarged prostate with a firm right lobe and median groove. Magnetic resonance imaging (MRI) of the prostate identified a 12 mm × 7 mm x 19 mm lesion in the peripheral zone, extending from the apex to the mid gland with possible capsular involvement, and was assigned a PI-RADS score of 5. An additional pedunculated mass, measuring 17 mm × 19 mm x 14 mm, was found in the bladder adjacent to the left ureterovesical junction, suspicious for a primary bladder tumor.

One month later, the patient underwent a transurethral resection of the bladder tumor and an ultrasound-guided prostate biopsy. The bladder tumor was confirmed to be a high grade non-invasive papillary urothelial carcinoma. The pathology report for the prostate biopsy revealed Gleason score 3 + 4 = 7 (grade group 2) adenocarcinoma, involving seven of twelve cores collected bilaterally. Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) showed a high level of PSMA uptake in the prostate bilaterally, correlating with the biopsy-proven adenocarcinoma.

Two months after the initial biopsy, the patient underwent a robot-assisted radical prostatectomy and pelvic lymph node dissection. Histologic sections of the prostate showed multiple, spatially distinct foci of prostatic adenocarcinoma. The index (dominant) nodule measured 30 mm and involved the left midgland and base, with extensive extraprostatic extension by carcinoma at the left posterolateral neurovascular bundle, including perineural invasion. The cancer was of the usual acinar type and assigned Gleason Score 4 + 5 = 9 (Grade Group 5; 10 % pattern 5, 70 %pattern 4, 20 % pattern 3; Fig. 1), with pattern 4 seen as cribriform architecture and pattern 5 as solid sheets of carcinoma. The seminal vesicles and surgical margins were negative for involvement by carcinoma.

A 5 mm focus of carcinoma with definitive squamous differentiation was identified at the left posterolateral midgland, seen as invasive nests of carcinoma with definitive keratin formation (Fig. 1). The focus was entirely within the prostatic parenchyma, without extraprostatic extension. The squamous carcinoma was directly adjacent to the usual acinar prostatic adenocarcinoma. The prostatic tissue located between this focus and the bladder was entirely submitted, and showed only usual acinar prostatic adenocarcinoma, with no evidence of carcinoma with squamous differentiation. The prostatic urethra was entirely submitted and showed no evidence of in situ neoplasia. The squamous carcinoma was 12 mm from the prostatic urethra. Immunohistochemistry showed the prostatic adenocarcinoma of the acinar type was positive for the prostate linear marker NKX3.1, and negative or focally/weakly positive for the squamous marker CK903/34BetaE12(Fig. 1). This included the acinar carcinoma directly adjacent to the squamous carcinoma (Fig. 2).In contrast, the squamous carcinoma was negative for NKX3.1and strongly and diffusely positive for CK903/34BetaE12 (Figs. 1 and 2).

The main pathologic differential diagnosis included involvement of the prostate by urothelial tract cancer with squamous differentiation, prostatic adenocarcinoma with focal squamous differentiation, and metastatic squamous cell carcinoma. Given the lack of in situ neoplasia in the urothelial tract, the great distance between the squamous cancer and the urothelial tract, and apparent transition from acinar to

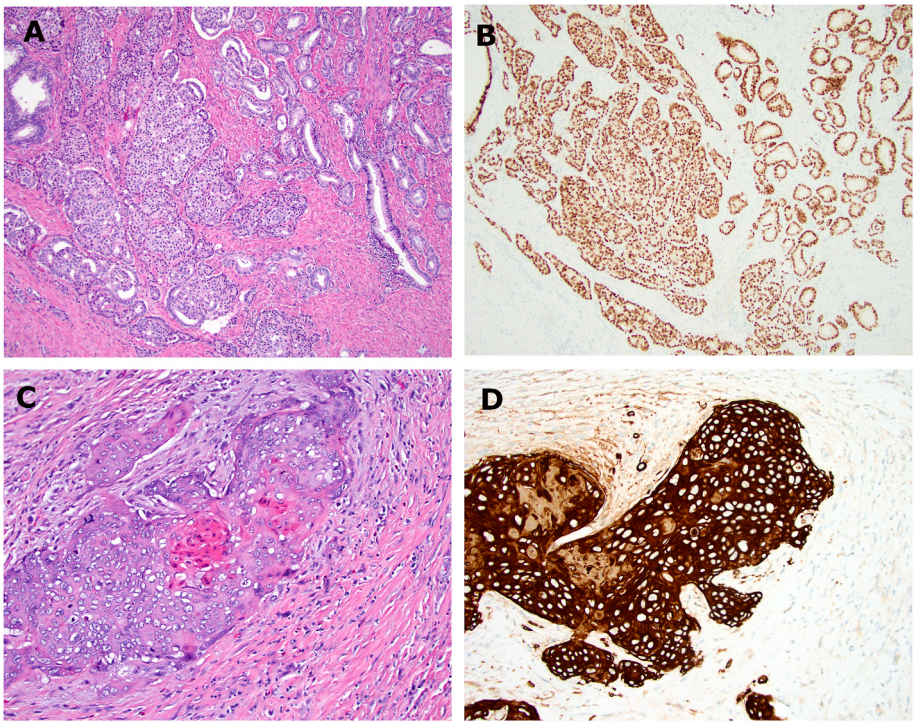

Fig. 1. Invasive acinar prostatic adenocarcinoma and squamous cell carcinoma. (A) Sections of the prostate showed predominantly prostatic adenocarcinoma of the usual acinar type, Gleason Score 4 + 5 = 9. (B) Immunohistochemistry showed neoplastic cells were positive for NKX3.1, corroborating the diagnosis. (C) Carcinoma with squamous differentiation was seen as invasive nests of carcinoma with definitive keratin formation. (D) It was strongly and diffusely positive for CK903/34BetaE12, corroborating this interpretation.

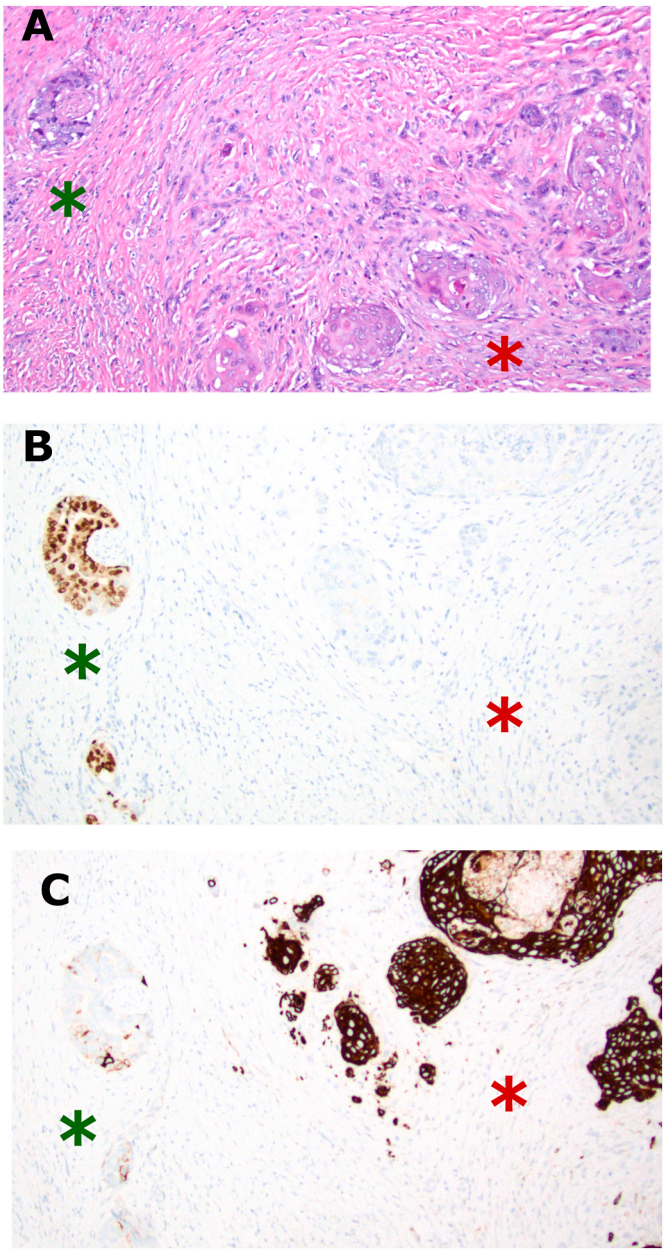

Fig. 2. Transition from acinar prostatic adenocarcinoma to invasive squamous cell carcinoma. (A) Carcinoma with squamous differentiation was present in the left posterolateral midgland (red asterisk), directly adjacent to acinar prostatic adenocarcinoma (green asterisk). (B) Immunohistochemistry for the prostate marker NKX3.1 was positive in the acinar adenocarcinoma (green asterisk) and negative in the squamous carcinoma (red asterisk). (C) In contrast, immunohistochemistry for the squamous marker CK903/34BetaE12 was positive in the squamous component (red asterisk) and focally/weakly positive in the acinar adenocarcinoma (green asterisk).

squamous carcinoma, we diagnosed the tumor as prostatic adenocarcinoma with focal squamous differentiation.

3. Discussion

While PCa most commonly manifests as adenocarcinoma, the presence of rare histological variants such as squamous differentiation introduces unique diagnostic and therapeutic challenges. Most described carcinomas of the prostate with squamous differentiation are either pure SCC or ASC with a sizeable fraction of squamous histology. This is a case of a conventional acinar adenocarcinoma of the prostate with less than 1 % squamous histology. The patient also had no history of radiation or androgen deprivation therapy. Thus, this appears to be an extremely rare example of de novo focal transdifferentiation of prostatic adenocarcinoma to squamous histomorphology.

The immunohistochemical profile of the squamous component in this case, characterized by focal expression of NKX3.1 and p63, and negative staining for GATA3, supports a diagnosis of squamous differentiation from prostatic adenocarcinoma. NKX3.1 is typically expressed in prostatic adenocarcinoma, while GATA3 is more commonly associated with urothelial carcinoma. The expression of p63 and CK903, which are associated with squamous differentiation, indicates that the squamous tumor had shifted from prostatic to squamous lineage. This distinction is crucial for accurate diagnosis and appropriate management, as the therapeutic strategies for SCC can differ significantly from those for adenocarcinoma.

The challenges posed by ASC lie at the intersection of its histological variability and clinical complexity. Had only the squamous component been sampled on needle biopsy, this case would have presented an extremely difficult diagnostic challenge. Given the patient's history of urothelial carcinoma, the immediate concern would have been invasive urothelial carcinoma with squamous differentiation, either invading the prostate from the bladder or arising from the prostatic urethra. It would have been very difficult to determine the primary site in this case, potentially leading to an unnecessary cystoprostatectomy.

To our knowledge, there have been 18 reports of de novo ASC in the literature. In 1999, Basler et al. documented the first case of de novo ASC diagnosed on core needle biopsy.[14] Then, in 2004 Parwani et al. reported 7 cases of de novo ASC in a retrospective review of PCa cases.[10] One other case was published in 2018,[15] and since then, three other studies have been published in 2024 describing de novo ASC, with two being singular case reports[11,16] and one being a review identifying 4 cases.[17] Our case adds to this literature as the 19th case of de novo ASC and further suggests the need for more comprehensive terminology that can describe the nuisance of such pathology.

As of now, there is no definitive unique treatment for PCa exhibiting squamous differentiation.[16] Although PSA has always been a surrogate for disease status post-prostatectomy, it is unclear if any additional imaging would be of benefit as the squamous differentiation may be less likely to secrete PSA. Our patient received a prostatectomy, which has been shown to be of most benefit. Wang et al. suggested a longer 1-year survival rate among patients with local or regional ASC who received a prostatectomy compared to those that did not undergo prostatectomy. Furthermore, at comparison of 3 and 5 years, none of the patients who did not undergo prostatectomy survived.[9] Thus, it is imperative to consider radical prostatectomy in patient diagnosed with PCa exhibiting squamous differentiation as soon as possible.

This case underscores the importance of thorough histopathological and immunohistochemical evaluations to avoid misdiagnosis and ensure appropriate treatment. Clinicians should remain vigilant for rare cancer variants and consider them in the differential diagnosis, especially in patients with complex or atypical presentations. It is very possible for a squamous component in the prostate to be missed on needle biopsy. Furthermore, we suggest that the term "adenocarcinoma with focal squamous differentiation" be used to describe such cases to clearly communicate the pathology of this variant of PCa. The insights gained from this case contribute to a deeper understanding of prostatic malignancies and emphasize the need for continued research into the mechanisms underlying histological transformations and their implications for patient management. Future studies should focus on elucidating the molecular and genetic factors driving such transformations and their impact on prognosis and treatment outcomes.

4. Conclusion

This case illustrates a rare instance of squamous differentiation within high-grade prostatic adenocarcinoma, challenging typical

classifications and diagnostic expectations. It serves as a critical reminder of the need for thorough histopathological and immunohistochemical analyses to avoid misdiagnosis and ensure accurate treatment planning. Future studies should focus on elucidating the molecular and genetic factors driving such transformations and their impact on prognosis and treatment outcomes.

CRediT authorship contribution statement

Abdul-Jawad J. Majeed: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Joshua Warrick:** Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jay D. Raman:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Financial support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest disclosure

The authors have no conflicts of interest to report.

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