ISSN: 2755-0176

Journal of Cancer Research Reviews & Reports

SCIENTIFIC Research and Community

Case Report

Open Access

Challenges of a Complex Rectal Cancer Diagnosis as a Primary Site of Metastatic Prostate Cancer. A Case Report and Literature Review

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ABSTRACT

Prostate cancer (PCa), the most common cancer among men worldwide, remains a complex and challenging diagnosis for clinicians. Difficulties in diagnosing PCa arise from several factors, including, overdiagnosis, time efficient presentation to the clinic, use of insufficiently sensitive screening tools, discomfort testing procedures for instance needle biopsy procedure, and the presence of clinically insignificant PCa patients, leading to unpredictable prognosis [1-3]. Alternatively, pathological findings that determine the primary site of cancer and assess distant metastases are integrated with clinical history, imaging studies, and laboratory tests to distinguish the type and etiology of lesions, thereby establishing a comprehensive diagnosis and therapy. In this article, we present a rare case of prostate cancer metastasizing to an unusual site: the rectum. The patient exhibited typical gastrointestinal symptoms, including constipation, rectal bleeding, and weight loss. Through meticulous investigation, endoscopy, radiological tests, lab tests, and immunohistochemical (IHC) analysis, we confirmed that the ectopic primary tumor was originating from the prostate. This case highlights the importance of considering rare metastatic sites in PCa, as such occurrences can pose diagnostic challenges and lead to delays in treatment. Given the rarity of such cases, further research is needed to improve cancer assessment methods and develop novel, highly specific screening tools that could aid in the early and accurate diagnosis of prostate cancer [4-7].

The challenges in diagnosis range from relatively straightforward cases to those complicated by misdiagnosis, underscoring the need for more effective diagnostic strategies in oncology.

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Received: January 21, 2025; **Accepted:** January 24, 2025; **Published:** February 10, 2025

Keywords: Prostate Cancer, Rectal Metastasis, Immunohistochemistry, Androgen Deprivation Therapy, Adenocarcinoma

Introduction

PCa is the second most common cancer found in men, characteristically effecting more than a million worldwide in 2024.

14.2 percent of men that are eventually diagnosed with PC, with higher incidence rates among African, African-American and Caribbean men populations [8-10]. Active surveillance of metastatic-PC for 5-year Progression-free-survival (PFS) is estimated at 54.9%.

By contrast, for all metastatic-PC including those on Androgen deprivation therapy, chemotherapy and immunotherapy, the value of PFS is generally moderately higher compared to high grade cancer only. Prostate adenocarcinoma, one of the most prevalent forms of cancer, originates from the glandular cells of the prostate [10-12].

Genetic alterations, such as mutations in key genes, are important prognostic factors, often associated with a more aggressive cancer phenotype and earlier onset. Hereditary genetic factors show significant penetrance in first-degree relatives. Genome-wide association studies (GWAS) have demonstrated strong correlations between PCa and specific gene mutations, particularly BRCA1/2 and HOXB13, which have been identified in recent years [13].

PCa typically presents as a poorly to moderately differentiated malignant tumor with a high grade. It can either spread locally or metastasize to distant sites, including bones, lungs, and lymph nodes. The incidence of route of invasion to these sites most common is first leaded by bone metastases, followed by lymph node involvement and lung metastasis[13,14].

Extraprostatic extension (EPE) and metastasis to the intestinal wall, including the rectum, are rare occurrences in PCa metastasis. Anatomically, the mesorectal fascia, which encircles the rectum, and the fibromuscular fascia behind the bladder and prostate, typically prevent direct contact between the prostate and

rectum, reducing the likelihood of PC invading the rectum. [14]. Consequently,when PCa metastasizes to the colon or rectum, it can sometimes be misdiagnosed as primary colorectal adenocarcinoma. This underscores the importance of differentiating between the two, particularly when the patient's history of prostate cancer might not be well known. [11, 14]

Histologically, metastatic PC in the colon often presents as a mass or infiltrative lesion that disrupts normal colonic architecture. Diagnostic imaging methods, such as transrectal ultrasound or transperineal needle biopsy, can help identify the tumor's origin. Key histological features of metastatic PC include the absence of the basal cell layer, perineural invasion, and neoplastic cellular changes within a heterogeneous tissue background. The Gleason Score (GS), which is based on histological grading, provides additional insight into the aggressiveness of the cancer. Another pivotal test in confirming the origin of metastatic-PC is immunohistochemistry (IHC), which helps differentiate PC metastasis from other malignancies, particularly primary colorectal adenocarcinoma [5-7]. Specific markers, such as PSA (Prostate-Specific Antigen) and PSAP (Prostate-Specific Acid Phosphatase), are commonly used in IHC to establish the diagnosis of prostate cancer, even when metastasis occurs in unusual locations like the rectum or colon [15, 16].

Case Presentation

An 83-year-old male presented to the gastroenterology clinic with a 2-month history of rectal bleeding, constipation, and unintentional weight loss of 15 kg. The patient had a history of long-standing hypertension but no prior history of benign prostatic hyperplasia or lower urinary tract symptoms.

On clinical evaluation, the patient was pale but hemodynamically stable. Laboratory investigations revealed anemia (hemoglobin: 9.8 g/dL). Afterward, a colonoscopy was planned which identified a suspicious thick, light brown lesion in the rectal wall, and biopsy samples were taken for histopathological analysis.

Figure 1: a/b Colorectal Endoscopic Examination

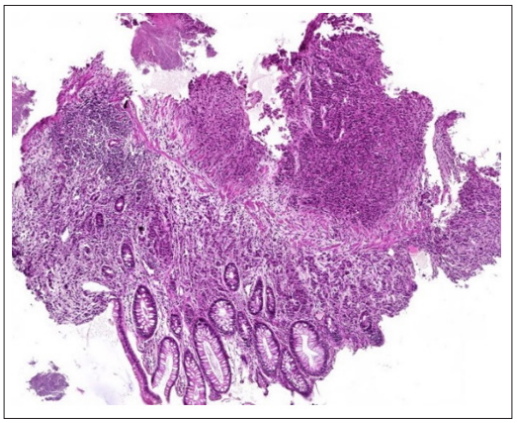

Figure 2: (H-E x4HPF) Discohesive Malignant Cell Infiltration in the Rectal Mucosa

Microscopic examination of rectal biopsy revealed neoplastic glands infiltrating the rectal mucosa. The glands exhibited features of poorly to moderate differentiated carcinoma (Figure2).

However, IHC studies were performed to confirm the diagnosis. Surprisingly, the IHC profile resulted positive for PSA, Cytokeratin AE1/AE3, Ki67 of nucleus 10% positive, and it tested negative for Chromogranin and CK20 indicating that primary site of tumor was not rectum but prostate, consistent with metastatic prostatic adenocarcinoma (Figure 3a,b,c,d,e,f).

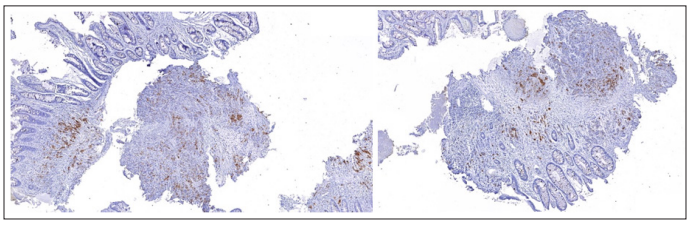

Figure 3: a/b IHC /CK20-Negative PSA+Positive

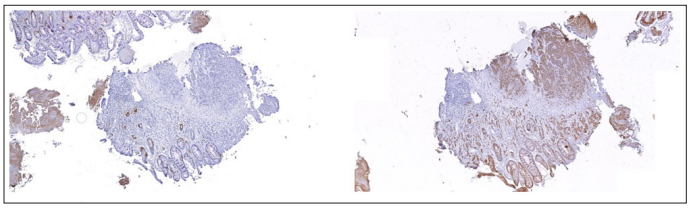

Figure 3: c/d IHC (Chromogranine-Negative) PANCK+Positive

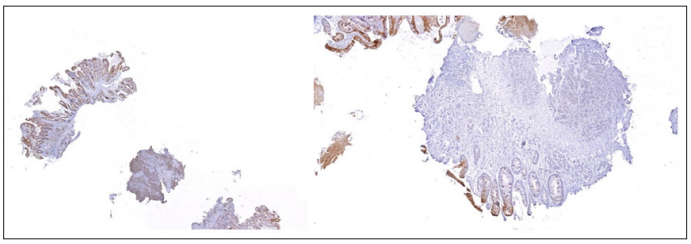

Figure 3: e/f IHC (PKAE1/AE3)+ Ki-67

Discussion

Prostate cancer metastasizing to the rectum is rare, as the primary metastatic sites are the pelvic bones and lymph nodes. The absence of classical symptoms of prostate cancer, such as urinary obstruction or prostate enlargement, compounded the diagnostic complexity in this case. Histopathological differentiation between primary rectal adenocarcinoma and metastatic lesions is essential, as treatment strategies and prognosis vary significantly. An extending discussion about overdiagnosis in PCs is a significant concern, particularly with widespread screening practices of PSA. Identifying biomarkers that can accurately predict the extension of metastatic prostate cancer (mPCa), oligometastatic PCa (omPCa) and aggressive tumor versus benign variants [1, 2].

Recent studies have highlighted promising outcomes for using non-invasive liquid biomarkers, bilayer extracellular vesicles (EVs) from blood and urine, in detecting and monitoring tumor burden, biology and disease progression. By far, application in prostate cancer has shown that liquid EVs can distinguish between indolent and aggressive forms of prostate cancer, reducing unnecessary biopsies. Encouraging findings, suggesting that these biomarkers could complement PSA testing and imaging in mPCs diagnosis, EVs must first be standardized and validated as an investigative method to ensure their utility as a high sensitivity diagnostic test [17-18].

Until a highly sensitive and specific diagnostic tool is developed, the IHC profile will remain a valuable support for differential diagnosis between colon and mPCa. Expression of NKX3.1 stain is supportive for localized PCa, omPCa, and mPCa diagnosis. This marker in combination with other stains PSA, PrAP, ERG, AR concomitant to other form of investigation to diagnosticate and prognosticate PCa for a target treatment approach and monitoring of the disease.

In contrast, beside known gastrointenstinal markers CEA and Ca19-9 there are other immunostainings used to differentiate primary adenocarcinomas and metastatic adenocarcinomas arising from colorectal tract including CDX2 and SATB2. Immunostain markers are preferably to be evaluated at the same time. Compelling data shows the overexpression of two markers have good therapy response compare to down expression markers. Combining SATB2 and CDX2 with immunostains CK20 increase diagnosis specificity [19, 20].

Conclusion

This case highlights an unusual presentation of PC mimicking rectal adenocarcinoma. Clinicians should maintain a high index of suspicion and utilize advanced diagnostic modalities, including immunohistochemistry, to avoid misdiagnosis.

Timely initiation of targeted therapy can lead to favorable outcomes even in rare metastatic scenarios.

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