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A rare case of prostatic ductal adenocarcinoma presenting as papillary metastatic carcinoma of unknown primary: A case report and review of the literature☆

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ABSTRACT

Prostatic ductal adenocarcinoma is an uncommon form of prostatic carcinoma. We report a case of a 63-year-old man who presented with non-infective thrombotic (marantic) endocarditis and an incidental finding of a destructive lesion in the left iliac crest. Core biopsy of the lesion showed a carcinoma with papillary architecture and was initially diagnosed as "metastatic carcinoma of unknown origin". The patient experienced a cerebral infarction and expired six days later. Postmortem examination revealed extensive mixed acinar and ductal adenocarcinoma (Gleason score $5 + 4 = 9$) in the prostate. Further studies confirmed the bone lesion as metastatic prostatic ductal adenocarcinoma. Although rare, metastatic prostatic adenocarcinoma should be considered in the differential diagnosis in a male patient when the carcinoma shows predominantly papillary architectures. A review of literature is presented to enhance the awareness of this entity.

1. Introduction

Prostatic ductal adenocarcinoma (PDA) is uncommon, accounting for about 0.4–0.8% of prostate cancers [1–3]. Few studies of metastatic PDA have been reported [4]. In contrast to the more common acinar type carcinoma which is composed of cuboidal cells arranged in acini, PDA is histologically characterized by papillary or cribriform architectures lined by tall columnar cells with abundant cytoplasm and pseudostratification. PDA can be found in isolation; however it is most commonly admixed with the more typical acinar type prostatic carcinoma. Mixed PDA-acinar type carcinoma is reported in 5% of prostate carcinomas [2,5]. PDA is generally associated with a poor prognosis [3,6,7], and has a propensity to metastasize to the penis, testis, bone, liver, lungs, and brain [2,4,5,8]. Metastatic PDA typically shows papillary or cribriform patterns which can cause diagnostic difficulty because the cytologic and histologic features do not clearly reveal a prostatic origin. Papillary or cribriform architecture can be found in metastatic carcinomas arising from many other organs such as the gastrointestinal tract, pancreaticobiliary tract, lung, kidney, thyroid, and urinary bladder [4]. Given the rarity of this tumor and its overlapping morphological characteristics with other carcinomas, diagnosis of a metastatic PDA on a core biopsy can be challenging. As the clinical behavior of PDA is more aggressive, it is imperative to accurately diagnose this entity [9]. We describe herein a case of metastatic prostatic ductal adenocarcinoma in a 63-year-old man which was diagnosed only upon postmortem examination. Review the relevant literature on this rare entity is provided.

1.1. Case history

A 63-year-old Caucasian man with a past medical history of hypertension and coronary artery disease presented with bilateral lower extremity claudication, and was diagnosed with bilateral deep vein thrombosis. He was treated with systemic anticoagulation and discharged home. Three weeks later, he presented with acute dysphagia and dysarthria; brain imaging demonstrated multiple acute cerebral infarctions. He subsequently showed significant neurological recovery. Ten days later, however, he developed bilateral lower extremity ischemia requiring embolectomies and a right below-the-knee amputation. Further workup included a transthoracic echocardiogram which revealed bilateral mitral leaflet mobile masses consistent with endocarditis. Multiple blood, sputum, and urine cultures were negative for bacterial or fungal growth during his hospitalization. The patient was diagnosed with non-infective thrombotic (marantic) endocarditis. A CT scan of the abdomen unexpectedly revealed a 3×2 cm lytic lesion in the left iliac bone concerning for malignancy (Fig. 1A). A core biopsy

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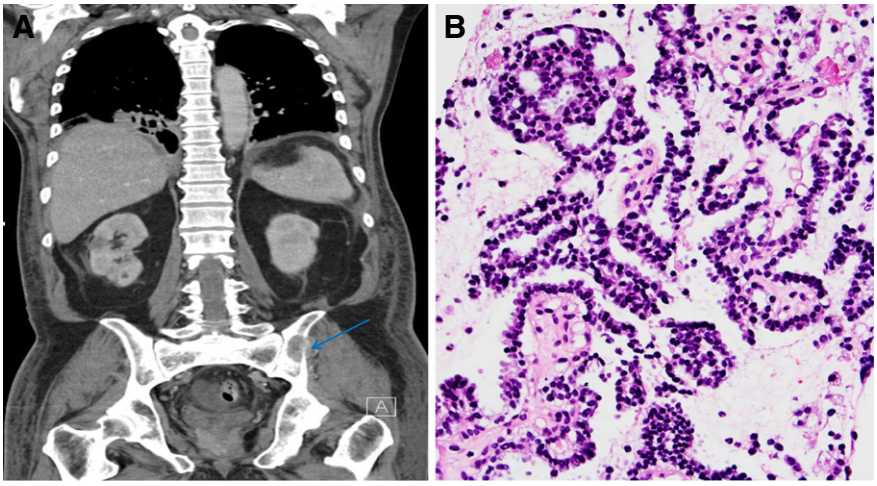

Fig. 1. The iliac bone lesion. A, CT scan showed a 2 × 3 cm destructive lesion of left iliac bone eroding through the cortex and into the surrounding soft tissue. B, Core biopsy of the bone lesion showed a metastatic carcinoma composed predominantly of papillary architecture with focal cribriform areas, lined by a single layer of cuboidal to low columnar tumor cells, with edematous to sclerotic fibrovascular cores (H&E, original magnification ×200).

was performed showing a carcinoma with papillary architecture and diagnosed as "metastatic carcinoma of unknown origin" (Fig. 1B). Serum prostatic specific antigen (PSA) was not tested, nor was there a prior prostatic biopsy. The patient continued to experience embolic events including numerous cerebral infarcts, was transitioned to hospice care, and expired six days after the core biopsy. The clinical causes of death were respiratory failure, cardiac arrest, stroke and embolic events. His family consented to a complete autopsy.

1.2. Core biopsy findings

An antemortem core biopsy of the left iliac bone lesion was performed under CT guidance. The histological sections demonstrated an epithelial lesion composed predominantly of papillary architecture with focal cribriform patterns, lined by single layer of cuboidal tumor cells with crowded, round-to-ovoid hyperchromatic nuclei and abundant eosinophilic cytoplasm (Fig. 1B). A broad differential was considered including papillary renal cell carcinoma, papillary thyroid carcinoma, papillary urothelial carcinoma, papillary lung carcinoma, mesothelioma, and an unusual type of carcinoma of the digestive system. Immunohistochemical stain demonstrated positive staining for AE1/AE3 and EMA, and negative staining for vimentin, CK7, CK20, CD10, GATA3, PAX8, calretinin, and WT1. The case was signed out as "metastatic carcinoma of unknown origin."

1.3. Autopsy findings

Upon postmortem examination, there was no evidence of mass lesion in the kidneys, bladder, thyroid, lungs, gastrointestinal tract, pancreas, liver, pleura, or peritoneum. The prostate was diffusely enlarged (4.5 × 4 × 4 cm) and bulky with a tan-yellow nodular parenchyma. The left iliac bone lesion was identified, which was a 3 × 2 × 2 cm irregular, soft, red-brown lytic lesion Initial sections of prostate revealed extensive prostatic acinar adenocarcinoma, Gleason score of 5 + 4 = 9 (Fig. 2A). The bone lytic lesion revealed metastatic carcinoma with a pure PDA pattern showing numerous papillae with overlying high grade epithelium composed of cuboidal to low columnar cells with glands showing focal cribriform architecture. The morphology was similar to prior biopsy (Fig. 2C). A panel of immunostains was performed, and both the prostatic carcinoma and metastatic carcinoma in the bone were positive for prostate-specific acid phosphatase (PSAP, Fig. 2D) but negative for PSA. In addition, the metastatic carcinoma was also positive for NKX3.1 and P501S (Fig. 2E and F). Additional sections of the prostate showed a minor portion of carcinoma with papillary and cribriform architecture, similar to the metastatic tumor, which further confirmed the diagnosis of metastatic prostatic ductal adenocarcinoma in the bone (Fig. 2B). Approximately 10% of tumor within prostate showed PDA features with the remaining 90% of the tumor showing high grade acinar-type morphology. Extraprostatic extension and seminal vesicle invasion was also present.

Other significant autopsy findings included nonbacterial thrombotic (marantic) endocarditis of the mitral valve, three vessel atherosclerotic coronary artery disease, multiple thromboemboli in the superior mesenteric artery and bilateral small renal arterial branches, multiple cerebral infarctions, infarctions of right lower of the lung, small and large bowel, spleen, prostate, and renal cortex. The cause of death was complications of metastatic prostatic adenocarcinoma.

2. Discussion

Prostate cancer is the second most common cancer and the sixth leading cause of cancer-related death in males worldwide [10]. The vast majority of prostate carcinomas are of the acinar type in which 75–80% arise in the peripheral zone and are histologically characterized by cuboidal cells arranged in acini. Prostatic ductal adenocarcinoma (PDA) is a relatively rare variant of prostate cancer. PDA is diagnosed in its pure form in 0.4–0.8% of prostate malignancies [1–3,5]. More commonly, PDA is admixed with more typical acinar type adenocarcinoma in up to 5% of prostate carcinomas [2,5]. Prostatic ductal carcinoma, initially described by Melicow and Pachter in 1967, was originally believed to be a malignancy derived from remnant paramesonephric tissue. Due to its histologic similarity to uterine endometrial carcinoma, it was given the name "endometrioid" carcinoma [11]. Further ultrastructural and histochemical studies as well as positive response to androgen deprivation showed these tumors are derived from prostatic ductal epithelial tissue and thus renamed prostatic ductal adenocarcinoma [1–6,8,12].

PDA commonly arises in the large primary periurethral ducts and is clinically associated with a gross hematuria and urinary obstructive symptoms [2]. As PDA typically forms in a periurethral location, digital rectal examination has poor sensitivity in diagnosing this tumor [13]. PDA often shows exophytic growth into the prostatic urethra with involvement of the verumontanum [5]. PDA can also arise in the smaller peripheral zone prostatic ducts, which is typically diagnosed by needle biopsy [13,14]. Serum prostate specific antigen (PSA) is variable in ductal adenocarcinoma and often not predictive of findings upon radical prostatectomy [6,15].

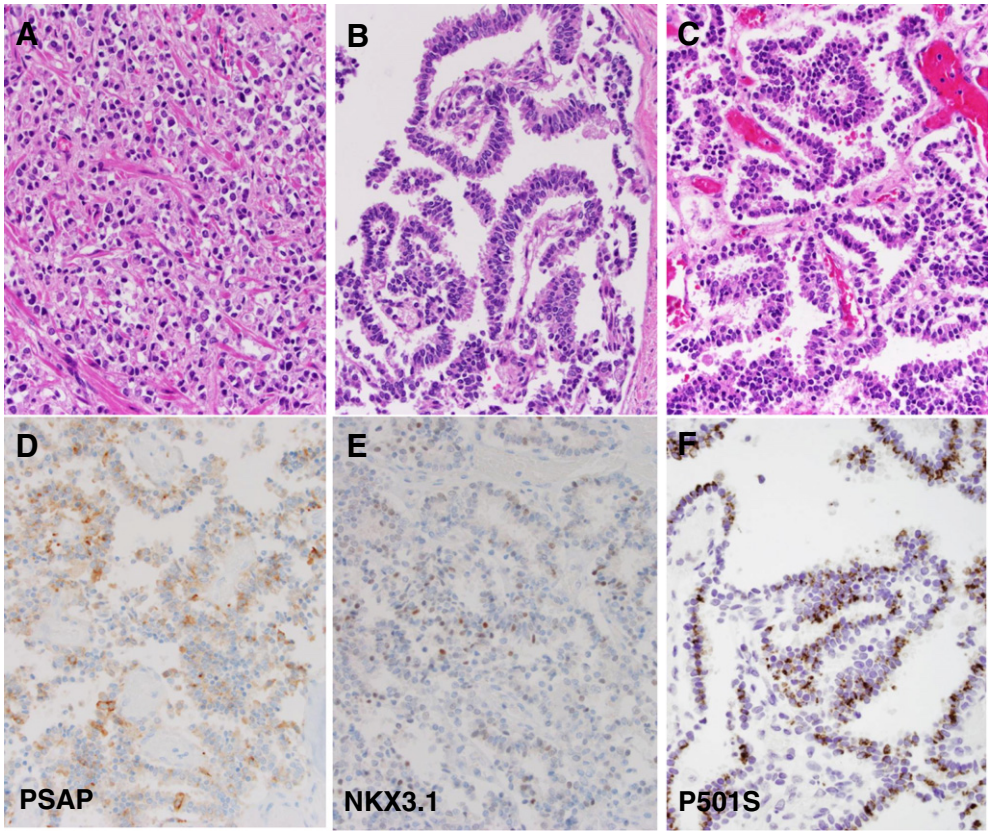

Fig. 2. Findings at autopsy. A, Prostatic adenocarcinoma predominantly showed Gleason 5 pattern. B, Prostatic adenocarcinoma focally with papillary architecture, consistent with ductal adenocarcinoma. C, Metastatic carcinoma in the iliac bone lesion, morphologically similar to prior biopsy (Fig. 1B) and the prostatic ductal adenocarcinoma (Fig. 2B). D–F, Immunohistochemical study showed that the metastatic carcinoma in the iliac bone was positive for PSAP, NKX3.1, and P501S. (original magnification ×400).

The diagnosis of PDA is based largely upon histologic morphology [16]. While typical acinar type carcinoma is characterized by acini lined by a simple cuboidal epithelium, a common histologic feature of PDA is pseudostratified, tall, columnar epithelium [6]. The cells typically contain abundant amphiphilic cytoplasm which can be pale or clear. The nuclei are large, elongated, with a variably prominent nucleolus and a greater degree of chromatin irregularities and hyperchromasia when compared to acinar carcinoma. Mitotic figures are present at a higher rate than that seen in acinar carcinoma [3,6,8]. Seipel et al. investigated the interobserver variability of the diagnosis of PDA among 20 expert urologic pathologists. For 11 consensus cases of PDA, the histologic features reported to be most important were papillary architecture (86% of responses), followed by nuclear stratification (82%), high grade nuclear features with prominent nucleoli (54%), tall columnar epithelium (53%), elongated nuclei (52%), cribriform architecture (40%), and necrosis (7%) [17]. The antemortem core biopsy of this patient's left iliac bone lesion showed a single layer of predominately non-stratified cuboidal epithelium which is atypical for PDA. The papillary structures and focal cribriform architecture, however, provide an important clue to a possible prostatic origin and should have led to immunohistochemical evaluation with prostatic markers including PSA, PSAP, androgen receptor, or NKX3.1. In addition, regardless of morphology, prostate carcinoma should always be considered in the differential diagnosis for metastatic carcinoma to bone in middle aged to elderly men.

PDA can show various architectural patterns including papillary, cribriform, individual gland, solid, and the more recently characterized "prostatic intraepithelial neoplasia-like" morphology. Multiple patterns can be present within a single tumor [9,18]. The most common patterns are papillary and cribriform [6,13]. The papillary pattern, a distinct architecture not seen in usual acinar carcinoma, consists of true papillary fronds lined by crowded pseudostratified columnar cells with a variable nuclear pleomorphism and hyperchromasia. The papillae are complex, branching and often fused [19]. The cribriform pattern, being somewhat similar in appearance to endometrioid adenocarcinoma, is the reason for these tumors being initially referred to as "endometrioid carcinoma of the prostate" [13]. The cribriform pattern consists of enlarged, back-to-back cribriform glands containing multiple lumina separated by cell bridges. The lumina are lined by tall, pseudostratified columnar cells with elongated hyperchromatic nuclei. The cribriform glands often show central necrosis. In both papillary and cribriform architectures, the background stroma typically shows prominent desmoplasia and/or fibrosis [2,6,20]. The "individual gland" pattern is characterized by single glands with a malignant-appearing pseudostratified tall columnar epithelium, resembling adenocarcinoma of the colon [13,21]. A solid pattern has been described where the malignant cells proliferate in solid nests or cribriform glands showing central necrosis, which is difficult to distinguish from poorly differentiated acinar carcinoma [13]. Practically in all cases, the cells of PDA are at least focally PSA or PSAP-positive. Seventy-seven percent of PDA stain positive for AMACR, and the predominance of cases is negative for p63 or HMWCK (34βE12). However, a study by Herawi and Epstein showed 31% of cases have patchy detectable basal cells by p63 or HMCK (34βE12) [22]. The newer prostatic markers such as P501S and NKX3.1 are also shown to be positive in both ductal adenocarcinoma and high-grade acinar carcinomas of the prostate [23–25].

A needle biopsy study by Brinker et al. in 1999 suggested that surgically resected cases of PDA had a prognosis between that of Gleason score 7 and Gleason score 8 acinar carcinoma [6]. Therefore, the current consensus is to treat cases of pure ductal adenocarcinoma as Gleason score 4 + 4 = 8; however the presence of comedonecrosis justifies increasing to Gleason grade 5. In mixed ductal and acinar adenocarcinoma, ductal component is assigned Gleason pattern 4 (or 5 if

comedonecrosis is present), while the acinar component is scored separately [13,26]. The majority of studies show PDA to be more aggressive than acinar carcinoma with a more advanced clinical and pathologic stage at presentation, and a worse 5 year survival rate. Studies have shown PDA to be less responsive to traditional hormonal, radiation, and radical surgical therapies [3,5–7]. When diagnosed on needle biopsy, greater than 50% will have high volume disease [6]. PDA reportedly has a propensity to metastasize to the penis, testis, bone, liver, lungs, and brain [2,4,5,8]. In 1991, Christensen et al. reported a study of 15 cases of PDA treated by radical prostatectomy, in which all of the patients appeared to have resectable disease. Final pathology revealed large tumors, with a mean volume of 8.4 ml and involving a mean of 23% of the prostatic parenchyma. Extraprostatic spread was reported in 93%, positive margins in 47%, and seminal vesicle involvement in 40% of the patients [3].

Studies have identified a gene rearrangement between the androgen related gene TMPRSS2 and the transcription factor gene ERG which is present in 40–60% of conventional acinar carcinoma of the prostate [27–29]. A study by Lotan et al. showed the rate of the TMPRSS2-ERG gene fusion to be less frequent in PDA as compared to conventional acinar carcinoma (11% vs 45%). The significantly lower rate of the gene fusion in PDA emphasizes the fact that the genetic and biologic differences between PDA and acinar carcinoma may be important in future therapeutic strategies [30].

In this patient, autopsy examination revealed nonbacterial thrombotic endocarditis of the mitral valve and thromboemboli in the superior mesenteric artery and bilateral renal arterial branches with infarctions of the cerebrum, lung, small and large bowel, spleen, prostate, and renal cortex. Malignancy is associated with a hypercoagulable state and is major risk factor for thrombosis [31]. Certain malignancies, particularly mucin-secreting adenocarcinomas of the ovary, pancreas, stomach, and brain are associated with a higher risk of venous thromboembolism (VTE) [32,33]. However, many non mucin-producing tumors, such as prostate carcinoma, are also associated with hypercoagulability. In a study by Ording et al., the overall VTE rate was 2.8 times higher in the prostate cancer cohort than in the general population [34]. Although the incidence of VTE in prostate carcinoma is lower relative to mucin producing tumors, due to the high prevalence of prostate carcinoma, VTE in this patient population presents a major medical burden [35]. In a study by Nickel et al., the authors showed that prostate cancer cells produce small vesicles (prostasomes) rich in polyphosphate that promote thrombin generation via activation of coagulation factor XII [36].

Nonbacterial thrombotic endocarditis (NBTE), formerly known as marantic endocarditis, is characterized by sterile heart valve vegetations, consisting of fibrin and platelet aggregates, in the absence of a bacterial bloodstream infection. Recurrent emboli are a hallmark of NBTE, occurring in up to 50% of patients, with a tendency to embolize to the brain, kidney, spleen, mesenteric bed or the extremities [37]. The etiology of NBTE is thought to involve endothelial injury in the setting of a hypercoagulable state. Endothelial damage caused by circulating cytokines (e.g., tumor necrosis factor, interleukin-1) in the presence of a malignancy associated hypercoagulable state, may result in deposition of platelets and fibrin upon heart valve leaflets [38]. One autopsy series reported that, compared to the general population, patients with underlying malignancy have a higher rate of NBTE (1.25% vs 0.2%). Higher rates of NBTE were reported in patients with adenocarcinoma (e.g., lung, colon, ovary, biliary and prostate) (2.7% vs 0.47%) with the highest rates observed in patients with pancreatic adenocarcinoma (10.34%) [39].

3. Conclusion

PDA is an uncommon variant of prostate adenocarcinoma which is histologically characterized by papillary or cribriform architecture lined by tall columnar cells with abundant cytoplasm and pseudostratification. PDA is associated with aggressive behavior with an overall poor prognosis when compared to typical acinar prostate carcinoma. Metastatic PDA can be diagnostically challenging as papillary and cribriform architecture can be found in metastatic carcinomas arising from many other organs [4]. Prostatic ductal adenocarcinoma should be included in the differential diagnosis of a metastatic carcinoma showing papillary or cribriform architecture in middle-age to elderly male patients.

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