Case Report

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Metastatic prostate adenocarcinoma and high-grade appendiceal mucinous neoplasm mimicking acute appendicitis in a post-radiation therapy patient

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Abstract

Prostate cancer is the most common visceral malignancy diagnosed in males. Surveillance for post-treatment neoplasms is very crucial. Here we report the first case of recurrent metastatic prostate cancer presenting as acute appendicitis in a background of a high-grade appendiceal mucinous neoplasm. In addition, this case also includes an unusually early presentation of a secondary primary malignancy after radiation therapy. A 70-year-old male with a history of prostate adenocarcinoma status post-proton radiation therapy presented with recurrent poorly differentiated prostate adenocarcinoma with disease progression and extra-prostatic extension. He underwent salvage proton therapy and testosterone replacement therapy. Two years later, the patient presented with right lower quadrant pain. A computed tomography scan showed perforated acute appendicitis with intra-abdominal abscess, which was treated with interval appendectomy. Upon histologic analysis, metastatic prostatic adenocarcinoma was noted in the appendiceal wall and mesoappendix. In addition, an incidental background of high-grade appendiceal mucinous neoplasm was found. Four months later, he presented with persistent abdominal pain, rapid weight loss, fatigue, and fever for 3 months. An abdominal CT scan revealed a 6.1 cm rectal mass. Pathologic analysis diagnosed an aggressive post-radiation spindle cell sarcoma, intermediate to high grade. The patient opted for palliative care. This case shows that a clinical presentation of acute appendicitis in an older patient may sometimes portend a neoplastic rather than infectious etiology. Clinical history and patient epidemiology should always be considered when evaluating an older patient with clinical signs and symptoms of acute appendicitis.

Keywords

Prostate cancer, high-grade appendiceal mucinous neoplasm, post-treatment neoplasm, secondary primary malignancy, post-radiation spindle cell sarcoma, acute appendicitis

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Introduction

Prostate cancer is the most common malignancy diagnosed in males in the United States, excluding skin cancers.[1] The majority of prostate cancer diagnoses are confined to the prostate gland, with only 6% of newly diagnosed prostate cancers presenting with metastasis.[2] However, prostate cancer recurrence rates after radical prostatectomy have been shown to occur between 24% and 34% of the time within 15 years of the surgery.[3] Risk factors which are associated with prostate cancer metastasis status post-radical prostatectomy include positive surgical margins, prostate-specific antigen (PSA) doubling time <3 months, invasion of the seminal vesicle seen in the radical prostatectomy specimen, high Gleason score (score of 8–10), and recurrence of prostate cancer within 3 years of the radical prostatectomy.[4–9]

Prostate cancer metastasis is most commonly seen in pelvic lymph nodes and bones, with other rare incidences of metastases also seen such as the brain, lungs, and liver.[10] There have been case reports of metastatic prostate cancer

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presenting as acute appendicitis; however, it is an extremely uncommon occurrence with only 1%–2% of metastatic prostate cancer presenting as acute appendicitis.[11–14] Acute appendicitis is the most common surgical emergency of the abdomen in the United States, with a lifetime incidence of 8.6% in men and 6.7% in women. Although currently uncertain, the pathophysiology of acute appendicitis has been hypothesized to involve obstruction of the appendiceal lumen, resulting in ischemia and secondary bacterial infection of the appendiceal wall.[15] The mean age of a patient diagnosed with acute appendicitis is 24–25 years.[16] The specific entity causing appendiceal obstruction can vary, but a rare cause of obstruction is an appendiceal neoplasm.

Sarcomas developing after radiation therapy have been reported in the English literature since 1948, when 11 cases of sarcoma were seen in patients status post-radiation therapy for osteosarcoma.[17] Factors that positively influence second primary malignancies (SPMs) developing after radiation therapy include increased time since radiation therapy, decreased age during irradiation, female sex, and irradiation of specific high-risk organs such as the lung, stomach, colon, and bone marrow.[18] Specifically, studies following patients diagnosed with prostate cancer treated by radiation therapy have shown a 6% increased incidence of solid tumor SPMs, with a relative risk increasing by up to 34% 10 years after treatment.[19] Prostate radiation therapy has been shown to be positively correlated with rectal cancer, with an odds ratio of 2.22 by 10 years post-radiation. While showing an increased odds ratio, the incidence of rectal cancer after radiation treatment for prostate cancer remains very low.[20,21]

Appendiceal mucinous neoplasms (AMNs) are rare tumors, and account for between 0.2% and 0.3% of all appendectomy specimens.[22] AMNs, a term which encompasses low-grade appendiceal mucinous neoplasms (LAMNs), high-grade appendiceal mucinous neoplasms (HAMNs), and mucinous appendiceal adenocarcinomas, are usually asymptomatic, and they may remain asymptomatic for years. When AMNs are symptomatic, they typically show clinical signs and symptoms of acute appendicitis. HAMN is an extremely rare, and recently described, entity which may represent an intermediate group between LAMN and mucinous adenocarcinoma. HAMN is described histologically as displaying features of LAMN architecture, but is cytologically high-grade and tends to behave more aggressively than LAMNs.[23] We report the first case of metastatic prostate adenocarcinoma presenting concurrently with a background of an HAMN. In addition, a secondary post-radiation primary rectal sarcoma was identified.

Case report

A 70-year-old male with history of a PSA value of 3.97 was diagnosed in 2010 with prostate adenocarcinoma (Gleason score 7, Grade 2) in 8/12 cores.[24] He subsequently underwent proton radiation therapy in 2011. Subsequent low testosterone levels were noted and testosterone replacement therapy (TRT, Androgel 20.25 mg/1.25 g (1.62%) GlPm, two pumps per day) was started after stabilization of PSA. The PSA levels slowly increased from 0.2 ng/mL in 2013 to 0.40 ng/mL in 2015. Repeat prostate biopsy was performed due to concerns of malignancy recurrence. The biopsy revealed recurrent prostate cancer with disease progression, showing a Gleason score 9, Grade 5 adenocarcinoma, in 6/10 cores, with perineural invasion (Figure 1(a)), and a Gleason score 8, Grade 4 adenocarcinoma, in 2/10 cores.

Robotically assited laparoscopic radical prostatectomy and bilateral pelvic lymph node dissection was performed. The microscopic examination showed moderately to poorly differentiated adenocarcinoma (prostatic acinar type, Gleason score 9, Grade 5) with perineural invasion (Figure 1(b)). The dominant nodule size was 1.6 cm with approximately 30% of prostate involved by tumor. The tumor was confined to the left side of the prostate with focal involvement of the inked surgical margin, and extra-prostatic extension with one out of eight lymph nodes positive for metastatic cancer. The pathologic staging was yT3aN1. Patient underwent salvage proton radiation therapy in 2015 and TRT (Depot testosterone 200 mg IM Q 2 weeks) due to subsequent low testosterone levels.

Robotic cystectomy with bilateral laparoscopic pelvic lymph node dissection was performed secondary to intractable urinary infections and episodes of urosepsis, attributed to a cavity in the area of the ureterovesical anastomosis. The histologic analysis of the lymph node dissection revealed positive right common iliac, inferior vena cava lymph node, and right pelvic lymph nodes for poorly differentiated metastatic prostate adenocarcinoma (Figure 1(c)). A small 2 mm focus of poorly differentiated metastatic prostate adenocarcinoma was found in the outer wall of the urinary bladder (Figure 1(d)).

Two years later, in 2019, the patient presented with right lower-quadrant abdominal pain (rated 7/10) for 3 days. The abdominal computed tomography (CT) showed a perforated appendix with intra-abdominal abscess, and he was treated conservatively with antibiotics. Approximately 4 weeks later, he returned to the emergency department with a chief complaint of right lower-quadrant abdominal pain that radiated to the right upper quadrant. Another abdominal CT scan was performed and showed resolution of the intra-abdominal abscess with a dilated appendix measuring 1.8 cm in diameter, suggestive of an appendiceal mucocele or obstruction. He underwent subsequent laparoscopic appendectomy, and histologic examination of the appendix showed poorly differentiated metastatic prostate adenocarcinoma (Figure 2(a)), involving the appendiceal wall with mesoappendix, perineural, and lymphovascular invasion. Besides the metastatic carcinoma, HAMN of appendix was also found incidentally, with acellular mucin extending to the muscularis mucosae in a background of mild focal early acute appendicitis (Figure 2(b)–(d)).

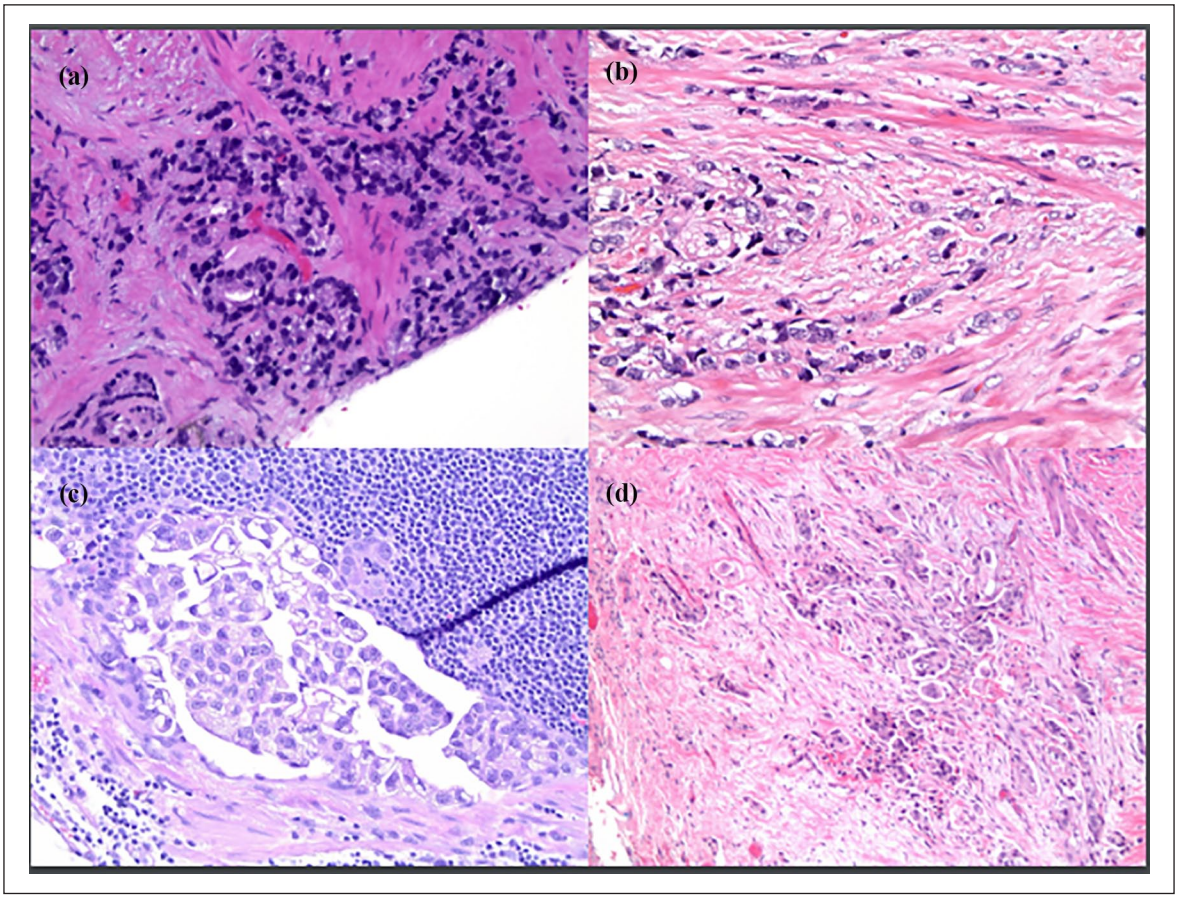

Figure 1. The repeat prostate biopsy revealed recurrent prostate cancer with disease progression, showing a Gleason score 9, Grade 5 adenocarcinoma (a). The microscopic examination of radical prostatectomy showed moderately to poorly differentiated adenocarcinoma (prostatic acinar type, Gleason score 9, Grade 5) (b). The histologic analysis of cystectomy with bilateral pelvic lymph node dissection revealed poorly differentiated metastatic prostate adenocarcinoma (c), and a small 2 mm focus of poorly differentiated metastatic prostate adenocarcinoma was found in the outer wall of the urinary bladder (d).

Four months after appendectomy, the patient was admitted to the emergency department for chronic abdominal pain with a 55 lb unintended weight loss over the previous 3 months. An abdominal CT scan showed a 6.1 cm large heterogeneous rectal mass concerning for recurrent prostate cancer (Figure 3(a)). A biopsy was performed and showed a poorly differentiated malignancy with spindle cell features (Figure 3(b)). Immunohistochemical analysis of the tumor cells revealed non-specific staining for p63, GATA3, and p53. Further immunohistochemical stains showed cytokeratin markers (pancytokeratin, Cam 5.2, and CK34betaE12), prostate markers (PSA, PSAP, and NKX3.1), neural marker (S-100), muscle markers (Desmin, SMA), and vascular marker (CD34) were negative. In addition, an immunostain for a gastrointestinal stromal tumor (CD117) was also negative. Based on these findings, the tumor was most consistent with a spindle cell sarcoma. SARCP (sarcoma-targeted gene fusion panels) was performed, and no gene fusion was identified. These findings are most compatible with a post-radiation spindle cell sarcoma, intermediate to high grade. A retrospective review of a previous CT scan performed prior to his appendectomy, as well as a positron emission tomography (PET) CT scan performed 2 months prior to the diagnosis of his rectal mass revealed no mass, indicating that the tumor had developed within only the 2 months prior to his presentation to the emergency department. A diverting ostomy was offered; however, the patient declined and expressed a desire for palliative care and instead opted for home hospice care.

Discussion

Our patient presented with symptoms mimicking acute appendicitis as a manifestation of his metastatic prostate adenocarcinoma, after two previous rounds of radiation therapy and a radical prostatectomy. Of the known risk factors for prostate cancer metastasis, he showed positive surgical prostatectomy margins, a high Gleason score, invasion of the urinary bladder, and recurrence of his prostate adenocarcinoma within 8 years of radical prostatectomy.[4–9] In addition, he showed extra-prostatic extension of the adenocarcinoma and two lymph nodes positive for metastatic disease

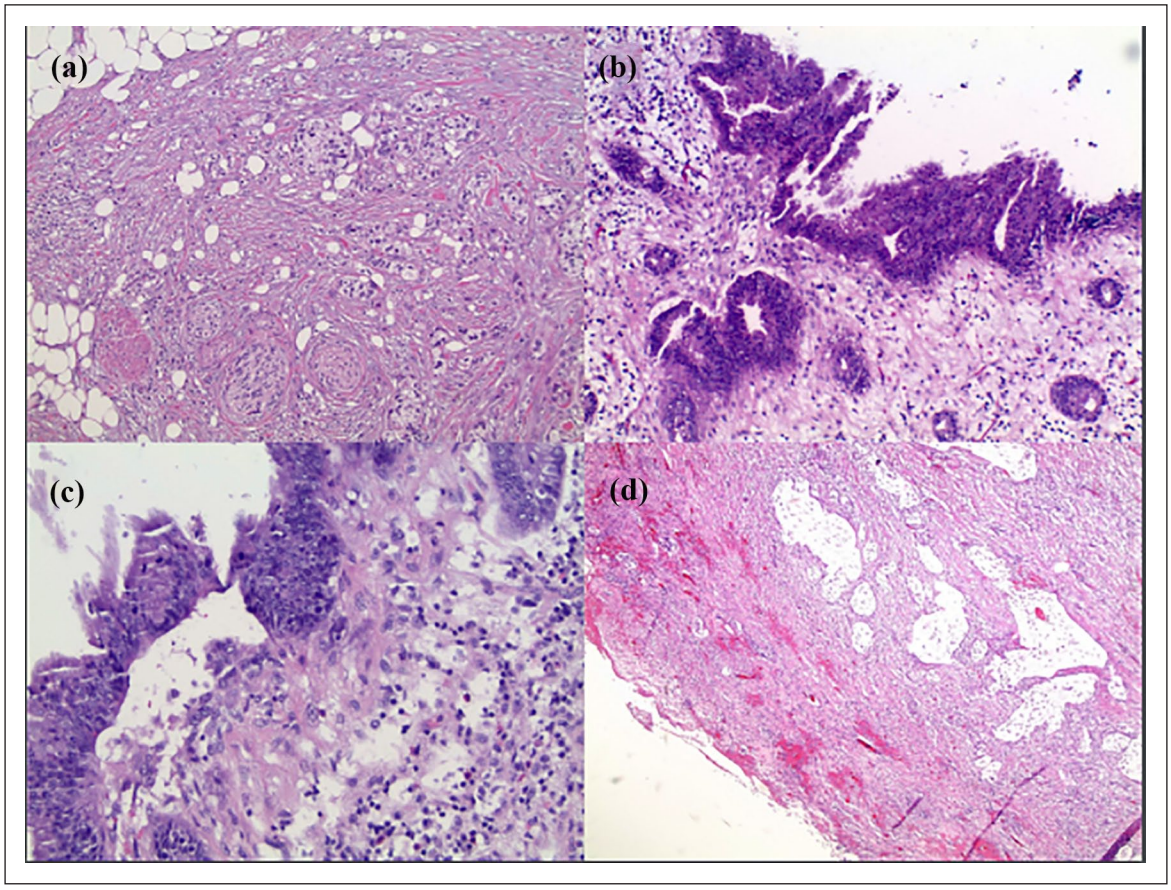

Figure 2. The appendix showed poorly differentiated metastatic prostate adenocarcinoma, involving the appendiceal wall with mesoappendix, perineural, and lymphovascular invasion (a). Besides the metastatic carcinoma, high-grade appendiceal mucinous neoplasm (HAMN) of appendix was also found incidentally, with acellular mucin extending to the muscularis mucosae in a background of mild focal early acute appendicitis (b, c, d).

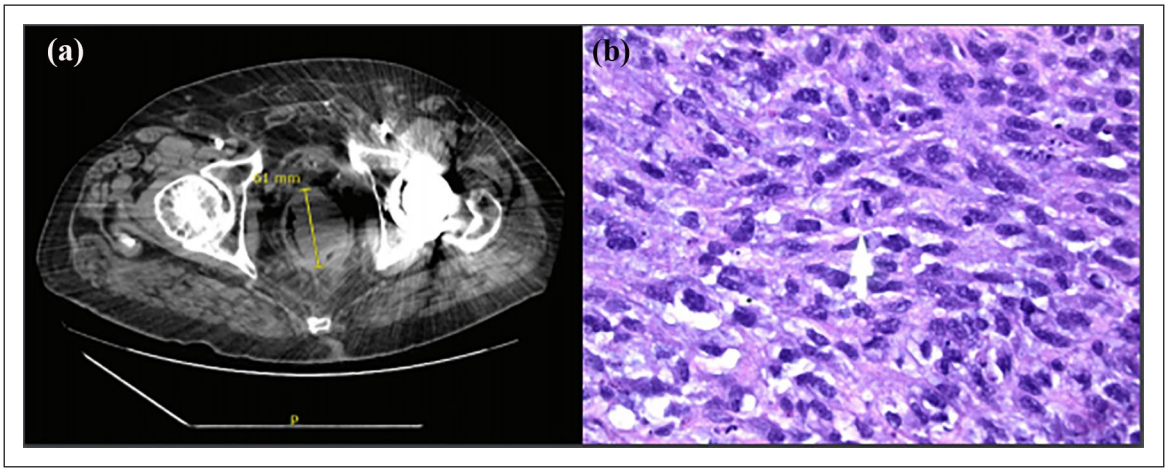

Figure 3. An abdominal CT showed a 6.1 cm large heterogeneous rectal mass (a) and biopsy showed a poorly differentiated malignancy with spindle cell features (b).

on histologic examination. When he presented with right lower-quadrant pain with imaging supporting acute appendicitis and intra-abdominal abscess, he was prescribed an antibiotic regimen. Antibiotic therapy as a treatment for appendicitis secondary to metastatic cancer may not be beneficial and may actually be harmful due to delay of treatment

of the metastasis. The mean age of a patient diagnosed with acute appendicitis is between 24 and 25 years old.[16] An elderly patient who presents to the emergency department with signs and symptoms mimicking acute appendicitis must be worked up for a malignancy. It was only after appendectomy that metastatic prostate cancer was seen with a background of HAMN. There are no case reports in the literature describing metastatic prostate cancer presenting as acute appendicitis in a background of HAMN. The incidence of concurrent HAMN and metastatic prostate cancer is rare. Certain clinical signs should increase suspicion for malignancy. Unlike acute appendicitis, AMNs tend to occur in patients in the sixth decade of life.[25] Therefore, if an older patient particularly with a history of malignancy presents with clinical signs and symptoms of acute appendicitis, a neoplastic etiology must be ruled out.

Our patient was prescribed TRT twice due to low testosterone levels after his radiation therapy treatments. Testosterone treatment is generally contraindicated in patients with prostate cancer due to concerns of etiological recurrence or tumor progression, based on research by Huggins and Hodges in the 1940s on the role of androgen therapy in prostate cancer progression.[26–28] Recent studies have challenged this axiom that androgen therapy plays a major role in the progression and/or recurrence of prostate cancer.[29–33] These recent studies have raised a hypothesis that due to a limited number of androgen receptors, there is no increased harm by increased testosterone levels once there is androgen-receptor saturation. Despite the evidence provided by these recent studies, the recommendations today remain that testosterone therapy is typically contraindicated in patients with prostate cancer. The fact that our patient received testosterone therapy in the midst of a treatment plan for high-grade prostate cancer and later presented with tumor recurrence and progression is significant, and it is unclear to what extent the testosterone therapy contributed to his prostate cancer progression.

In addition to the concurrent HAMN and metastatic prostate cancer to the appendix, our patient complained of persistent abdominal pain, rapid weight loss, and B-symptoms status post-appendectomy. A large rectal mass diagnosed as a spindle cell sarcoma, likely secondary to previous radiation therapy, was diagnosed. Radiation-induced rectal cancers are rare and are commonly only seen many years after initial radiation therapy, with the highest risk being seen at least 10 years after therapy.[19] Our patient developed a large, aggressive sarcoma within 8 years after his initial radiation proton therapy.

Conclusion

Clinical history and a broad differential diagnosis are critical to evaluate when an older patient presents with signs and symptoms of acute appendicitis. It is important to keep a clinical suspicion for metastatic cancer, primary appendiceal neoplasms, or in our case a combination of both, when evaluating such a patient. In addition, primary treatment-related neoplasms can develop within 10 years of radiation therapy. These SPM must be ruled out, especially in the context of persistent malignant signs and symptoms after treatment.

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