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Case Report

Polypoid Large Intestinal Involvement of Metastatic Castrate-Resistant Prostate Cancer: A Case Report

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Keywords
Castrate-resistant prostate cancer · Gastrointestinal metastasis · Gastrointestinal bleeding · Large intestinal polyps

Abstract
Introduction: Prostate cancer most commonly metastasizes to the bone and lymph nodes. Gastrointestinal metastasis has been noted in the literature but appears to be an exceedingly uncommon phenomenon. Large intestinal involvement in particular has been reported on only a few occasions, and never concomitantly with small intestinal metastatic involvement. ***Case Report:*** We report the case of a 69-year-old gentleman with metastatic castrate-resistant prostate cancer with development of gastrointestinal symptomatology with extensive investigation eventually revealing small and large intestinal polyps subsequently confirmed to be representative of metastatic prostate cancer. ***Conclusion:*** This case demonstrates the importance of maintaining a wide differential diagnosis in the context of gastrointestinal symptomatology in malignancy. Thorough endoscopic evaluation may be necessary in such cases in order to identify potential metastatic malignancy in otherwise relatively unremarkable appearing polyps.

Introduction

We present the case of a 69-year-old male with lower gastrointestinal bleeding in the context of metastatic prostate adenocarcinoma with endoscopic evidence of discrete polypoid lesions in the small and large intestine, subsequently histologically confirmed to

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be representative of metastatic prostate adenocarcinoma. Involvement of the gastrointestinal tract by prostate cancer appears to be a rare phenomenon and is poorly characterised in the literature. To our knowledge, involvement of the large intestine is only described on a few occasions in existing literature, and never concomitantly with small intestinal involvement. The clinical ramifications of this unique presentation are not known. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000539783).

Case Report

We describe a case of a 69-year-old gentleman with metastatic castrate resistant prostate cancer initially diagnosed with localised disease in 2006. At this point, he had a radical prostatectomy, with histology confirming Gleason 3 + 4 = 7 disease. He received androgen-deprivation therapy in the form of leuprorelin acetate for 2 years in the adjuvant setting. His past medical history was significant for ischaemic heart disease, with prior coronary artery bypass grafting, peripheral vascular disease, type 2 diabetes mellitus (T2DM), hypertension, and hyperlipidaemia. Of note, his T2DM was poorly controlled with an HbA1c varying from 7.5 to 9% since his diagnosis of prostate cancer. He was managed with basal-bolus insulin. From a social perspective, he worked as a waterside labourer, was a lifelong non-smoker, and was fit and independent (Eastern Cooperative Oncology Group performance status = 0), living at home with his wife.

Unfortunately, his PSA became detectable in August 2018 at 2.84 ng/mL, gradually rising to 11.8 ng/mL in June 2019, representing a PSA doubling time of roughly 3 months. Prostate-specific membrane antigen – positron emitting topography (PSMA-PET) scan imaging demonstrated no bony uptake but did confirm metastatic involvement in several thoracic, retroperitoneal, and pelvic nodal stations. Most of these areas were only mildly enlarged and hence not visualised on CT. He was recommenced on androgen deprivation with a biochemical response. Unfortunately, his PSA began to rise again in 2020, with subsequent addition of enzalutamide. His response to second-generation androgen inhibition was short-lived, with a rising PSA within 9 months. He was enrolled on to CONTACT-02 clinical trial (clinicaltrials.gov ID NCT04446117) and commenced on combination of anti-programmed death ligand 1 inhibitor atezolizumab and multi-kinase inhibitor cabozantinib in January 2022.

The patient experienced significant gastrointestinal side effects, namely Common Terminology for Adverse Event (CTCAE) criteria grade 2 nausea and anorexia as well as grade 1 diarrhoea with around 5 kg of unintentional weight loss within first month of therapy. His symptoms abated very little with dose interruption of cabozantinib. He proceeded to have an oesophagogastroduodenosocopy and colonoscopy in April, with the paramount concern being that of immune-mediated gastritis/colitis. Both studies revealed no significant macroscopic abnormalities. Random biopsies of the oesophagus, gastric antrum, duodenum, and large bowel were mostly normal, with only mild superficial gastritis and ileitis noted. The patient subsequently continued on his trial treatment, with a presumed diagnosis of diabetic gastroparesis/enteropathy due to gastrointestinal autonomic dysfunction.

In August, an acute decline in haemoglobin levels from 114 to 87 g/L was noted on routine blood tests over the course of 3 weeks. The patient reported haematochezia over 3 weeks before which had not recurred. He denied melena or abdominal pain at this time. His anorexia continued although his nausea had actually improved from previous. He reported

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that his urine was very dark. Of note, there was no biochemical evidence of haemolysis, with a bilirubin and haptoglobin within normal limits. His urea at the time was normal.

Subsequently, he was referred for repeat endoscopic interrogation. His gastroscopy demonstrated moderate flat erosive gastritis in the antrum (Fig. 1) as well as moderate erythematous duodenitis in the 1st part of the duodenum (Fig. 2). Biopsies were collected from the antrum and duodenum. His colonoscopy proceeded without difficulty, with access to the terminal ileum. Mild erythema was noted in the ileum, with a small sessile polyp in the ascending colon (Fig. 3), which was resected with a cold snare and sent for histological analysis. Random biopsies were collected from the ileum, caecum, ascending colon, transverse colon, sigmoid colon, and rectum. He also had a capsule endoscopy, with the device reaching the caecum successfully at the end of the study. Extensive duodenitis and jejunitis were observed in the proximal half of the small bowel with no focal active bleeding.

The snared ascending colonic polyp demonstrated infiltration of the large bowel mucosa and submucosa by poorly differentiated cells of metastatic prostate carcinoma Gleason 4 + 5 = 9. These cells were described as epithelioid, arranged in rounded sheets, with probable lymphovascular invasion into the mucosa and the submucosa. Immunostaining revealed positivity for pan-cytokeratin and NKX3.1 with negative stains for LCA, Melan-A, SOX10, and p40. Biopsies taken from the small bowel revealed poorly differentiated malignant cells of similar morphology to those described earlier in the large bowel with background chronic reactive changes with evidence of mild villous blunting and associated hyperplasia of Brunner's glands, with patchy congestion. No epithelial dysplasia, erosion, or ulceration was noted. The histopathology is shown in Figure 4.

We attempted to delineate the extent of malignant gastrointestinal involvement further by arranging a PSMA-PET study. The study revealed extensive PSMA avid nodal and bone disease, as well as two small PSMA avid foci in the liver potentially representing early metastatic disease. In addition, there was evidence of extensive PSMA avid bilateral adrenal metastases. However, there was no evidence radiologically of involvement of the gastrointestinal tract. Subsequently, he proceeded onto docetaxel (75 mg/m^2 3-weekly) with an excellent PSA response (110–61 ng/mL) following 2 cycles.

Discussion

Prostate cancer is the second leading cause of cancer death in men worldwide [1]. Metastatic involvement occurs in around 15% of new cases [2]. Distant metastasis is a poor prognosticator, with the 5-year survival being 32% for stage IV disease, compared to almost 100% for earlier stages [3]. Patterns of metastatic involvement are well described in the literature. A large autopsy series revealed that bone is the most frequent site of metastasis, being involved in 90% of cases of metastatic disease. Other sites in descending order of frequency included lungs (46%), liver (25%), pleura (21%), and adrenals (13%) [4]. A rare, but previously described site of metastatic involvement is the gastrointestinal tract.

An extensive population-based analysis of patterns of metastatic spread in prostate cancer including over 70,000 patients revealed involvement of the "digestive system" in 2.7% of cases [5]. The definition of digestive system in this analysis, however, is broad, extending beyond the alimentary tracts to include the spleen and hepatopancreaticobiliary system. Specific involvement of the stomach, small intestine, large intestine, and rectum appears to be an extremely rare phenomenon.

Cases of prostatic metastases to the stomach have been reported [6, 7] and appear to be relatively more common than intestinal involvement. Cumulatively, it appears that three cases

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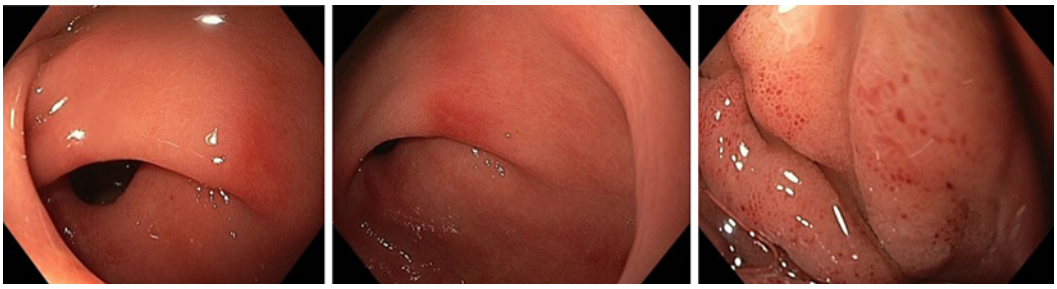

Fig. 1. Moderate flat erosive gastritis at endoscopy.

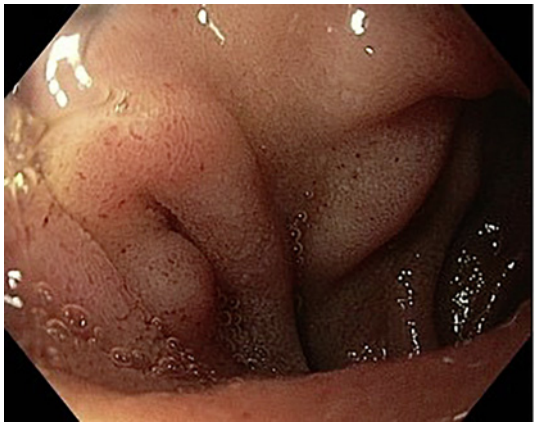

Fig. 2. Duodenitis at endoscopy.

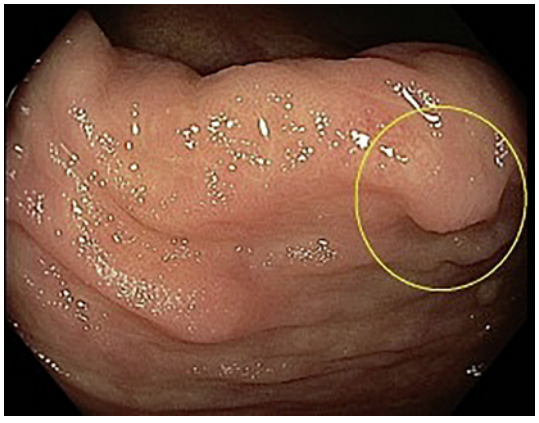

Fig. 3. Ascending colon polyp.

of small intestinal metastasis [8–10] and around 15 cases of gastric involvement have been described. Large intestinal involvement appears to be particularly infrequent, with isolated case reports described in 3 cases to our knowledge [11–13]. Concomitant discrete small and large bowel involvement by prostate cancer in the same patient has never been previously reported. Cases of intestinal involvement are summarised in Table 1 below. Peritoneal metastases from prostate cancer have also been identified. These appear to be associated with certain histological subtypes [14].

The precise mechanism of metastasis to the gastrointestinal tract is poorly understood. Prostate cancer preferentially metastasises to the lymph nodes and bone. Metastasis typically

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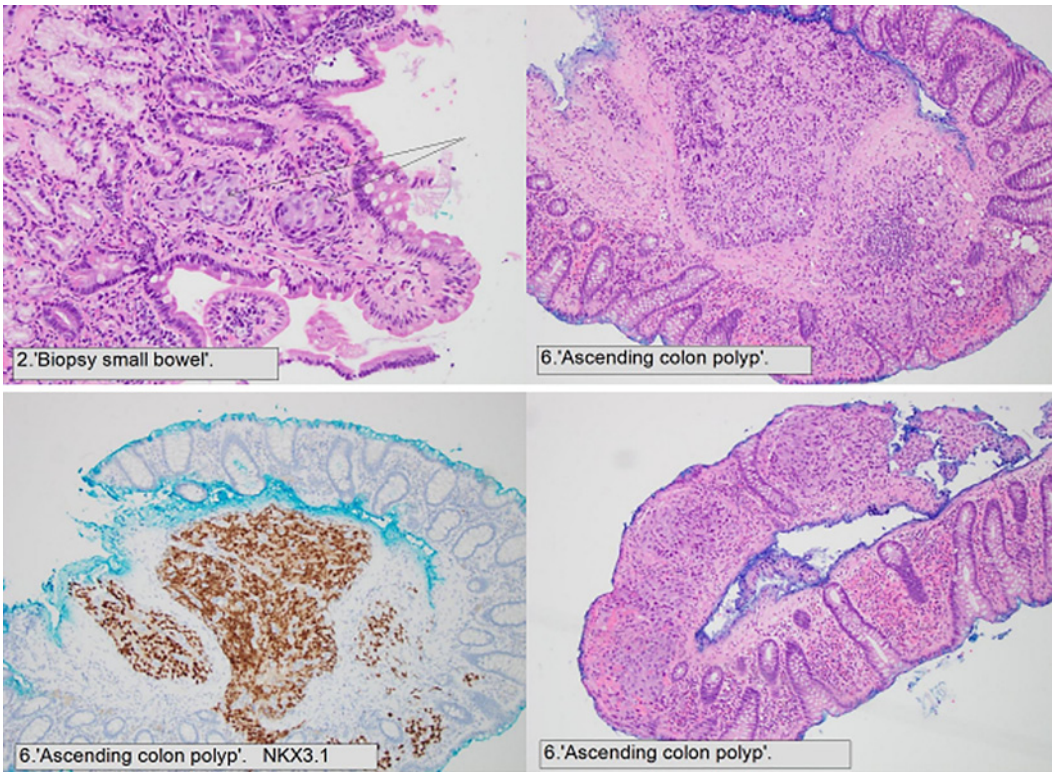

Fig. 4. Histopathology demonstrating metastatic involvement of small bowel and ascending colon by prostate cancer. NKX3.1 staining in bottom left quadrant.

occurs via lymphatic or haematogenous spread, or direct infiltration [5]. The gland is richly supplied by lymphatic channels, suggesting metastases develop through the lymphatic pathway [6]. Spread via the haematogenous cava-type system has also been proposed [5]. The metastatic process to the gastrointestinal tract, similarly to other sites, relies on the activation of cellular pathways mediated by cytokines and chemokines [15]. A complex series of events including extracellular matrix remodelling, epithelial-to-mesenchymal transition, tumour invasion, premetastatic niche creation, remodelling of the microenvironment and angiogenesis must occur [7].

The clinical ramifications of involvement of the gastrointestinal tract on diagnosis and outcomes are not clear. Rectal infiltration, for example, as commented by Llarena Ibarguren et al. [16], appears to confer a worse prognosis. Similarly, metastases to the stomach are associated with a worse prognosis, with an overall survival of 5–14 months [17]. In general, the presence of visceral prostate cancer metastases is an independent predictor of poor outcome [14].

Prostate cancer metastases to the gastrointestinal tract, albeit rare, present a diagnostic challenge for clinicians, especially due to the similar symptomatology of metastatic prostate cancer and a primary gastrointestinal malignancy. It is paramount to differentiate between the two when a patient presents with gastrointestinal symptoms, especially when there is a history of prostate cancer, to ensure appropriate management. It is difficult to distinguish metastatic prostate cancer from primary carcinoma using H&E staining alone [17].

Immunohistochemical stains that aid diagnostically include prostate-specific antigen (PSA), prostate specific acid phosphatase (PSAP) and alpha methylacyl CoA racemase

Table 1. Summary of reported cases of small and large intestinal metastasis from prostate cancer

Case	Reference	Age	Initial presentation	Site of metastasis	Endoscopic findings
1	Mahli-Chowla et al. [8], (2001)	69	Anasarca due to protein-losing enteropathy	Small intestine	Normal macroscopic appearance. Random biopsies showed infiltrating adenocarcinoma of prostate origin
3	Kaswala et al. [9], (2014)	42	Haematochezia and abdominal pain	Duodenum	Normal macroscopic appearance. Random biopsies showed lymphangitic carcinoma of prostate origin
4	Lee et al. [10], (2009)	81	Abdominal fullness, anorexia, and weight loss	Duodenum	Single soft tumour with hyperaemic mucosal change and luminal narrowing. Poorly differentiated carcinoma with positive PSA staining on biopsy
6	Patel et al. [11], (2014)	71	Fatigue, reduced exercise tolerance due to anaemia	Stomach and sigmoid colon	Sessile polyps in stomach and sigmoid colon, consistent with adenocarcinoma, with immunohistochemical pattern consistent with prostate origin
7	Kabeer et al. [12], (2007)	72	Abdominal discomfort, per rectal bleeding and abdominal mass	Caecum	No endoscopy. Right hemicolectomy performed for caecal mass presumed colorectal cancer. Histopathology consistent with adenocarcinoma staining positive for PSA
8	Tjarks and Muirhead [13], (2016)	78	Asymptomatic. Routine surveillance colonoscopy	Caecum	Polyp evident. Biopsy showing adenocarcinoma with PSA positivity

(AMACR) [6]. PSA and PSMA are most commonly used with high sensitivity and specificity [18]. AMACR, also known as P504S, is an enzyme upregulated in prostatic adenocarcinoma which has been used if diagnostic uncertainty remains [6].

Conclusions

This case illustrates the importance of maintaining a broad differential diagnosis for gastrointestinal symptomatology in the context of metastatic prostate cancer. The diagnosis of gastrointestinal metastasis may be confounded by patient comorbidities, such as poorly controlled T2DM, or toxicity of anticancer therapy, both of which were considered in our patient. Furthermore, in the absence of investigation for gastrointestinal bleeding, the patient may never have undergone repeat endoscopic interrogation. In addition, the macroscopic appearance of the polyp was relatively unremarkable and may have not been identified as sufficiently suspicious to merit proceeding with histological evaluation. As such, the phenomenon of gastrointestinal metastasis of prostate cancer may be under-reported in the literature. Further clarity is required regarding the pathophysiologic mechanism of gastrointestinal involvement and implications on prognosis. However, knowledge of this rare but

potentially symptomatic pattern of metastatic involvement may be useful in formulating a comprehensive differential diagnosis of gastrointestinal symptomatology in the context of metastatic prostate cancer.

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. This study protocol was reviewed and approval was obtained by the Clinical Innovation and Audit Committee, Macquarie University (Ref: MQCIAC2023012).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Case report conceptualization and data curation: S.N. and A.A.; writing – original draft: S.N. and S.D.; writing – review and editing: S.N., A.A., and S.K.; supervision: H.G. and R.C.

Data Availability Statement

All data supporting the findings of this report are included in the article. Further enquiries can be directed to the corresponding author.

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