

Gastrointestinal metastasis in prostate cancer and therapeutic implications: A case report

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Abstract. Prostate cancer remains one of the most commonly diagnosed malignancies in men globally, with a notable proportion presenting at the metastatic stage. Whilst metastases predominantly affect lymph nodes, bones, lungs and liver, reports of metastasis to the digestive system are rare, posing unique challenges in prognosis and management. The present study reports a rare case of metastatic prostate adenocarcinoma to the colon, providing information on its clinical characteristics and therapeutic approach. The patient began hormonal intensification therapy resulting in a rapid decline in prostate specific antigen levels and a favorable clinical response over 3 years. Understanding the management of digestive metastases is crucial for optimizing patient outcomes. Diagnostic evaluation should include a colonoscopy, whilst therapeutic decisions are guided by hormonal therapy with or without chemotherapy. Local treatments have limited utility and molecular profiling aids in tailoring treatment strategies.

Introduction

Prostate cancer remains a major public health issue worldwide, being the second leading cause of death. In 2020, the number of cancer patients exceeded 50 million. Moreover, it accounts for >19 million new cases and nearly 10 million deaths globally

each (1). Approximately 10% of patients are diagnosed at the metastatic stage, according to data from sources such as the French National Cancer Institute. The therapeutic management of metastatic, hormone-sensitive prostate cancer has undergone a drastic evolution in the past decade, with intensification emerging as the standard therapeutic approach (2-7).

Whilst the primary metastatic sites typically involve the lymph nodes, bones, lungs and liver, reports of metastatic involvement in the digestive system are scarce. The prognosis and management of such cases are inadequately described in the current literature (8). In the present article, a rare case of prostate adenocarcinoma with metastasis to the colon is presented, providing information on its unique challenges and outlining the approach taken for its management.

Case report

The patient, a 72-year-old man, was initially asymptomatic but had a medical history of amebiasis and sigmoid colectomy due to diverticulosis. The family history of the patient included leukemia in a nephew and a brother, as well as micro-satellite stability colonic cancer in a daughter (diagnosed at 45 years old) and a brother (diagnosed at 50 years old). Due to this familial predisposition, the patient underwent regular colorectal cancer screenings, involving colonoscopies with resection of low-grade dysplastic polyps.

In January 2020, during a routine screening at Bégin Military Hospital (Saint-Mandé, France), three sub-centimeter polyps were resected. A total of two were conventional colonic adenomas with low-grade dysplasia, whilst the third consisted of non-signet-ring isolated cells forming small clusters, occasionally with small lumina, infiltrating the lamina propria between normal colonic glands (Fig. 1A). Immunohistochemical staining demonstrated diffuse positivity for NK3 homeobox 1 (NKX3.1; Fig. 1B), cytokeratin AE1/AE3 and prosaposin (PSAP), and negativity for caudal

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type homeobox 2, transcription termination factor 1, GATA binding protein 3 and paired box 8 (Fig. 2). Due to the high specificity and sensitivity of NKX3.1 for prostate adenocarcinoma, with negative markers not suggesting intestinal, pulmonary, urothelial or renal primary cancer, the presented staining profile required further clinical investigation to identify if there was a prostatic primary with metastasis to the colon (9).

Following this unexpected potential diagnosis, a prostate specific antigen (PSA) test revealed an elevated level of 1,286 ng/ml (reference range, 0–4 ng/ml). Imaging studies, including a thoraco-abdomino-pelvic CT scan, showed diffuse secondary bone lesions, pelvic and retroperitoneal lymphadenopathy and prostatic hypertrophy without identifiable suspicious lesions (Fig. 3). Bone scintigraphy demonstrated a ‘super bone scan’, indicative of diffuse osteomedullary involvement (Fig. 4).

Prostate needle biopsy (Fig. 5) showed a Gleason score of 4+5=9 adenocarcinoma [The International Society of Urological Pathology (ISUP) grade group 5] (9). Gleason pattern 5, consisting of single cells infiltrating prostatic tissue, appeared morphologically similar to those seen in the colonic lesion of the patient which stained positive for NKX3.1 (8). Finally, as subsequent investigations into the initial histological observations revealed an aggressive prostatic primary tumor by PSA test and prostate needle biopsy, the clinical and histological data were consistent with a metastatic prostatic adenocarcinoma with a rare colonic metastasis.

The patient underwent molecular screening of the prostate and colonic metastases tissues, as well as circulating tumor DNA (ctDNA) and germinal screening, all of which were negative (data not shown). Saliva and blood samples were analyzed for germline alterations using the Invitae Multi-Cancer panel, which includes the Fanconi anemia complementation group A gene. Plasma derived from blood was also tested for cell-free DNA using the Resolution ctDx HRD™ assay by Exact Sciences. Additionally, tumor tissue was analyzed to detect tumor-derived alterations using the FoundationOne® CDx test by Foundation Medicine, Inc.

The treatment choice for the patient was based on three key factors: i) The prognosis of the disease, which was poor due to visceral involvement; ii) the patient and comorbidities, particularly age; and iii) the maintenance of quality of life. Based on these points, two options were possible: i) Intensification with androgen deprivation therapy (ADT) + androgen receptor pathway inhibitor (ARPI); or ii) a triplet with ADT + abiraterone acetate (AA) + docetaxel or ADT + enzalutamide + docetaxel. Data from PEACE 1 indicate that for patients aged >70 years old, there is no overall survival (OS) benefit from the triplet, and it is associated with a marked increase in adverse effects, such as cardiovascular issues and cytopenias (7). In the ENZAMET study, which evaluated the combination of ADT + enzalutamide + docetaxel compared with the standard arm of ADT +/- docetaxel, no benefit was demonstrated for the enzalutamide + docetaxel combination (10). All trials evaluating intensification with a doublet have demonstrated a clear OS benefit for this population, along with a marked improvement in quality of life, as measured by standardized scales (7,10). Therefore, the doublet was chosen as the therapeutic option for the patient in the present case.

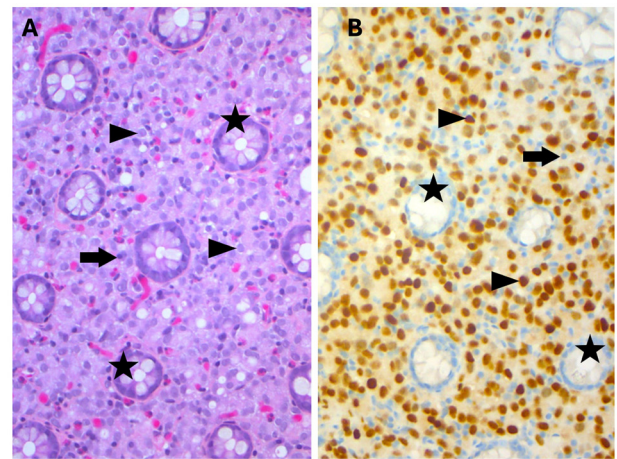


Figure 1. Light microscopy of a colonic polyp. (A) H&E staining showing infiltration of lamina propria of colonic mucosa by tumoral non-signet-ring single cells (arrowheads), normal and evenly distributed colonic epithelial crypts (stars) and background inflammatory cells (arrows). A destructive pattern or epithelial dysplasia would be expected in a carcinomatous colonic primary, which was not present in the current case. (B) Immunohistochemical staining demonstrated positive NKX3.1 staining with both strong and diffuse nuclear staining. NKX3.1 staining was observed in all tumoral single cells (arrowheads), whereas epithelial cells of normal colonic crypts (stars) and background inflammatory cells (arrows) were negative (both appearing blue), serving as internal negative controls. Positive staining for NKX3.1 is highly indicative of a prostatic primary tumor. Magnification, x200. NKX3.1, NK3 homeobox 1.

The patient began anti-hormonal treatment with the gonadotropin hormone-releasing hormone antagonist, degarelix, at an initial dosage of 240 mg, administered only once, followed by an 80-mg injection 1 month later, which was then repeated monthly, leading to a rapid decline in PSA levels to 687.5 ng/ml at 15 days. After 1 month, an androgen synthesis inhibitor, abiraterone acetate, was also administered at a dosage of 1,000 mg/day, orally. The patient showed a rapid, clinical, biological (PSA <0.02 ng/ml at 6 months onwards) and radiological response over a 3-year period, indicating successful disease management, 3 months of the initiation of the association. The patient experienced no side effects aside from grade 1 hot flashes, decreased libido and mild grade 1 anxiety, according to the CTCAE version 5 (11).

Monitoring of efficacy and tolerance was conducted through telemonitoring and an in-person medical visit every 3 months.

Histology. Specimens were fixed in 10% neutral buffered formalin (4% formaldehyde solution) at room temperature (20–25°C) for 24–48 h depending on the size and type of tissue. After fixation, the tissue was processed using a series of alcohols for dehydration (70, 80, 95 and 100%) and xylene for clearing, followed by embedding in molten paraffin wax at 58–60°C. The paraffin block was cut into 4- to 5-μm sections. The slides were then incubated in xylene to remove paraffin wax, followed by rehydration through graded alcohols (100, 95 and 70%) to water. The slides were incubated in hematoxylin for 3–5 min at room temperature and then rinsed under running tap water for 1–2 min. Differentiation was performed in acid alcohol (optional) and bluing in alkaline water or Scott's tap water substitute for 30 sec. Slides were immersed in eosin for

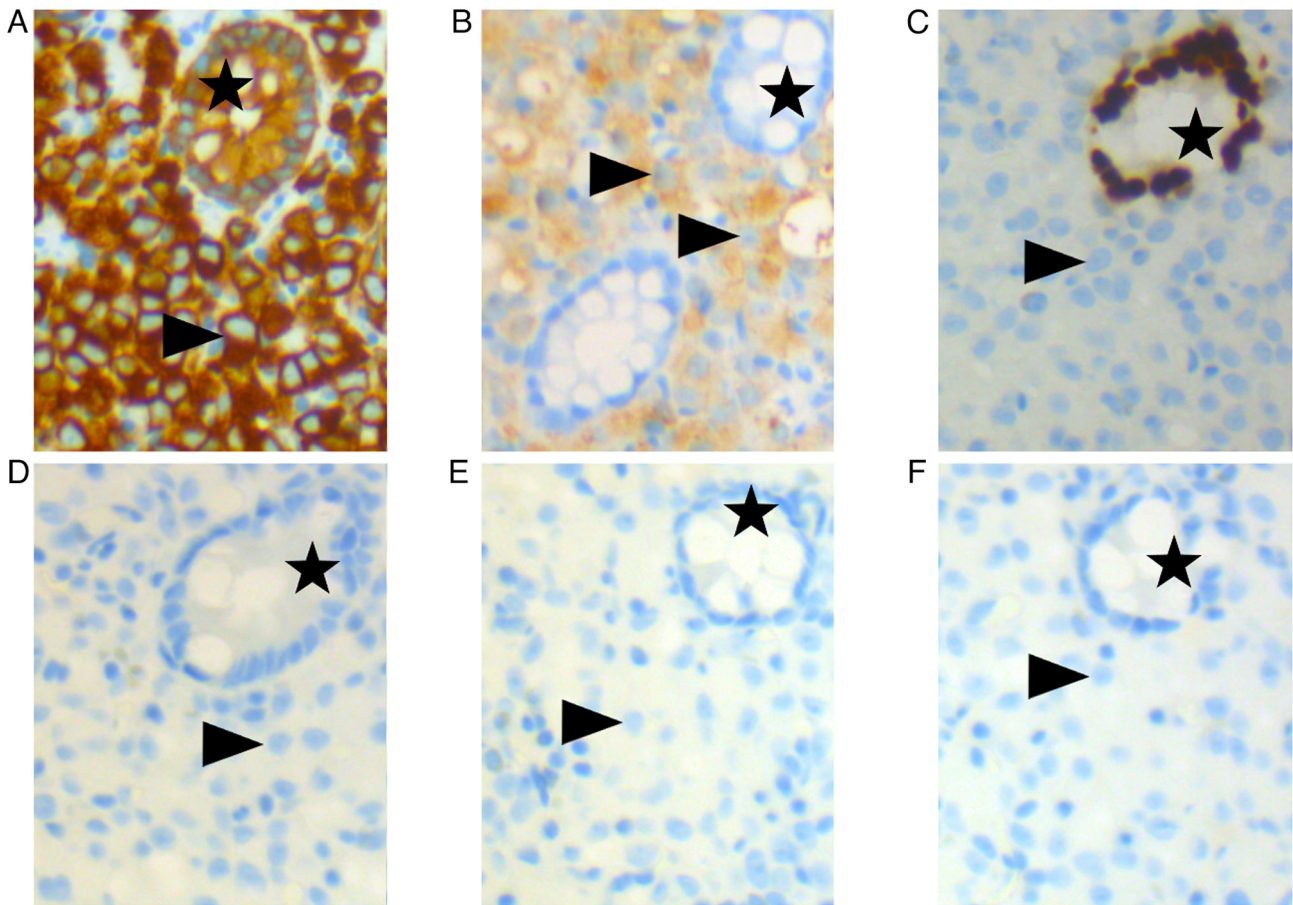


Figure 2. Immunohistochemical staining performed on a colonic polyp. (A) Positive, brown-colored cytoplasmic staining of cytokeratin AE1/AE3 was observed in tumoral single cells (arrowheads), indicating an epithelial nature, and in cells of normal colonic crypts (stars), which serve as a positive internal control. (B) Positive cytoplasmic staining of prosaposin was observed in tumoral single cells (arrowheads), suggesting, in addition to NK3 homeobox 1, a prostatic primary, whereas normal blue-colored cells of normal colonic crypts (stars) were negative. (C) No nuclear stain was observed in tumoral single cells (arrowheads) stained with caudal type homeobox 2 antibodies, suggesting this was not an intestinal primary, whereas cells of normal colonic crypts (stars) were positive, serving as a positive internal control. No nuclear stain was seen in tumoral single cells (arrowheads) with (D) transcription termination factor 1, (E) GATA binding protein 3 and (F) paired box 8 antibodies, nor in cells of normal colonic crypts (stars); therefore not indicating a lung, urothelial or kidney primary. Magnification, x200.

1-2 min at room temperature. For dehydration, slides were passed through graded alcohols (70, 95 and 100%) and cleared in xylene. Finally, the slides were mounted with a coverslip using a mounting medium. A brightfield microscope was used for observation.

Immunohistochemical staining was performed using a Ventana Benchmark Ultra stainer with UltraView Universal DAB Detection Kit (Roche Diagnostics). Positive staining for NKX3.1 (EP356 clone; Bio SB, Inc) is highly indicative of a prostatic primary tumor. Immunohistochemical staining was performed on a colonic polyp. Positive, brown-colored cytoplasmic staining of cytokeratin AE1/AE3 (PCK26 clone; Roche Diagnostics) was observed in tumoral single cells, indicating an epithelial nature, and in cells of normal colonic crypts (stars), which served as a positive internal control (Fig. 2A). Positive cytoplasmic staining of prosaposin (PASE/4LJ clone; Cell Marque™; Sigma-Aldrich; Merck KGaA) was observed in tumoral single cells, suggesting, in addition to NK3 homeobox 1, a prostatic primary, whereas normal blue-colored cells of normal colonic crypts (stars) were negative (Fig. 2B). No nuclear stain was observed in tumoral single stained with caudal type homeobox 2 antibodies (PASE/4LJ clone; Cell

Marque™; Sigma-Aldrich; Merck KGaA), suggesting this was not an intestinal primary, whereas cells of normal colonic crypts were positive, serving as a positive internal control (Fig. 2C). No nuclear stain was seen in tumoral single cells with transcription termination factor 1 (SP141 clone; Roche Diagnostics) (Fig. 2D), GATA binding protein 3 (L50-832 Clone; Zytomed Systems GmbH) and paired box 8 (MRQ-50 clone; Cell Marque™; Sigma-Aldrich; Merck KGaA) antibodies, nor in cells of normal colonic crypts; therefore not indicating a lung, urothelial or kidney primary (Fig. 2E). Magnification at x200 was used.

Discussion

Globally, a total of ~10% of patients presenting with prostate cancer are at a metastatic stage (12). A previous meta-analysis demonstrated that the baseline presence of visceral disease is a negative prognostic factor and the distribution of metastases markedly influences OS (13). Most patients with prostate cancer present with bone metastases, either with (72.8%) or without lymph node involvement, followed by visceral disease (20.8%) and lymph node-only disease (6.4%). Liver metastases

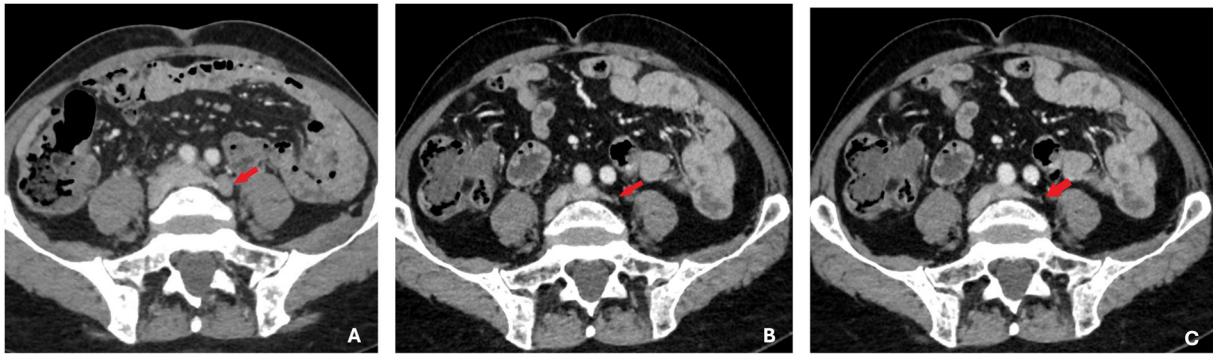


Figure 3. Iconographic evaluation. (A) Initial thoraco-abdomino-pelvic scan at baseline, performed during the portal phase after intravenous injection of contrast agent, revealed pelvic and retroperitoneal lymphadenopathies on the abdomino-pelvic slices. A left primitive iliac lymphadenopathy (arrow) was selected as a target. CT follow-up at (B) 5 and (C) 15 months after the start of treatment demonstrated a complete response, with the short axis of the left primitive iliac lymph node becoming millimetric.

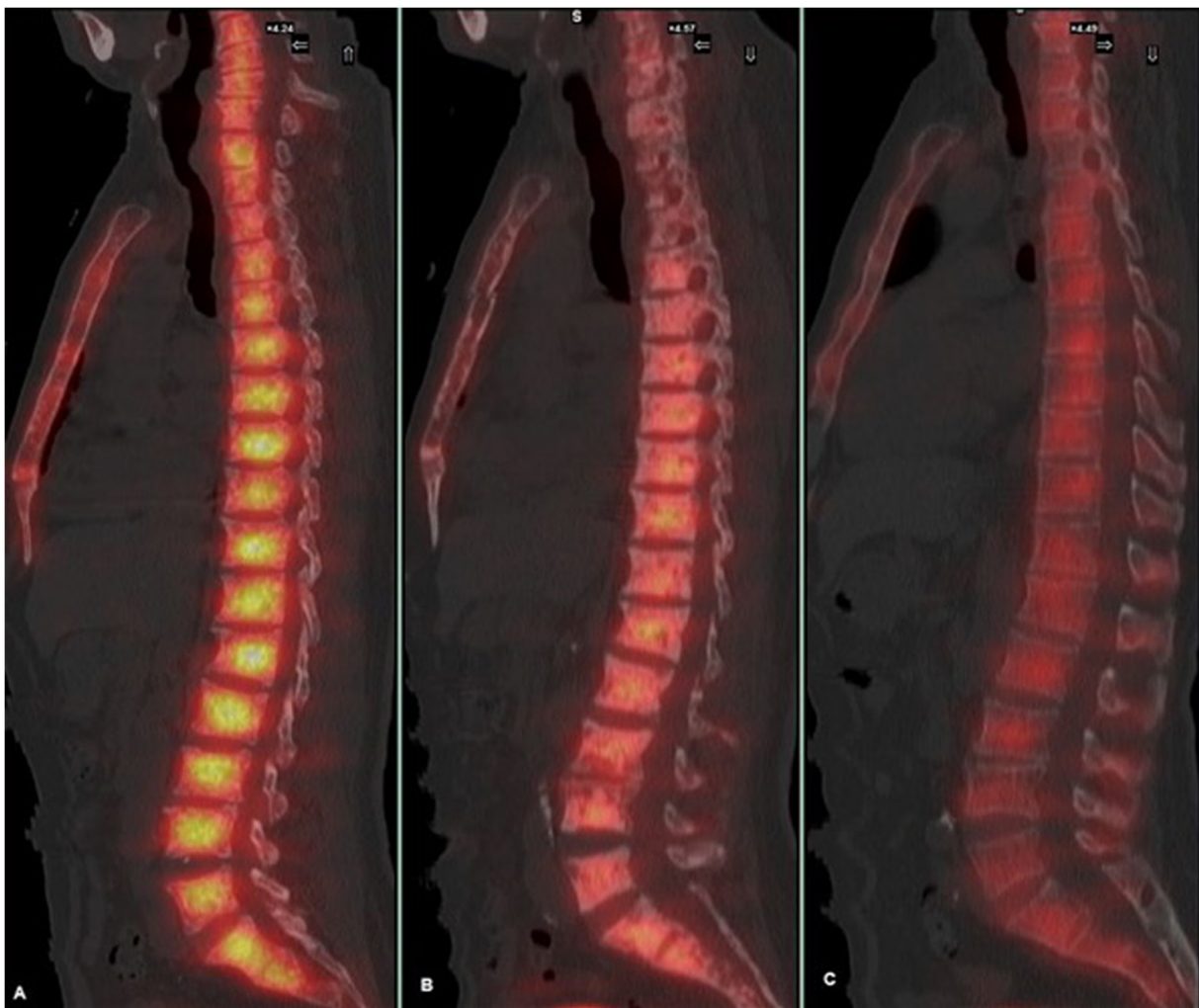


Figure 4. Single-photon emission computed tomography in sagittal sections. (A) The osteomedullary lesions initially showed a mixed pattern, with a predominance of sclerotic (condensing) changes. (B) After initiation of treatment, a marked increase in the osteo-condensing nature of the lesion appeared, potentially linked to osteolytic metastases in the regressive phase taking on an osteo-condensing appearance under treatment. (C) A total of >2 years after the implementation of the treatment, almost complete disappearance of the scan lesions and normalization of the scintigraphic fixation was observed.

are associated with the shortest median OS (13.5 months), whilst lung metastases have shown an improved median OS (19.4 months) compared with liver metastases, but worse than non-visceral bone metastases (21.3 months). Lymph node-only

disease is associated with the longest median OS (31.6 months). Furthermore, hazard ratios for mortality are markedly higher in men with lung or liver metastases compared with those with bone metastases (13). However, there is limited data on other

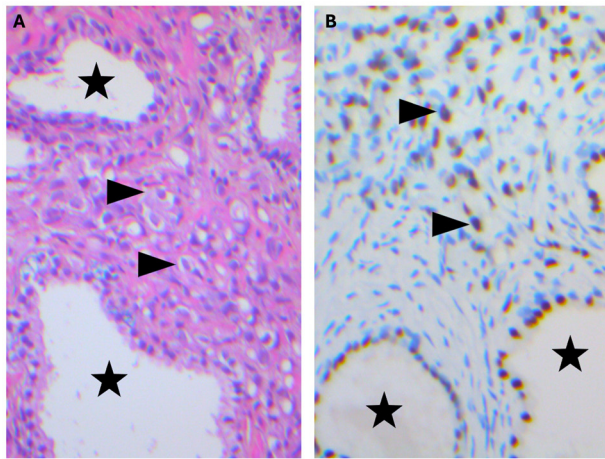


Figure 5. Light microscopy of prostate needle biopsy. (A) H&E staining showing single tumoral cells (arrowheads) infiltrating prostatic tissue between normal prostatic glands (stars), graded as Gleason pattern 5. (B) Immunohistochemical stain performed with NK3 homeobox 1 antibodies showing positive nuclear staining in tumoral single cells (arrowheads), in the tumoral single cells of the colonic polyp and in cells of normal prostatic glands (stars), indicating a prostatic primary and normal prostatic tissue. Magnification, x200

metastatic sites. Gandaglia *et al* (8) reported that digestive locations accounted for 2.7% of metastatic sites. Among patients with exclusively digestive metastases, 52% had additional concomitant metastatic sites; however, only 2.7% of patients with digestive metastases presented a second metastatic site in bone (8).

To the best of our knowledge, the present case report is the 9th published case of a patient with prostate cancer presenting with secondary digestive localization (13-21). The majority of patients (n=7) presented with a metastatic metachronous evolution with a long disease-free interval. Patients presenting synchronous disease have histologically demonstrated a more aggressive form (ISUP >4, Gleason score >7) (22). The circumstances of discovering metastatic digestive disease of prostate cancer were often noisy digestive symptoms, more closely resembling those of a primary colorectal origin. Only a few patients reported urinary symptoms, which, from an endoscopic perspective, could initially suggest a primary digestive pathology. Nevertheless, immunohistochemical analysis is essential, particularly with specific markers of prostate cancer such as NKX3.1.

The present clinical case is one of the only cases with molecular biology data at the tissue, germinal and ctDNA levels. In the present case, no anomalies were identified. However, Swami *et al* (23) presented differences in the genomic, transcriptomic and immune landscape of prostate cancer based on the site of metastasis at the American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium (2024). Different molecular and immunological profiles between the primary and metastatic sites were reported, explaining distinct evolutions and providing avenues for therapeutic adaptation. For these patients, a complete colonoscopy must be performed to assess the volume of the disease, in addition to a bone and CT scan. Moreover, molecular screening on the metastatic site should be performed.

The management of patients with prostate cancer has markedly evolved in previous years, with the addition of a second-generation hormonal therapy +/- docetaxel to

ADT. However, to date, no study has included this digestive metastatic site, to the best of our knowledge, and therapeutic management remains challenging. Data from the literature suggests a notable role for local treatment +/- ADT in patients with secondary digestive localization (13-21).

Similar to the patient in the present case report, patients with digestive localization, according to the CHAARTED classification, are classified as high volume (visceral metastases and/or 4 bone metastases, including at least one outside the pelvis and spine) (2). Furthermore, if there is the presence of >3 bone lesions and/or Gleason >7, the patient will be classified as high risk, according to the LATITUDE classification. The patient in the present case report was thus classified as high volume and high risk, with >4 bone locations, a Gleason score of 9 and the presence of visceral localization (2,3).

The high-risk classification of the patient according to the CHAARTED and LATITUDE criteria warranted a more aggressive treatment approach (2,3). Based on the data from STAMPEDE and PEACE 1, primary radiotherapy does not provide a survival benefit to high risk patients (7,24). The combination of ADT + ARPI has demonstrated a survival benefit for high risk patients regardless of the molecule used (AA, enzalutamide, apalutamide) (2-5). The PEACE 1 and ARASENS studies (6,7) reported a benefit from adding docetaxel to the ADT + ARPI doublet, which could be an option for the present patient. For the patient in the present study, a doublet was chosen to limit side effects. Moreover, there is no reported benefit of the triplet ADT + AA + docetaxel in patients aged >70 years old. In addition, considering the high metastatic volume and comorbidities of the patient and potential side effects, the decision to avoid chemotherapy and radiotherapy was taken to provide a tailored and less burdensome therapeutic regimen. Despite the severe initial prognosis of the patient, the sustained reduction of their PSA levels markedly improved their prognosis. The use of PSA and its reduction and duration are key tools in the management of the patients.

At present, the triplet treatment with the combination of ADT + darolutamide + ARPI could be considered, as it has demonstrated a benefit in the high-volume hormone-sensitive metastatic population, with this benefit maintained in patients aged >70 years old (6). However, this treatment option was not available at the time of the present case.

Despite the valuable insights gained from the present study, the small sample size, unique case presentation and absence of randomized controlled trials limit the generalizability of the findings, highlighting the need for larger studies and further research to validate and expand upon these conclusions.

In conclusion, although digestive localizations are infrequent, understanding their management is essential to maintain the benefit in OS. Thus, a complete colonoscopy is an indispensable complementary examination for diagnosis. Therapeutic options are based on ADT + ARPI +/- docetaxel, considering the clinical status and history of the patient. There is currently no role for local treatment of prostate cancer with secondary digestive localization. A molecular biology examination should also be performed to inform the choice between doublet and triplet therapies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MAA, ATN, EP, JLL, DL, CH, MP, HP, ALR, AB, MD, HV and AS made substantial contributions to the conception of the work; the acquisition, analysis, interpretation of data; or the creation of new software used in the work; drafted the work; and approved the submitted version; and agreed to be personally accountable for the their own contributions. MA and CH confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the local ethics committee, Bégin Military Hospital and the national ethics committee, Sud-Ouest et Outre-Mer II (approval no. 2020-A0003138).

Patient consent for publication

The patient, as a participant in a larger study, provided written informed consent for the publication of their data and gave additional verbal consent specifically for the publication of the present case report, including the use of their data and images.

Competing interests

The authors declare that they have no competing interests.

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