Case Report

in

Unusual small bowel metastatic localization in a castration-resistant prostate cancer patient

Francesca Maines*[,1], Orazio Caffo[1], Antonello Veccia[1] & Enzo Galligioni[1]

[1]Medical Oncology Department, S. Chiara Hospital, Largo Medaglie d'Oro 9, 38122, Trento, Italy

*Author for correspondence:
Tel.: +39 0461 902121
Fax: +39 0461 903364
francesca.maines@apss.tn.it

Practice points

- The availability of active new drugs has changed the natural history of advanced castration-resistant prostate cancer, significantly improving overall survival and thus leading to an increased risk of observing metastases in atypical sites.
- Bone and lymph nodes are usually the most frequent sites for distant metastases arising from prostate cancer. Visceral metastases are rare and when they occur, they usually involve the liver and lungs.
- The gastrointestinal (GI) tract is usually directly invaded from adjacent organs or enlarged lymph nodes. Hematogenous or lymphatic spread from prostate cancer to GI tube is uncommon, but the incidence seems to be increasing.
- The presenting symptoms of GI metastases, such as nausea, vomiting and abdominal pain and body weight loss are usually nonspecific, and all of them are often related to anticancer treatments or progressive disease.
- In patients with a history of prostate cancer and new-onset GI symptoms, GI metastases should be considered in the differential diagnosis.

The introduction of docetaxel into clinical practice and the more recent availability of other active therapeutic options, such as cabazitaxel, abiraterone acetate, enzalutamide and radium-223, have significantly improved the clinical outcomes of patients affected by castration-resistant prostate cancer (CRPC). Bone and nodes metastases are usually the first presentation of advanced disease, but the improvement in overall survival and the greater use of imaging techniques for restaging of metastatic CRPC patients have led to a previously unexpected clinical scenario characterized by an increased incidence of visceral metastases not only in the liver and lungs, but also in atypical sites such as the brain or gastrointestinal tract. We describe a rare case of CRPC metastasizing to the small bowel with particular endoscopic and radiographic findings.

Keywords: castration-resistant • prostate cancer • small bowel metastases

Presentation of case

This 71-year-old patient was diagnosed as having prostate adenocarcinoma (Gleason score 7: 4 + 3) in June 2000. The initial clinical stage was T3b N0 M0. After a short course of androgen deprivation therapy, the patient was treated by radical external radiotherapy from March 2001 to May 2001, and received 78 Gy in 39 fractions. In November 2008, after the occurrence of a biochemical relapse, the patient underwent androgen deprivation therapy until January 2011, followed by maximal androgen blockade because of further biochemical progression. In July 2011, an ^{18}F-choline positron emission tomography (PET) showed a metastatic spread to the retroperitoneal and pelvic lymph nodes. From July 2011 to October 2011, the patient

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received three courses of weekly docetaxel, which led to the normalization of prostate specific antigen (PSA) levels (from 16.53 to 1.2 ng/ml). In July 2012, after biochemical progression, a docetaxel re-challenge was proposed. Unfortunately, 3 months later, in October 2012, PSA levels increased and an ^{18}F-choline PET scan showed bone progression with the appearance of multiple skeletal metastases. From November 2012 to April 2013, the patient received enzalutamide but the treatment did not induce any biochemical or radiological response: PSA increased from 3.4 to 11.5 ng/ml, and an ^{18}F-choline PET showed the metabolic progression of bone and nodal metastases. It is worth noting that pathological ^{18}F-choline uptake around the head of the pancreas was also observed (Figure 1). The findings of a physical examination were normal except for tenderness of the lumbar spine; there were no abdominal signs. In June 2013, a new treatment with abiraterone acetate was started, but PSA levels continued to increase. A few months later, in October 2013, a new ^{18}F-choline PET not only revealed a further increase in the number and metabolic uptake of pathological abdominal lymph nodes and bone metastases, but also the appearance of supra-diaphragmatic lymph nodes. It also confirmed abnormal radiotracer uptake in the area around the pancreas head. A few weeks later, in November 2013, the patient underwent esophagogastroduodenoscopy because of the occurrence of nausea, weakness, occasional vomiting, abdominal pain and moderate body weight loss. The main endoscopic findings were a number of small white duodenal lesions with pale mucus but without any narrowing of the lumen; duodenum biopsies revealed a poorly differentiated adenocarcinoma (focal but significantly positive for PSA; negative for keratins 7 and 20), with the same morphological aspect of the primary prostate cancer, thus supporting a diagnosis of small bowel metastases arising from prostate cancer. Owing to the patient's progressive disease, medical history, previous treatments and worsened performance status, no further active anti-cancer treatments have been proposed, and the patient is currently receiving supportive care.

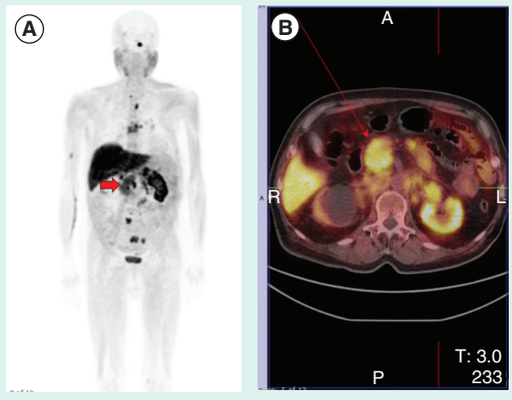

Figure 1. Abnormal ^{18}F-choline positron emission tomography uptake in the second portion of the duodenum, the site of small bowel metastases arising from prostate cancer.

Discussion

The small bowel is a rare site for metastases from distant primary tumors. Hematogenous or lymphatic spread to the small bowel is very rarely observed in the absence of peritoneal carcinomatosis or extrinsic bowel involvement from adjacent or contiguous organs such as the pancreas or gallbladder. Malignant melanoma, lung cancer or breast carcinoma (especially the lobular subtype) are the most frequent primary tumors leading to small bowel metastases [1,2]. In the case of prostate cancer, one series of 1589 autopsies performed from 1967 to 1995 showed metastases to the stomach or bowel in 1.8% of cases, thus confirming their rarity [3]. However, although bone and lymph nodes are the most frequent targets of metastatic spread, the incidence of visceral metastases arising from prostate cancer seems to be substantially increasing [4]. Improved overall survival, probably due to the availability of active anticancer therapies [5–9] and the consequent lengthening of the later phases of the disease, may be related to a greater risk of developing metastases in uncommon sites [10,11]. Moreover, the greater sensitivity of diagnostic procedures and the increasing number of patients undergoing radiological evaluation for the restaging of advanced CRPC have certainly increased the likelihood of detecting them. A retrospective study of 359 CRPC patients found that visceral metastases were detected by the last imaging evaluation before death in 32% of cases, and in 49% of the patients who underwent a radiographic assessment within 3 months of death [4], thus further confirming that visceral metastases are usually related to advanced disease. To the best of our knowledge, only three cases of small bowel metastases from prostate cancer have been reported in the last 40 years [12–14]. In the case observed by Lee *et al.* endoscopic findings of a solitary tumor lesion in the duodenum and the close proximity of the small bowel to known liver metastases and pathological retroperitoneal lymph nodes, suggested possible direct infiltration rather than a lymphatic or hematogenous spread of the primary tumor [12]. In the other two case reports [13,14], only random biopsies of normal small bowel mucosa revealed the presence of an adenocarcinoma with morphological aspects and immunohistochemical staining consistent with prostate cancer metastases. Our patient developed small

bowel metastases 13 years after the diagnosis of primary prostate cancer, and about 2 years after the development of CRPC with an extensive metastatic spread, thus confirming the findings of the cases mentioned above in which small bowel metastases were observed years after the diagnosis of prostate cancer in a clinical context of progressive CRPC involving different organs [12–14]. Our endoscopic findings were different from those described in previous case reports: the duodenal mucosa was covered by numerous small white lesions whose clearly pathological appearance led to biopsies being carried out. Furthermore, the endoscopic findings supported the hypothesis of hematogenous dissemination rather than direct infiltration from pre-existing contiguous metastases.

In this patient, hematogenous spread to small bowel has been hypothesized on the basis not only of endoscopic findings but also of the absence of a direct involvement from adjacent organs or enlarged lymph nodes. In similar cases of metastatic tumors, the blood-detection of circulating tumor cells (CTCs) could provide further evidence of hematogenous spread. In prostate cancer, CTCs isolated from peripheral blood seem to be useful to provide prognostic information, to predict treatment efficacy and to provide a noninvasive real-time liquid biopsy for molecular characterization of the disease, suggesting their promising role to guide patient management in the next future [15]. However, at this point, CTCs detection is currently still considered experimental and clinical and/or analytic validation of the role of CTCs in prostate cancer has yet to be established before their routine use can be considered.

Further mention needs to be made of the use of ^{18}F-choline PET and its findings. In our case, ^{18}F-choline PET restaging revealed the pathological radiotracer uptake not only in bone and lymph node metastases, but also around the head of the pancreas. This last finding, which was consistent with pathological uptake at the level of the secondary portion of the duodenum, may have aroused the suspicion of small bowel involvement. However, the rarity of this occurrence did not lead to its earlier recognition. It is worth noting that our case supports the view that this radiographic means of detecting GI metastases involving the small bowel is highly sensitive.

Small bowel metastases should be included in the differential diagnosis of prostate cancer patients developing gastrointestinal symptoms such as nausea, vomiting, abdominal pain or body weight loss because they may prelude severe complications such as severe GI bleeding, bowel obstruction or perforation arising shortly afterwards.

Future perspective

Recent reports of prostate cancer metastasizing to the stomach, peritoneum, pancreas and rectum [16–19] should increase the awareness of clinicians and radiologists that prostate cancer can present with metastases in atypical GI sites, contributing to an early detection, an accurate diagnosis and when feasible, appropriate management. Although the GIm-related symptoms are often being related to anticancer treatments, GI metastases from prostate cancer should be considered in the differential diagnosis, in order to early detect GI metastases at the time of the first occurrence of gastrointestinal symptoms, mainly in the future where the life expectancy of the patients affected by prostate cancer could be further prolonged by the availability of new active drugs also in early phases of the disease.

Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

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