Case report

Leptomeningeal involvement by prostate carcinoma an ominous head of a well-known Hydra

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SUMMARY

A 67-year-old male patient presents to the hospital complaining of severe nausea and vomiting failing oral antiemetics. He carries the history of initial diagnosis of stage III prostate cancer. He underwent radical prostatectomy followed by external beam radiation. After 5 years of initial excellent control with androgen deprivation therapy (ADT), imaging study showed retroperitoneal adenopathy denoting ADT failure. His prostate-specific antigen continued to rise while on enzalutamide and then abiraterone reflecting disease progression. He maintained excellent functional capacity through 23 cycles of docetaxel however he started developing hip pain after the last cycle with imaging studies suggesting new hip metastatic disease. Following the first cycle of radium-223, the patient presented with intractable nausea and vomiting. MRI showed a high suspicion of leptomeningeal spread which was confirmed through a meningeal biopsy after lumbar puncture showed negative results. The patient had excellent symptomatic response to high-dose dexamethasone. After receiving whole-brain radiation, the patient opted to be on best supportive care and succumbed to his illness 3 months later.

CASE PRESENTATION

A 67-year-old man with an initial diagnosis of stage III prostate cancer in 2011 with Gleason score 4+3=7. Patient underwent radical prostatectomy followed by external beam radiation therapy. Due to continuous elevation of prostate-specific antigen (PSA) after surgery, patient was started on androgen deprivation therapy (ADT) with leuprolide. After successful disease control for almost 5 years later, imaging done as part of the evaluation for left-sided abdominal pain revealed retroperitoneal lymphadenopathy. He was started on enzalutamide 160 orally mg once daily. The patient was later switched to abiraterone with prednisone due to persistent elevation of PSA denoting enzalutamide failure. Approximately 5 months later, repeat imaging showed the progression of disease with the new diffuse osteoblastic metastatic disease. During this time, the total testosterone level was 14 ng/dL, but PSA increased from 225 to 502 ng/mL corroborating castrate-resistant metastatic prostate cancer. The patient was started on docetaxel 75 mg/m² intravenous every 3 weeks in combination with prednisone. After 23 cycles of docetaxel chemotherapy, the patient complained of a decreased range of motion of the hip joint with PSA elevation. Imaging studies were

BACKGROUND

Prostate cancer is the most commonly diagnosed cancer in men. It is estimated that 164 690 new cases of prostate cancer will be diagnosed in 2018, accounting for 19% of new cancer cases in men. It is also estimated that prostate cancer will contribute to 9% of male cancer deaths in 2018 second to lung cancer.¹ Prostate cancer typically metastasises to pelvic lymph nodes and axial skeleton with visceral involvement occurring at late stages of disease course. Central nervous system (CNS) complications related to prostate cancer usually occur due to direct extension or pressure from bony structure to the brain or spinal cord rather than the haematogenous spread. Leptomeningeal involvement refers to the involvement of meninges of CNS by malignancy. Leptomeningeal involvement by prostate cancer is extremely rare with only few limited cases reported in medical literature. Due to rare incidence and poor prognosis, there is no definitive standard of care for treatment of such cases compared with leptomeningeal spread of lung and breast carcinoma. We are presenting a case of advanced castrate-resistant adenocarcinoma of prostate whose sole complain of persistent nausea and vomiting prompted the discovery of this unusual site of metastatic spread.

Figure 1 MRI brain with and without contrast axial view depicting diffuse dural enhancement with areas of nodular dural thickening (arrow).

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Figure 2 MRI brain with and without contrast coronal view depicting diffuse dural enhancement with areas of nodular dural thickening (arrow).

consistent with disease progression. Due to the painful bony metastatic disease, he was referred for radium-223 treatment with a palliative goal. After receiving first treatment session. The patient developed severe headache with protracted nausea and vomiting.

Figure 3 H&E stain at 200x magnification showing initial prostatectomy specimen with adenocarcinoma surrounding nerves (arrows) and focally extending into extra-prostatic adipose tissue (A). Leptomeningeal biopsy at 200x magnification revealing infiltrative tumour nests with vague glandular formation (B). At 400x magnification, the tumor is composed of sheets of mitotically active, crowded, hyperchromatic cells with prominent nucleoli (C). A prostate-specific antigen immunostain showing strong diffuse positivity of tumour cells, diagnostic of metastatic prostate adenocarcinoma (D).

INVESTIGATIONS

MRI of the brain with contrast (figures 1 and 2) showed abnormal thickening and enhancement throughout the dura. There was more focal thickening and enhancement to the anterior right dura measuring 20×7mm nodularity along the meninges concerning for leptomeningeal spread. Cerebrospinal fluid (CSF) analysed through lumbar puncture (LP) was negative for any malignant cells. A right temporal meningeal biopsy (figure 3) with immunohistochemical staining was positive for PSA staining confirmed metastatic prostatic adenocarcinoma with the leptomeningeal spread.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis before performing a biopsy included severe meningeal inflammatory reaction to radium-223 due to the presence of widespread skull metastases. Differential diagnosis also included a leptomeningeal spread of prostate cancer or intracranial spread. Diagnosis of the leptomeningeal spread was confirmed after a meningeal biopsy confirmed involvement.

TREATMENT

The patient was started on high dose dexamethasone with marked symptomatic improvement of headache, nausea and vomiting. The patient received whole-brain irradiation with symptomatic improvement but with a marked gradual decline of functional status.

OUTCOME AND FOLLOW-UP

Following radiation therapy, the patient opted to receive best supportive care and after 3 months he succumbed to his illness.

DISCUSSION

Adenocarcinoma of the prostate is the most common cancer in male population in united states and worldwide. It comes second as a leading cause of death among population of patient with cancer after lung cancer. According to SEER database 2008–2014, patients usually present with localised stage (78%) followed by regional spread to lymph nodes (12%) and widely spread metastatic disease (5%). The 5-year survival rate of all stages of prostate cancer is 98.2%. Nevertheless, the 5-year overall survival (OS) for metastatic disease remains at 30%.² This propitious OS data are possibly attributed in part to non-aggressive nature of prostate cancer in general and the abundance of treatment options between chemotherapy and ADT.

The largest cohort of a pattern of metastatic disease was reported by Gandaglia *et al* after studying 74 826 patients.³ The study showed the skeletal system to be the most common site of metastasis (84%), followed by distant lymph nodes (10.6%), liver (10.2%), thorax (9.1%) and brain (3.1%). Leptomeningeal involvement was not reported as a separate entity in that study. Site of metastatic disease appears to largely affect prognosis and OS, with skeletal metastatic denoting better prognosis compared with visceral disease.⁴

CNS metastatic disease and mostly involved structure are the leptomeninges (67%), followed by the cerebrum (25%) and cerebellum (8%).⁵ Rare case reports describing direct perineural neoplastic infiltration of prostate adenocarcinoma via the pelvic plexus to the lumbosacral plexus have been reported.⁶ In a retrospective study at MD Anderson, only 7 patients were diagnosed with leptomeningeal involvement out of 41 830 patients with prostate cancer between 1979 and 2011.⁷ Both studies were done in the pre-docetaxel era. The introduction of docetaxel as denovo treatment in patients with metastatic prostate cancer has

led to improved OS and quality of life,⁸ but increased incidence of unusual CNS metastatic disease.⁹ It is well understood that docetaxel has poor penetration through blood–brain barrier, thus while docetaxel is exhibiting excellent control of systemic disease, we are observing a surge in incidence of CNS metastatic disease. This surge in incidence was reported by Caffo *et al* in Italy who reviewed 943 cases of metastatic prostate cancer between 2002 and 2010 and identified 31 cases of leptomeningeal involvement by prostate cancer (LPMC) (incidence 3.3%).¹⁰

It is hypothesised that LPMC can occur through two different pathways; by haematogeneous spread through paravertebral plexus as described by Batson or through direct extension from skull metastasis.¹¹ Our patient had heavy skull involvement which might have penetrated to the meninges although a biopsy of skeletal tissue that was in direct contact with leptomeningeal deposit was negative for malignancy. Diagnosis of LPMC is made through cytology examination obtained through a lumbar puncture (LP). However, the sensitivity of a single cerebrospinal fluid (CSF) examination is only 50%, but increases to >80% when two analyses are performed and to 90% with three analyses.¹² The role of gadolinium-enhanced MRI is helpful in establishment or confirming LPMC especially among patients with negative LP.⁹ Unfortunately, clinical diagnostic criteria for LPMC is controversial and it remains difficult to diagnose. Specific MRI findings are considered highly suggestive but the confirmatory tests such as repeated CSF cytology or meningeal biopsy are invasive and are needed for pathologic confirmation. Often times due to late diagnosis, patients are symptomatic with decline in functional status which might limit the willingness to undergo invasive diagnostic procedures.¹³ In our case, the negative LP with the absence of intracerebral disease, and the patient preference to seek active treatment dictated the confirmation of LPMC through a meningeal biopsy. The differential diagnosis in our case included possible meningeal irritation from radium-223.

Due to the paucity of cases, there is no golden standard of care for patients with LPMC and treatment is usually individualised based on pathological diagnosis and patient presentation. Management options vary between steroids, CNS irradiation, intrathecal chemotherapy and surgery in selected cases. Neurosurgery intervention is limited to patients presenting with compressive symptoms or obstructive hydrocephalus. ADT can be administered in patients with castration-sensitive metastatic prostate cancer as the ADT mechanism of action is systemic rather than local.^{14 15} However, this scenario is extremely rare and patients with LPMC almost always present with castration-resistant metastatic prostate cancer. Lin *et al* described three cases of LPMC who were treated with CNS irradiation with encouraging results of decreased symptoms burden.⁹ Till now there are no published data to support safety or effectiveness of the administration of intrathecal chemotherapy except for single-institute single-case reports. Orphanos *et al* described marvellous improvement of patient symptoms after the administration of three intrathecal injections of methotrexate.¹⁶ Bernstein *et al* treated a patient with LPMC who presented with diplopia and third cranial nerve palsy with intrathecal liposomal cytarabine (ARA-C) with improvement of diplopia.¹⁷

Cabazitaxel is a new taxane that has shown promising improvement of overall survival (OS) for patients with metastatic castration-resistant prostate cancer whose disease has progressed during or after docetaxel-based therapy.¹⁸ This study has included patients with visceral metastasis but did not include patients with CNS metastasis although it was not one of the exclusion criteria. Cabazitaxel can become of essential importance for this group of patients as murine studies showed an increased concentration of

drug in mice brain with increasing dose of cabazitaxel suggesting efficient blood–brain barrier penetration.¹⁹

Contemporary research has led to the development of multiple active treatment modalities for men with metastatic castrate-resistant prostate cancer, in addition to ADT. Agents that interfere with androgenic stimulation (abiraterone, enzalutamide, apalutamide and darolutamide), immunotherapy (Sipuleucel-T), radium-223 and chemotherapy (docetaxel, cabazitaxel and mitoxantrone) have improved OS in phase III trials.^{8 18 20–25} As patients are currently living longer with newer therapies, few rare manifestations of common malignancies like in our case are being reported. Treating physicians should maintain a high vigilance for such rare manifestations of common malignancies as we are making progress with improvement in outcomes.

Learning points

- ▶ Leptomeningeal involvement by adenocarcinoma of the prostate was historically a rare complication among patients with metastatic prostate cancer.
- ▶ Oncology society is currently witnessing a surge in the incidence of leptomeningeal spread due to increased overall survival and poor penetration of docetaxel to blood–brain barrier.
- ▶ Currently, there is no standard of care for this unfortunate group of patients and symptom control remains the main aim of treatment with overall poor prognosis.
- ▶ In light of increasing incidence, further studies need to be conducted for the establishment of a standard of care.

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