Isolated brain metastases as first site of recurrence in prostate cancer: case report and review of the literature

J. Craig,* J. Woulfe MD,† J. Sinclair MD,‡ and S. Malone MD*

ABSTRACT
Fewer than 2% of patients with metastatic prostate cancer (PCA) develop brain metastases. Autopsy series have confirmed the rarity of brain metastases. When present, brain metastases occur in end stage, once the PCA is castrate-resistant and spread to other sites is extensive. Here, we present a rare case of a patient with PCA who developed a solitary parenchymal brain metastasis as first site of relapse 9 years after radical therapy. The patient underwent craniotomy and excision of the tumour. A second recurrence was also isolated to the brain. In the literature, PCA patients with brain metastases have a poor mean survival of 1–7.6 months. The patient in our case report experienced a relatively favourable outcome, surviving 19 months after his initial brain relapse.

Key Words Prostate cancer, brain metastasis, recurrence

INTRODUCTION
Prostate cancer (PCA) is the most common cancer in men and the 2nd leading cause of cancer death in North America1. Treatment and prognosis vary and depend on initial stage, Gleason score, and level of prostate-specific antigen (PSA). Localized PCA can be treated with either surgery or radical radiation. Adjuvant hormonal therapy is used for patients with high-risk disease.

Prostate cancer can recur locally or systemically. The two most common sites of metastasis are bone and lymph nodes. Other sites of metastatic disease such as lung and liver occur less frequently. Standard treatment for metastatic PCA is androgen deprivation therapy (ADT), which achieves mean durations of response in the range of 18–24 months.

Once PCA becomes castrate-resistant, it progresses at sites of initial metastatic disease, but it can also progress at other visceral sites. Brain metastasis and leptomeningeal disease are rare in PCA; they typically occur in patients with end-stage disease who are castrate-resistant. Patients with brain metastases have very limited survival. This case report presents a unique situation, in which the first and second recurrences in PCA were isolated to the brain.

CASE DESCRIPTION
A 79-year-old white man presented with increased urinary frequency. A digital rectal exam noted a mass in the right lobe of the prostate, and PSA was elevated at 5 μg/L. The patient had a past medical history of a carotid endarterectomy, hypertension, and hypercholesterolemia. A biopsy performed under transrectal ultrasonography guidance demonstrated a Gleason 6 prostate adenocarcinoma. The patient was referred for radiation oncology consultation.

Examination revealed a tumour occupying 75% of the right lobe without extracapsular extension. The patient was diagnosed with clinical T2B, Gleason score 6 PCA. Options including surveillance, radiation, and hormonal therapy were discussed. The patient was treated with combined external-beam radiotherapy (76 Gy) and 6 months of adjuvant ADT (6 months of oral bicalutamide 50 mg daily, and two subcutaneous injections of goserelin 10.8 mg). Follow-up digital rectal exam showed a complete clinical response, with no palpable tumour. No residual cancer was evident on a 2-year post-treatment prostate biopsy. At 5 years after radical treatment, the patient’s PSA level was 0.2 μg/L.

Nine years after radiotherapy treatment, the patient developed biochemical recurrence with a rising PSA (to
3.23 μg/L from 0.1 μg/L within a period of 6 months). The patient remained asymptomatic, and no evidence of clinical local recurrence was observed.

In November 2012, cancer restaging was performed. Abdominopelvic computed tomography imaging and chest radiography showed no metastases. On bone scan, a small focus of radiotracer uptake was observed in the right frontotemporal lobe of the brain parenchyma, without involvement of any of the frontal or temporal flat bones of the cranium. The remainder of the bone scan was negative. The radiologist was concerned about the possibility of a coincidental malignant or benign primary brain tumour, such as a meningioma.

Magnetic resonance imaging (MRI) revealed a 3.5-cm right frontal intra-axial enhancing lesion with central necrosis and surrounding vasogenic edema (Figure 1). The solid component of the tumour had low signal intensity on T2 weighting and demonstrated restricted diffusion. No other mass or enhancing lesions in the brain, skull, or leptomeninges were noted. The differential diagnosis included a high-grade glioma and metastatic disease, and the patient was referred to a neurosurgeon (JS). The patient remained asymptomatic and had no history of headaches, cognitive problems, seizures, or motor deficits. Neurologic examination was normal.

The patient underwent an awake frontal craniotomy in December 2012. The overlying bone and dura were normal. Tissue from the tumour was sampled, and an intraoperative frozen-section diagnosis of metastatic carcinoma was rendered. A gross total excision of the tumour was performed under intraoperative frameless stereotactic guidance and awake cortical and subcortical mapping. Initially, the tumour was debulked using an ultrasonic aspirator, together with a neuro-navigation probe and subcortical mapping to confirm the cavity’s margins. The operating microscope was added to the field to debulk the deep borders of the tumour until healthy white matter appeared. The margins of the resection cavity were viewed under high magnification, and no evidence of residual cancer was seen. Postoperative MRI demonstrated a gross total resection.

Microscopic examination of permanent sections revealed a moderately differentiated metastatic adenocarcinoma consisting of monomorphic cells with small, round hyperchromatic nuclei containing conspicuous nucleoli and a moderate amount of eosinophilic cytoplasm (Figure 2). The cells were disposed in ribbons and distinct glandular configurations. Extensive necrosis was present. The tumour showed a pushing margin at its interface with adjacent brain. Immunohistochemical studies revealed intense diffuse immunostaining for PSA and nuclear staining for androgen receptor. The cells were negative for cytokeratin 7 and cytokeratin 20. Small foci of intense nuclear staining for thyroid transcription factor 1 were present. Additional immunohistochemical staining revealed scattered tumour cells showing intense cytoplasmic positivity for synaptophysin and for chromogranin A. That finding suggested the possibility of neuroendocrine differentiation in a small proportion of the tumour cells.

The patient tolerated the craniotomy well, with no postoperative complications. Postoperatively, his PSA fell to 0.2 μg/L. After surgery, the oncologist (SM) and neurosurgeon discussed treatment options with the patient, including surveillance, adjuvant radiotherapy, radiosurgery, and ADT. The patient opted for close surveillance.

At 6 months post-treatment, the patient was clinically well, with no neurocognitive problems, headaches, or seizures. Imaging (brain MRI, abdominopelvic computed tomography, bone scan, and chest radiography) showed no evidence of tumour recurrence or metastatic disease. The patient’s PSA remained at 0.2 μg/L (Figure 3).

In July 2013, 8 months after his first recurrence, the patient developed headaches, unsteady gait, and memory loss. Repeat bloodwork revealed a PSA of 5.4 μg/L. Brain MRI (Figure 4) demonstrated significant disease recurrence, with multiple extra-axial dura-based enhancing lesions overlying the right hemisphere and left convexity. The largest lesion, 2.6 cm, in the right middle cranial fossa, had infiltrated the brain parenchyma. The lesions demonstrated low T1 signal, heterogeneous slightly high T2 signal appearance, and heterogeneous gadolinium enhancement. Bone scan showed isolated uptake in the right frontal bone.

FIGURE 1 Intra-axial enhancing mass lesion measuring 3.5 cm (anterior–posterior) by 3.1 cm (transverse) by 2.9 cm (craniocaudal) in the right frontal lobe, with surrounding vasogenic edema and areas of necrosis.
in keeping with the prior craniotomy. Abdominopelvic computed tomography imaging revealed no evidence of metastatic disease.

The patient was initiated on oral dexamethasone 2 mg twice daily, experiencing an improvement in his symptoms. He was treated with whole-brain radiotherapy 3000 cGy in 10 fractions. The patient also received ADT with oral bicalutamide 50 mg daily and leuprolide 22.5 mg by subcutaneous injection every 3 months. After brain radiotherapy and ADT, the patient experienced relief from the headaches and impaired gait. He was tapered off dexamethasone 2 weeks after radiotherapy.

In January 2014, MRI demonstrated significant regression of the brain metastases. A restaging bone scan in January 2014 showed diffuse bone metastases. The patient developed anorexia and a 13.5 kg weight loss, but no bone pain. The oral antiandrogen was discontinued, but the patient failed to have a bicalutamide withdrawal response. In March 2014, MRI showed further regression of the brain metastases. The patient’s PSA level was rising, indicating castration resistance. The patient refused chemotherapy and in April 2014 was treated with oral abiraterone 1 g daily (250 mg tablet × 4) and oral prednisone 5 mg twice daily. He failed to respond clinically to abiraterone.

In June 2014, the patient was admitted to hospital with generalized weakness, dehydration, and diffuse bone pain. He displayed features consistent with disseminated intravascular coagulation secondary to his malignancy and was treated with supportive care. He died 1 week after the hospital admission and more than 19 months after his initial brain recurrence.

**DISCUSSION**

This unique case of metastatic prostate cancer demonstrates an atypical course and relatively long-term survival. Nine years after radical treatment for his primary tumour, the patient developed an isolated parenchymal brain metastasis. The metastasis was discovered during a radiologic investigation triggered by a rise in serum PSA. At PSA relapse, a restaging bone scan suggested underlying brain pathology, triggering a neuroimaging evaluation. The patient was asymptomatic and not receiving anticancer therapy at the time of relapse.

As in most cases of prostate cancer, serum PSA was a useful biomarker of disease activity. A PSA rise occurred with both the first and second central nervous system (CNS) relapse in our patient. After craniotomy and gross total excision of the tumour, the patient’s PSA normalized. Pathology revealed a moderately differentiated metastatic adenocarcinoma whose morphology and immunophenotype were...
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Brain metastases are common for many malignancies, including lung, breast, colon, and renal cell cancers and melanoma. Generally, once cancer has spread to the brain parenchyma, leptomeninges, or skull, patients experience neurologic symptoms, including headache, focal deficits, or seizures. Metastases to the brain parenchyma are extremely rare in PCa, occurring in only 1%–2% of patients with metastatic disease. In PCa, the brain is relatively resistant to establishment of metastases. Epidural metastases can develop through contiguous spread from the calvaria to the meninges.

Postmortem studies have confirmed the rarity of brain metastasis derived from PCa. In a large autopsy study, Saitoh et al. reported no cases of isolated brain metastasis. Moreover, CNS relapse occurred only subsequent to metastatic involvement of other sites. Clinically apparent brain metastases are rare and typically develop in the terminal phases of illness once the cancer is castrate-resistant and has spread to multiple sites and other visceral organs. In our patient, the brain metastases developed while the patient was not on ADT or other anticancer therapy. The biologic factors underlying the selective tropism of the prostatic malignancy for the brain in this patient remain to be defined.

In 1999, McCutcheon and colleagues published the MD Anderson experience of brain metastasis in PCa. The average time between a diagnosis of PCa and a first finding of brain metastasis was 28 months. In the 39 patients with brain metastases, only 1 underwent surgery as monotherapy. Our patient experienced a long latency (9 years) from initial radical treatment to CNS relapse.

The MD Anderson experience was updated and expanded in 2003 by Tremont-Lukats and colleagues. In a database of 16,280 patients, the incidence of brain metastasis was only 0.6%. The overall median survival in the MD Anderson series was just 1 month (95% confidence interval: 0.8 to 1.2 months). Patients receiving palliative radiotherapy experienced an improved median survival of 3.5 months (95% confidence interval: 2.4 to 4.6 months).

In published clinical series, the mean survival of PCa patients with CNS relapse is poor (range: 1–7.6 months, with 1-year survival rates of less than 20%). Our patient lived 19 months after his first relapse in the brain. The patient remained disease-free for 8 months after craniotomy and tumour removal. The second recurrence was again isolated to the CNS. At second relapse, the patient had diffuse CNS disease and developed headaches, ataxia, and memory loss. The neurologic symptoms completely resolved with palliative radiotherapy, steroids, and ADT.

The patient responded to therapy clinically, biochemically (PSA), and on MRI. He then developed castration resistance and died 19 months after CNS relapse. In the end, his death was attributable to extracranial complications (bone and bone marrow involvement) from his PCa, durable control of his CNS disease having been achieved.

SUMMARY

Brain metastasis is a rare event in PCa. When present, CNS metastases occur at the end stage of illness, once patients have castrate-resistant disease. Our patient represents a unique presentation of isolated brain metastasis as the only site of recurrence. His second recurrence was also isolated to the brain. The patient had a relatively favourable course after surgery for his CNS metastasis.

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FIGURE 4 Significant disease progression, with multiple dura-based enhancing lesions, vasogenic edema, and a mild midline shift toward the left, is seen. The brain parenchyma is involved by the largest exophytic lesion in the right middle cranial fossa.
CONFLICT OF INTEREST DISCLOSURES
We have read and understood Current Oncology's policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS
*The Ottawa Hospital Cancer Centre, Ottawa, ON; †The Ottawa Hospital, General Site, Ottawa, ON; ‡The Ottawa Hospital, Civic Site, Ottawa, ON.

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