Rare disease

Response of cerebral metastasis secondary to prostate cancer to primary androgen suppression

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Summary

We report the case of an 80-year-old man who presented with relapsing prostate cancer and cerebral metastases which showed evidence of radiological and clinical response to androgen suppression alone without additional whole brain radiotherapy.

BACKGROUND

Prostate cancer is now the most common cancer in men in the UK.¹ The majority of patients present with disease localised to the prostate. However, 20–30%² present with metastatic disease at diagnosis and for these patients the mainstay of treatment is androgen suppression. The most common sites of metastatic spread are bone and pelvic and para-aortic lymph nodes. Metastatic spread to the brain is a very rare event in prostate cancer, and when seen it is usually in the context of very advanced and androgen independent disease, or arising from an unusual histological variant such as small cell cancers.

Androgen suppression has been clearly demonstrated to improve bony pain and generate biochemical and radiological shrinkage of visceral metastases. The occurrence of brain metastasis in men with **metastasis** of the prostate is a very rare event and in the absence of other non-central nervous system (CNS) metastasis, rarer still. Our case report is of interest in that it suggests that treatment of brain metastasis in patients with prostatic cancer of adenocarcinomatous origin could be initially limited to hormonal manipulation alone, as are visceral metastases outside the CNS, without requiring whole brain radiotherapy (WBRT).

CASE PRESENTATION

We present the case of an 80-year-old man who presented with relapsing prostate cancer with cerebral metastases that showed evidence of radiological and clinical response to androgen suppression alone without additional radiotherapy. The patient was initially diagnosed in 2000 with a T1c localised low grade Gleason 2+3 carcinoma of the prostate. He was treated with radical radiotherapy and entered into follow-up with evidence of good clinical and biochemical response to treatment. He remained symptom free until November 2008, when he re-presented with deteriorating lower urinary tract symptoms which coincided with a rising prostate-specific antigen (PSA) of 8. Subsequently, he underwent a trans-urethral resection of the prostate (TURP) procedure in June 2009 for symptomatic relief. The histology demonstrated the presence of recurrent

Gleason 4+5 adenocarcinoma and there had been a further PSA rise to 32. In August he presented as an emergency with left sided hemiplegia and dysphasia. CT scan of the brain demonstrated the presence of multiple space occupying lesions throughout with associated extensive oedema and midline shift (figure 1), consistent with multiple cerebral metastases. Further staging investigations confirmed widespread metastatic disease in the liver, pelvic lymph nodes and superior pubic ramus consistent with the diagnosis of widespread metastatic carcinoma of unknown origin but likely prostate. He responded rapidly to high dose dexamethasone, with marked improvement in his neurological symptoms. Due to the extent of systemic disease and WBRT toxicity, radiotherapy was postponed pending further deterioration of neurological symptoms. He was, however, started on androgen suppression with a gonadotropin-releasing hormone (GnRH) agonist (Zoladex).

Although no histology is available from the cerebral deposits, it is likely that they are prostatic in origin given the high grade Gleason 9 disease at TURP and subsequent response to androgen suppression therapy. Furthermore, despite the liver metastases not responding to the same extent as the brain metastases, they did show a definite response consistent with metastatic prostate cancer.

INVESTIGATIONS

- ▶ PSA at presentation
- ▶ Original histology
- ▶ Histology from TURP procedure
- ▶ CT scan – figure 1 (pre-treatment)
- ▶ CT scan – figure 2 (post-treatment).

TREATMENT

- ▶ Androgen suppression – GnRH agonist (Zoladex)
- ▶ Dexamethasone.

OUTCOME AND FOLLOW-UP

In December 2009 the patient continued to have no neurological deficit off dexamethasone. His PSA had reduced to 5.6, indicating a good biochemical response. A repeat

Figure 1 CT image demonstrating significant cerebral metastases.

Figure 2 CT image clearly demonstrating resolution of cerebral metastases.

staging CT scan was performed in February 2010 showing a marked response to androgen suppression treatment with resolution of the pelvic lymph node disease and stable appearances of the liver lesions. Furthermore, it demonstrated that the cerebral metastases had reduced in size, with less oedema and midline shift (figure 2).

DISCUSSION

Androgen suppression has formed the backbone of the treatment of metastatic prostate cancer since Charles Huggins' demonstration in 1941 that androgen ablation therapy leads to regression of the majority of primary and metastatic prostate cancer cells.³ Androgen suppression has been clearly demonstrated to improve bony pain and

generate biochemical and radiological shrinkage of prostate cancer metastases.

Brain metastases are a rare event in prostate cancer. The very large 16 280 patient series reported by the M.D. Anderson Cancer Center found only 131 patients with evidence of cerebral metastasis (0.8%).⁴ The database identified all patients with either pre- or postmortem diagnosis of brain metastasis secondary to prostate cancer between January 1944 and July 1998, providing an observation time of 54.5 years. Seventy-eight of these were diagnosed at postmortem with only 53 patients (0.3%) presenting during their life. Of these 131 patients with craniospinal lesions, 103 were intraparenchymal, with 89 presenting with single lesions compared to 14 with multiple lesions.

Table 1 Summary of larger case series

Series	No. of patients	CNS metastasis	Adenocarcinoma	Small cell cancer	Other histology	Mean time to developing CNS metastasis
M.D. Anderson, 1944–1998	16 280	131	119 (91%)	6 (4.6%)	6 (4.6%)	No data
M.D. Anderson, 1980–1997	7994	38	24 (63%)	10 (26%)	4 (11%)	28.5 months (range 0–94)
Memorial Sloan-Kettering	673	16	13 (81%)	3 (19%)	0	67 months (range 7–144)

Only one patient presented solely with brain metastases; all others had metastatic disease elsewhere. Although the majority of patients were found to have adenocarcinomas at histological review, a disproportionate incidence of small cell and squamous cell carcinomas was found. The median prognosis following diagnosis was 1 month rising to 3.5 months in patients fit enough to undergo radiotherapy, indicating that the diagnosis of brain metastasis even when it does occur seems to be made in patients with very advanced late stage androgen independent disease.

Similar, though smaller, case series can be found in the literature, with similar results. Nolan *et al* report a series from the Memorial Sloan-Kettering Cancer Center.⁵ This retrospective analysis of a database covering a 7-year period from 1993 to 2000 identified 16 patients with brain metastases out of 673 (2.4%) patients diagnosed with prostate cancer. Of these, 13 were adenocarcinomas, three having small cell histology. Palliative WBRT was seen as being effective in improving symptoms. Of the five patients still living by the time of the report, and three who had died with non-neurological complications, all had received palliative radiotherapy, suggesting an advantage for WBRT.

It is interesting to note that despite advances in radiological diagnosis within the 54-year period of observation of the M.D. Anderson study, there was no greater incidence of intracranial metastasis after 1980 compared with before 1980, as shown by McCutcheon *et al* in their analysis of the 7994 patients in the M.D. Anderson database from 1980 to 1998.⁶ There may be several contradictory factors at work. First, the authors concede that progressively fewer post-mortem examinations are carried out, and therefore there is decreased detection of asymptomatic brain metastasis. They argue that earlier detection and more effective treatment of prostate cancer leads to fewer cases of metastatic disease overall. However, a counter argument is that modern treatment of metastatic disease itself is becoming more effective, although not curative, and therefore men are increasingly living with metastatic disease for longer periods of time, and so will go on to develop brain metastasis in greater numbers. This argument may not be as firm for the cases of small cell prostate cancer, which are known to be more rapidly progressive and much less treatable than the more common adenocarcinomas, with a much shorter overall survival.

It can be seen that CNS metastases from prostate cancer are indeed rare, and although the majority of cases are adenocarcinoma in origin, small cell and other histological types are over-represented in the reported series, and therefore display more likelihood to metastasise to the brain. There have been no data to date that have shown that

the incidence is increasing, although it is not wholly inappropriate to suggest that this may be the case. Although the 9-year gap between our patient being diagnosed with prostate cancer and the diagnosis of brain metastasis is longer than the mean period from the data in this short review (table 1), it is still within the range reported by the Sloan-Kettering group.

Our case report is of interest in that it illustrates a patient presenting with neurological symptoms as the first presentation of metastatic disease and who showed response to androgen suppression similar to the response commonly seen for extra cranial disease. It suggests that the treatment of brain metastasis in patients with prostatic cancer of adenocarcinomatous origin could be initially limited to hormonal manipulation alone, as are visceral metastases outside the CNS. Serial CT scans have demonstrated that the brain lesions in our patient have undergone a radiological partial response to GnRH agonist therapy. Therefore, it is an indication that WBRT, or other radiosurgical management, is not absolutely necessary in hormone sensitive disease.

Learning points

- ▶ Brain metastases in prostate cancer are rare.
- ▶ Prostate cancers are hormone sensitive.
- ▶ Androgen suppression can successfully treat brain metastases as it does visceral metastases in prostate cancer.
- ▶ Whole brain radiotherapy may not be absolutely necessary in the treatment of brain metastases in hormone sensitive disease.

Competing interests None.

Patient consent Not obtained.

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