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PSA negative cerebellar metastasis from prostate cancer: a case report

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Summary. Brain metastases from prostate cancer are very rare. We report an unusual case of PSA-negative cerebellar metastasis in a 77-year-old man with known prostate cancer since 2003 and negative clinical and radiological follow-up for the following 10 years. The lesion was discovered during the radiological follow-up for his pre-existent cerebrovascular disease; at first the patient was completely asymptomatic and only after one year began to complain of symptoms related to the area involved rather than the mass-effect. Beside the highly unusual cerebellar site, another peculiarity is the lack of rise in PSA serum level and the cerebellum as the only and first site of distant spread. This suggests a particular type of cancer behavior with direct brain occurrence *via* the paravertebral venous plexus draining from the prostate, and a relatively benign growth; for some still unknown reason this has happened without a significant PSA increase. The case reported also suggests that in a patient with prostate carcinoma without any other secondary involvement but with even mild neurological symptoms, a brain imaging study should always be performed.

Key words: prostate cancer, brain metastasis, negative-PSA, cerebellar metastasis

«Metastasi cerebellare da carcinoma della prostata con PSA negativo: presentazione di un caso clinico»

Riassunto. Le metastasi encefaliche da tumore prostatico sono molto rare. Riportiamo il caso di una metastasi cerebellare con PSA negativo in un uomo di 77 anni con carcinoma prostatico noto dal 2003 e follow-up clinico e radiologico negativo per i successivi 10 anni. La lesione è stato diagnosticata durante un esame radiologico di follow-up eseguito per la preesistente patologia cerebrovascolare di cui il paziente era affetto. Al momento della diagnosi il paziente era completamente asintomatico mentre un anno dopo, a fronte di una evidente crescita della lesione, mostrava sintomi e segni legati alla localizzazione della metastasi piuttosto che all'effetto della massa stessa. Al di là della localizzazione del tutto inusuale, due peculiarità del caso in esame sono la costante negatività dei livelli di PSA sierici e l'unica e prima localizzazione secondaria a carico del cervelletto. Quest'ultimo elemento ci suggerisce, in accordo con la letteratura, un comportamento unico di alcuni tipi di tumore prostatico che potrebbero metastatizzare al cervelletto attraverso il plesso venoso paravertebrale mostrando un atteggiamento relativamente benigno; per ragioni ancora non note questo potrebbe accadere senza un incremento nei livelli di PSA. Il caso riportato pertanto può inoltre suggerire che un paziente con carcinoma della prostata senza note secondarietà, ma con sintomi neurologici anche modesti, debba essere sottoposto ad approfondimento con imaging cerebrale.

Parole chiave: cancro prostatico, metastasi del cervello, PSA negativo, metastasi cerebellare

Introduction

Prostate carcinoma is the most frequent cancer in the male population (1). This type of tumor metastasizes most commonly to the pelvic lymph nodes and the axial skeleton; conversely, brain metastases are very rare. The incidence of brain metastases from prostate cancer has been reported to range between 0.2% and 2% in several prior studies (3-7). All these reports refer to brain metastases identified only *post-mortem*. The most recent series of over 13,547 patients with prostate cancer at the Memorial Sloan-Kettering Cancer Center (NY) between 2000 and 2010 yielded an incidence of 0.16% (8) *ante-mortem*. McCutcheon *et al.* also reported an incidence of 0.17% (9). The lower rates obtained from these studies probably depend on the relative asymptomatic clinical presentation and they may have remained partly undetected because routine screening examinations for brain involvement are not usually performed (8).

The most common histologic subtype is adenocarcinoma (99.4%) (8), although rare non-adenocarcinoma cancers seem to be more likely to develop intracranial dissemination (8, 9).

The most common intracranial site of prostate cancer metastases are the leptomeninges (67%), the cerebrum (25%) and the cerebellum (8%) (10). This shows how rare localization is in the posterior cranial fossa. In fact, only 7 cases of cerebellar metastases without systemic dissemination from prostate cancer have been reported *ante-mortem* (2, 8, 10-13).

The mean patient age with diagnosis of brain metastases is around 68.8 (range 57-81) (8); thanks to earlier detection of primitive prostatic tumors and more advanced treatment options (14), patients are living longer and may develop brain metastases at greater rates than in the past (8, 15).

Case report

A 77-year-old man was diagnosed in July 2003 to have a poorly differentiated Gleason 4+4, pT3aN1 prostatic adenocarcinoma. He underwent radical prostatectomy and lymphoadenectomy followed by hormone therapy (HT) with Bicalutamide and Triptorelin. Afterwards he had negative clinical and radiological follow-up for almost 10 years. During this follow-up PSA levels were always within the normal range, but with an increasing trend. In July 2012 a brain MRI performed as a radiological control for his pre-existent cerebrovascular disease showed a small left hemispheric cerebellar lesion with central necrosis and peripheral enhancement. One year later the patient presented progressive dizziness and dysarthria; a second MRI showed a dimensional increase in the lesion with mass effect in the posterior cranial fossa with no hydrocephalus. The PSA level at that moment was 1.10 ng/ml (normal range 0-4 ng/ml). A suboccipital craniectomy was performed and a gross total resection (GTR) successfully achieved. A CT scan performed immediately after surgery showed complete metastasis removal without any complications (Fig. 1). Histological examination revealed metastatic prostatic adenocarcinoma, with positive immunohistochemistry for prostatic acid phosphatase (PSAP) (Fig. 2). The patient was then discharged after 11 days with partial neurologic recovery (persistent mild dysarthria and no dizziness).

Discussion

Cerebellar metastases usually arise from lung, kidney and cutaneous melanoma (12). Cerebellar deposits from prostate cancer are extremely rare, an extensive literature search revealing only 7 previous case reports (2, 8, 10-13).

Cerebellar metastases are usually solitary, in contrast to supratentorial ones, this feature making them amenable for surgical resection (12).

The diagnosis of most of infratentorial neoplastic lesions is first due to an acute onset with mass effect symptoms (headache, vomit, nausea, etc) (16); in contrast, a cerebellar metastasis from prostate cancer could be almost asymptomatic and the clinical evaluation can only highlight neurological deficit related to the area involved, as was well described in our case.

This can be explained by the relatively slow growing time of this kind of tumor: the mean time interval between the initial diagnosis of prostatic carcinoma and diagnosis of intracranial metastasis is around 5.1 years (3).

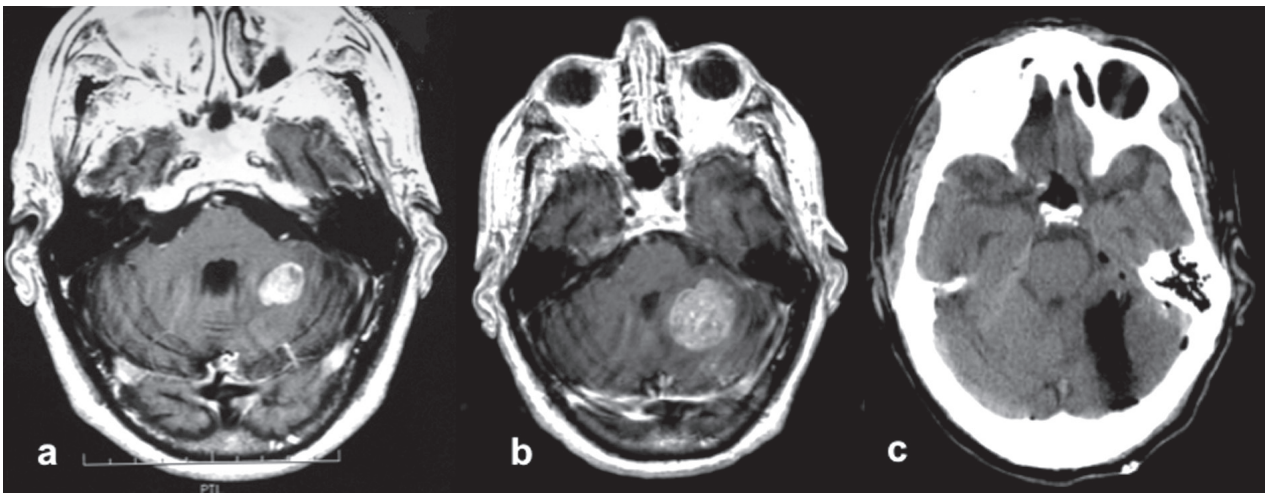

Figure 1. Radiological images. a) Brain MRI with gadolinium performed 1 year before surgery; b) Brain MRI with gadolinium performed 1 month before surgery: increased lesion volume; c) Post-operative CT.

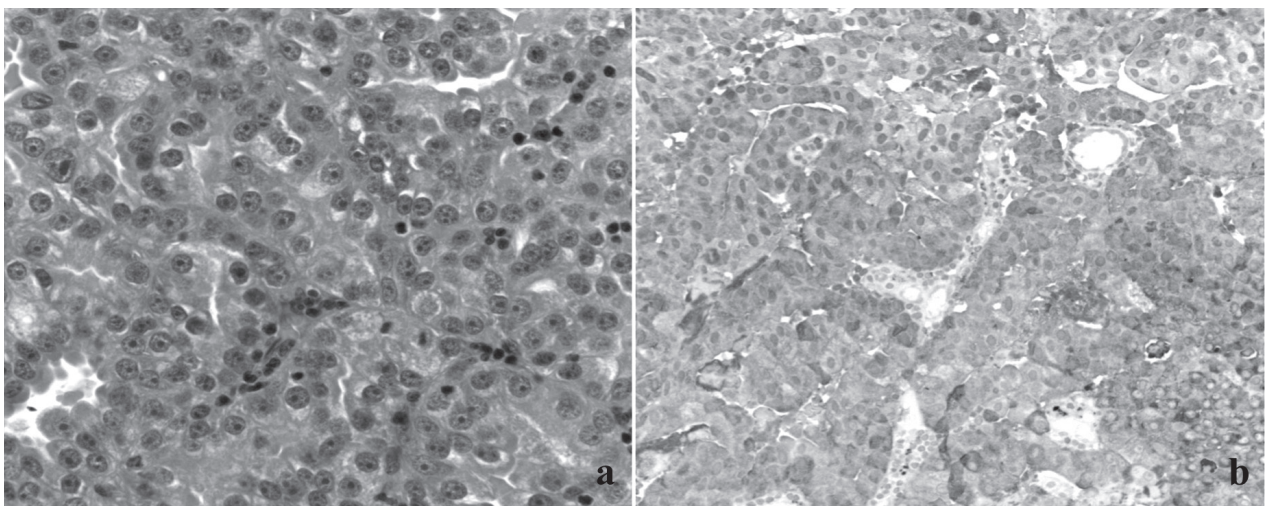

Figure 2. Histological and immunohistochemical features of the brain metastasis. The metastatic lesion was an adenocarcinoma composed of solid nests and small back-to-back glands. Cytologically, neoplastic cells showed enlarged, round, hyperchromatic nuclei with a single prominent nucleolus (a: H&E, original magnification 40x). At immunohistochemistry, a diffuse and intense immunoreactivity to prostatic specific acid phosphatase (PSAP) was observed (b: PSAP, original magnification 20x).

The reasons for the difficulty in diagnosis include the low incidence (0.9%) of tumors metastasizing to the brain (5), asymptomatology of prostatic brain metastases (10) and similarity of symptoms (if present) to vascular events (3, 13).

These lesions have a highly variable imaging appearance and may be difficult to differentiate from metastases originating from other primary tumor sites (7). This is confirmed from our case report where the brain MRI does not show specific characteristics suggesting a prostatic origin of the cerebellar lesion.

Despite many articles and reviews showing increased PSA levels in brain prostatic metastases (5, 12, 13), our patient's PSA level always remained in the normal range.

The role of prostate specific antigen (PSA) in the early detection of brain metastases is unclear. This glycoprotein is a sensitive indicator of the presence of dis-

ease and elevated levels commonly are taken to mean persistent renewal of the tumor, both locally and at distant sites, as well as correlating with tumor volume (9).

In our case report the patient had a single cerebellar metastasis with no other sites involved. This fact may help us understand the mechanism of metastases to be intracranial. It is possible that extension of metastases from the prostate occur directly to the brain via the paravertebral venous plexus draining the prostate, avoiding bone and viscera (17). Batson hypothesized that the low pressure in these veins would allow Valsalva's maneuvre to generate enough pressure to reverse the blood flow from the inferior vena cava to the plexus reaching the brain vessels (18).

As extensively shown by the literature, cerebellar metastases from prostate cancer are very rare and diagnosis of them has rarely been made in living patients. However, the rising incidence of this disease and the longer survival time thanks to better therapeutic options, could increase the detection rate of cerebellar localizations. In conclusion, in a patient with prostate carcinoma without any other secondary involvement but with even mild neurological symptoms, a brain imaging study should always be performed.

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