ISSN 1478-6672

Thoracic meningioma in a man with psychiatric disease: case report with hypothesis regarding hormonal risk factors

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Abstract

Objective and Importance: We present the case of a man with a thoracic meningioma and endocrine hormone abnormalities. **Clinical Presentation:** A fifty-eight year old man with severe bipolar disorder and psychotic features presented with progressive gait disturbance. Despite being treated with multiple neuroleptic medications, including both typical and atypical anti-psychotic drugs, the patient remained debilitated by psychiatric disease and was dependent upon 24-hour nursing home care. After undergoing a brain and cervical spine MRI, the patient was referred to neurosurgery for cervical stenosis and initially refused further imaging. By the time a thoracic spine tumor was diagnosed, the patient had not walked for six months and suffered from bowel and bladder incontinence. Thoracic spine MRI showed spinal cord compression at the T9-T10 level secondary to an enhancing intradural extramedullary tumor. After surgical resection, a neuropathologist made the diagnosis of oestrogen receptor-negative, progesterone receptor-positive WHO Grade I meningothelial meningioma. The patient made an excellent neurologic recovery and endocrinologic studies were significant for a low serum testosterone. **Discussion:** Meningiomas are predominantly female tumors and are thought to be sex hormone-responsive. Spinal meningiomas are especially rare in men and provide an opportunity to investigate hormonal risk factors. **Conclusion:** We discuss the rarity of spinal meningioma in men and hypothesize that testosterone may have a protective role against meningioma in men.

Key words: meningioma • oestrogen-receptor • progesterone-receptor • testosterone

Abbreviations: SSEP, somatosensory evoked potential; MRI, magnetic resonance imaging; BMI, body mass index; IMintramuscular

The incidence of meningiomas, regardless of location, is known to be higher in women than in men. This consistent female predominance and the discovery that meningiomas frequently carry receptors for various sex hormones supports a role for such hormones in the development and growth of these tumors. Epidemiological studies have found a female-to-male ratio of approximately 2:1 for intracranial meningiomas (8, 11). For unknown reasons, this ratio is much greater for spinal meningiomas and has been reported to be as high as 9:1 (40).

Spinal meningiomas are usually benign, slow-growing tumors which occur predominantly in the thoracic

spine of women. Surgical resection remains the primary therapy and can result in excellent outcomes even though there is commonly a long history of clinical symptoms before a diagnosis is made (43). These tumors are typically located in the intradural extramedullary space and present with pain, weakness, sensory loss, and bowel/bladder dysfunction (19). Pathological reports from large series of resected spinal meningiomas suggest that the main histologic subtypes are meningothelial and psammomatous (26, 45).

Besides the marked female predominance, a link between sex hormones and meningiomas has been supported by reports of meningioma growth during pregnancy and the luteal phase of the menstrual cycle (3, 17, 38), a positive association between the use of hormone replacement therapy and meningioma incidence (24), a reduced risk of meningiomas in women who have undergone natural or surgical menopause (41), and an increased risk of meningiomas in women with breast carcinoma (27, 28, 34). Most meningiomas (61-95%) have been found to carry progesterone receptors (PR) (9, 23, 44), about 50% possess androgen receptors [AR] (6), and a minority of meningiomas (<10%) express oestrogen receptors [ER] (12, 42). The function of these sex hormone receptors in meningiomas remains largely unknown, however there is data, especially from studies on the response of meningiomas to antiprogestins, which supports a role for the PR in promoting meningioma growth (14, 20, 21, 29, 32).

There is little known about sex hormone levels in men diagnosed with meningioma. One retrospective study found that men with intracranial meningiomas had a higher rate of obesity; since adipocytes convert testosterone to estradiol, this data indirectly incriminates sex hormones as influencing meningioma development in males (1). Given the overwhelming preponderance of spinal meningiomas in females, we feel that the rare occurrence of these tumors in males provides a good opportunity to investigate hormonal risk factors. A case of a 58 year-old man with refractory psychiatric disease and a thoracic meningioma is presented. We hypothesize that his exposure to several neuroleptics may have altered his sex hormone levels, which in turn predisposed him to a spinal meningioma.

Clinical Presentation

The patient was a fifty-eight-year-old army veteran who presented with four months of progressive gait disturbance. Due to severe psychiatric disease, the patient had been for the past decade dependent upon care in either group homes or more recently nursing homes with 24-hour support. His caretakers suspected that his gait problems were attributable to psychiatric medications and he was initially referred to a neurologist.

The patient was closely followed by psychiatry and carried a diagnosis of bipolar disorder with psychotic features and schizotypal personality disorder. In the last several years, he had been admitted to the VA hospital numerous times, frequently via police code #302, for manic episodes. He never exhibited homocidality or suicidality. The patient's most recent psychotropic regimen was olanzapine plus doxepin. However, in the previous two years, he had been treated with courses of haloperidol decanoate IM injections, valproic acid, benztropine, lorazepam, clonazepam, risperidone, and perphenazine. His most recent Axis V (Global Assessment of Functioning) score was 42, indicating severe impairment in memory, motor skills, and executive function. Other past medical history included hypertension, hypercholesterolemia, right eye blindness secondary to retinal detachment, and mild obesity (BMI = 30.1). His other medications were hydrochlorothiazide, metoprolol, and simvastatin.

The neurologist noted mild weakness (4+/5 power) in bilateral dorsiflexion as well as lower extremity hyperreflexia and clonus. A brain and cervical spine MRI was ordered. Brain MRI revealed mild volume loss and cervical MRI showed multilevel degenerative changes with moderate central stenosis (Figure 1a). The patient was subsequently referred to neurosurgery for presumed cervical spondylitic myelopathy. Upon neurosurgical evaluation, the concern arose that the patient's exam was not explained by his cervical pathology. A lumbar and thoracic MRI were ordered but the patient refused multiple requests to obtain these studies.

Approximately one year after the onset of symptoms, the patient returned to the neurosurgical clinic in a wheelchair. Neurological examination showed near plegia in the lower extremities with 0/5 power in bilateral ilopsoas, hamstrings, and quadriceps muscles and only flicker 1/5 power in bilateral dorsiflexors and plantarflexors. The patient had also developed bowel and bladder incontinence. Upper extremity strength and reflexes remained within normal limits. He agreed to further neuroimaging. MRI of the lumbar spine

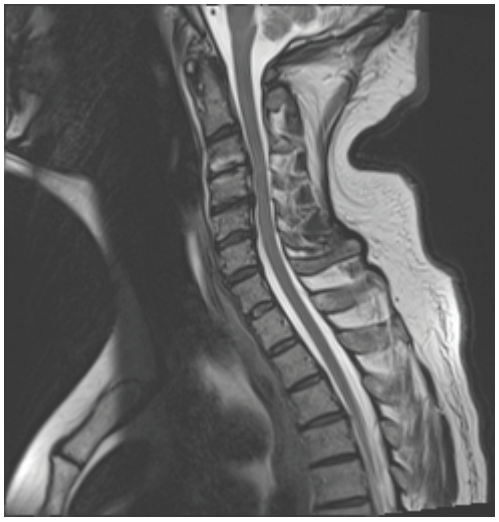

Fig. 1a

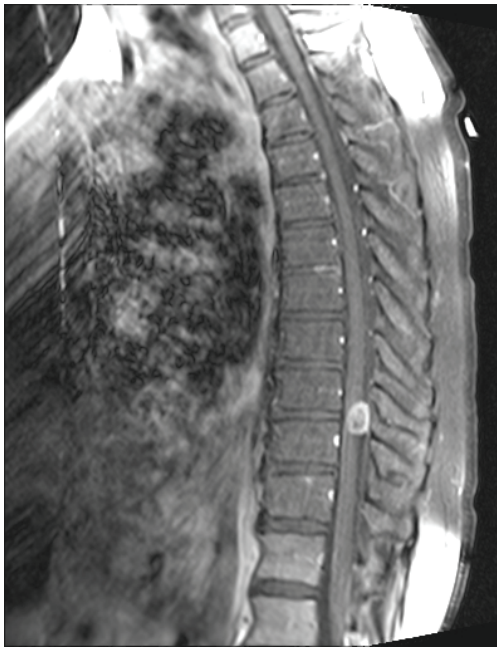

Fig. 1b

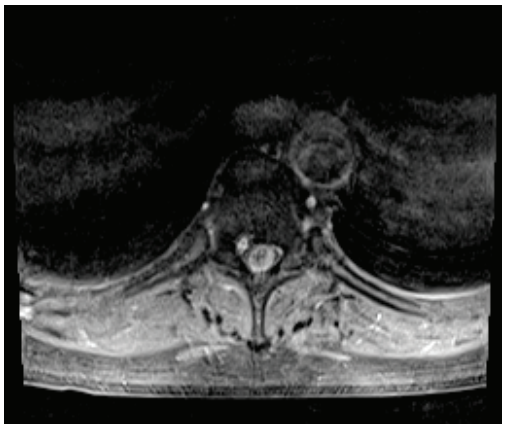

Fig. 1c

Figure 1. Sagittal MRI of the cervical spine (a) showing moderate stenosis and sagittal (b) and axial (c) MRI of the thoracic spine with contrast showing a left eccentric peripherally-enhancing intradural mass causing spinal cord compression.

showed mild degenerative changes whereas MRI of the thoracic spine (Figure 1b and 1c) demonstrated a left eccentric, enhancing intradural extramedullary mass (15 x 11 x 11mm) at the T9-T10 level causing spinal cord compression. The patient and caretakers were made aware of the diagnosis and he consented to surgical resection. He was admitted for anesthesia preoperative clearance and was taken to the operating room the next morning. The patient was placed on intravenous corticosteroids and a Foley catheter was placed for neurogenic bladder.

Operative Course. Using continuous somatosensory evoked potential (SSEP) monitoring, a T9-10 laminectomy was performed. The bony decompression was slightly weighted to the left to account for the eccentricity of the tumor. Once the dura was opened, a light brownish, encapsulated mass causing deformation of the underlying spinal cord was clearly visible. The mass had a broad attachment to the posterolateral dura. Under the operating microscope, arachnoid bands were carefully coagulated and sharply cut to detether the mass. Care was taken to not disturb the capsule and the mass was removed en bloc. The region of dural attachment was coagulated with the bipolar. The dura was closed primarily with a 4-0 Nurolon suture followed by DuraSeal onlay (Confluent Surgical, Waltham, MA).

Postoperative Course. On postoperative day one, the patient's motor exam had already improved to 2/5 power throughout the lower extremities bilaterally. He was discharged to a spinal cord rehabilitation and subsequently returned to his nursing home. At his 3 month follow-up, he had regained full power in his lower extremities but still reported intermittent urinary incontinence. At his 10 month follow-up, the patient has no more bowel or bladder incontinence. He is walking 2 miles daily without assistive device.

Pathology and Hormonal Studies. Histologic analysis by a neuropathologist (G.R.R.) revealed monomorphic large cells with abundant cytoplasm forming whorls; a lobular architecture with intervening fibrovascular septa was evident along with a thick collagenous capsule (Fig. 2a). The diagnosis of WHO grade I meningothelial meningioma was made. Immunohistochemical staining was positive for progesterone receptor [PR] (Figure 2b) and negative for oestrogen receptor [ER] (Figure 2c).

Due to a suspicion that psychiatric polypharmacy may have altered this patient's sex hormone levels,

we ordered an endocrine battery with his informed consent. The results revealed a low total testosterone level (Table 1).

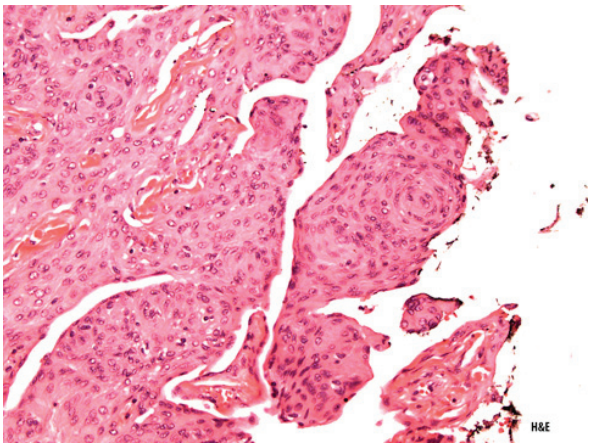

Fig. 2a

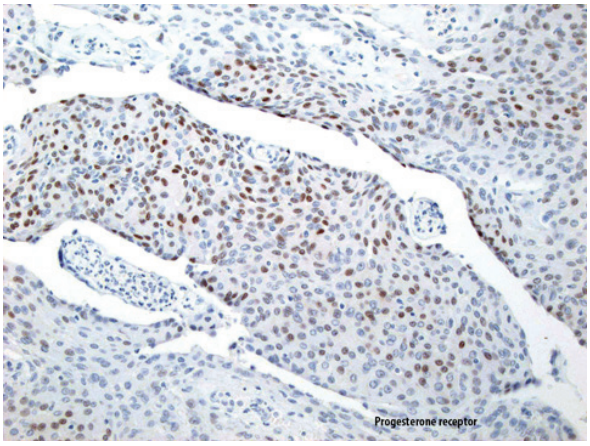

Fig. 2b

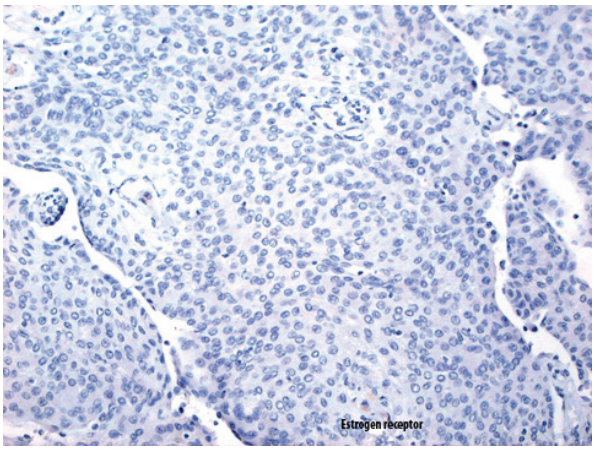

Fig. 2c

Figure 2. Histological analysis revealed characteristics consistent with a meningothelial meningioma on H & E stain (a). Immunohistochemical stains were positive for progesterone receptor (b) and negative for estrogen receptor (c).

Test	Values	Normal range
testosterone, total	139.0	241-827 ng/dl
testosterone, free	6.32	5-21 ng/dl
estradiol	28.0	0-54 pg/ml
estrone	82.0	12-72 pg/ml
progesterone	0.7	0.2-1.4 ng/ml
TSH	0.33	0.34-5.60 uIU/ml
free T4	1.31	0.58-1.64 ng/dl
FSH	5.26	1.27-19.3 uIU/ml
LH	0.31	1.82-8.62 mIU/ml
prolactin	4.36	2.64-13.1 ng/ml

Table 1. Endocrinological Test Battery

Discussion

Spinal meningiomas are rare tumors and complete surgical resection often carries a favorable prognosis. Both epidemiological and immunohistochemical data support that meningiomas are influenced by sex hormones. The successful application of endocrine therapies to other hormone-responsive tumors such as breast and prostate carcinoma provides the impetus for continued investigation of hormonal factors behind meningioma growth and development. Although surgery remains the first-line treatment strategy, hormonal therapy for meningiomas may be particularly beneficial in cases of recurrent or unresectable tumors.

There is considerable evidence that progesterone receptors [PR] in meningioma cells are functional and influence the biological behavior of theses tumors (13, 18, 31). Like other steroid hormone receptors, PRs are intracellular proteins which, after binding their respective steroid agonist, travel to the nucleus of the cell to alter gene expression (39). The end products of PR-regulated gene expression have begun to be elucidated, and there is evidence that genes in the collagen and extracellular matrix pathways, which may be involved in tumor growth, are influenced (14). Although most meningioma receptor studies have been based on intracranial tumors, spinal meningiomas appear to have a similar prevalence of PR positivity (36).

Most hormonal studies on meningioma have focused upon the female sex hormones oestrogen and progesterone. However, the abundant and frequent

expression of PR and relative absence of ER on meningiomas demonstrates that meningiomas differ from other sex hormone-responsive tissues in an important way. Whereas PR expression in breast and uterine tissue is regulated by estrogens acting via the ER, PR expression in meningiomas appears to be ER-independent (5). Estrogens therefore do not appear to explain the female proclivity of this tumor, and it is not clear if the scarce ERs found on some meningiomas are even functional (10). Meningioma PR levels in females have also been shown to be significantly higher than meningioma PR levels in males, suggesting that males may possess something which reduces PR synthesis (7, 37). Thus, there is room for hypotheses regarding regulation of PR expression in meningiomas.

One obvious candidate for a hormone that regulates meningioma PR expression is testosterone, whose androgen receptor (AR) is most closely related in structure to the PR (2). Testosterone and other androgens have been shown to bind PR and act as competitive antagonists of progesterone (35). Androgens have been shown to inhibit the growth of certain breast cancer cell lines, and the fact that this inhibitory effect cannot be completely reversed with AR antagonists suggests the antiproliferative tumor effects of androgens must be partially AR-independent (4, 16, 33, 46). High levels of testosterone and other androgens have been associated with decreased PR content in breast tissue and downregulation of PR in breast tissue by testosterone has been implicated in the antiproliferative effect of androgens on breast carcinoma (22). We hypothesize that testosterone may reduce PR expression in meningiomas and therefore may provide men, which have markedly higher testosterone levels than women throughout life, with some protection against meningioma development and growth.

The low total testosterone and low-normal free testosterone level in this man may have been engendered in part by his use of multiple antipsychotic medications. Many neuroleptic drugs can reduce serum testosterone levels, and both typical and atypical antipsychotics are notorious for decreasing testosterone levels via prolactin-dependent and prolactin-independent ways (15, 25, 30). His hypogonadism may also have resulted in part from the well-described metabolic syndrome, which was insinuated by his mild obesity and hypercholesterolemia (47).

Conclusion

The hormonal physiology behind meningiomas is slowly being uncovered. This case of a male patient with psychiatric polypharmacy, hypogonadism, and a spinal meningioma provided a unique opportunity to speculate on the hormonal risk factors underlying meningioma. We hypothesize that testosterone, via downregulation of progesterone receptors, may afford men with some protection against this tumor. Since adipose tissue enzymatically aromatizes androgens to estrogens, previous observations that meningiomas develop in obese men are consistent with this theory. Finding support for this hypothesis will require further research on progesterone receptor regulation in meningiomas and epidemiological studies which include hormone levels in addition to immunohistochemical testing of tumor tissue.

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