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Case Reports & Case Series

A rare brain tumor encountered: Phosphaturic mesenchymal tumor. Case report and review of the literature☆,☆☆,☆☆☆,☆☆☆☆

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ABSTRACT

Rational: Phosphaturic mesenchymal tumors (PMTs) are rare tumors often causing tumor-induced osteomalacia (TIO), with surgical resection being the first line in the treatment of TIO. There are very few reports of PMTs located in the brain. The authors present one such case, it's management and outcome as well as a review of the literature.

Patient concerns: The authors report of a 58 year old male with a background of osteoporosis, bone pain, muscle weakness and gait disturbances for the past several years. He presented to our institution with newly developed absence spells. He underwent imaging which revealed a brain tumor.

Interventions: The patient underwent surgery for what was suspected as a meningioma. A gross total resection was done. The pathological diagnosis was that of phosphaturic mesenchymal tumor.

Outcomes: Removal of the tumor helped in alleviating the patient's back symptoms immediately after surgery. The patient was discharged home and was followed up by an endocrinologist, with improvement of his bone pain, his muscle weakness and his gait disturbances.

Lessons: PMT with involvement of the brain can be treated surgically. Removal of the tumor will alleviate symptoms in patients harboring this rare brain tumor.

1. Introduction

Most cases of tumor-induced osteomalacia (TIO), known also as “oncogenic osteomalacia”, result from over-production of the phosphaturic hormone fibroblast growth factor 23 (FGF23) [1]. The tumors themselves are called phosphaturic mesenchymal tumors (PMT). The primary treatment for TIO is surgical removal of the tumor [1,2]. Most cases of TIO exist in the bone and soft tissue of the limbs, [2,3]. However, there are three known reports of an intracranial mesenchymal tumor, [4]. Although most often the tumors themselves are discovered due to osteomalacia, presenting as a paraneoplastic syndrome, [4], this case had an atypical presentation.

2. Clinical presentation

A 58-year-old, right handed male presented with newly appearing absence spells and bilateral hand tremor which started two months prior to admission. The patient's background was noticeable for Hyperlipidemia, bone pain, muscle weakness, and osteoporosis without a known cause for the past several years. His chronic medications were Atorvastatin, calcium and phosphorus supplements, and vitamin D (as Alfacalcidol).

Due to increasing absence-like seizure events, the patient arrived to our institution. There exists no previous relevant known family history. Upon admission the patient was alert and oriented to time, place and situation. No side weakness was noted or any cranial nerve deficit.

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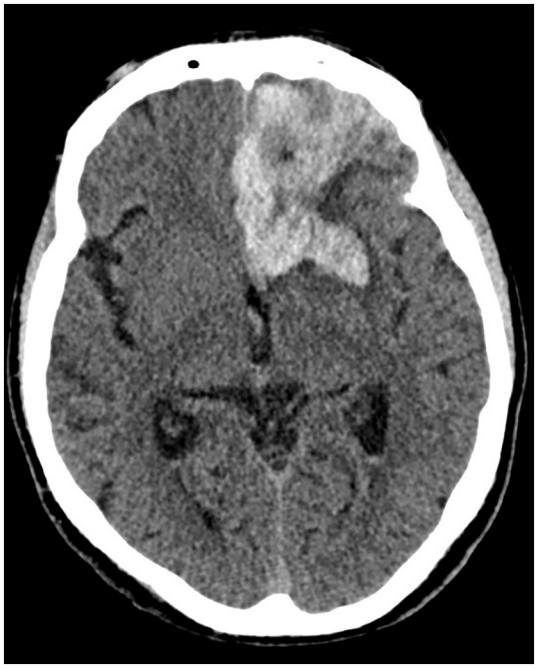

Fig. 1. An axial non-contrast brain CT displaying the tumor with blood and parenchymal involvement.

There was a subjective complaint of bilateral leg weakness however his neurological examination did not reveal any leg weakness on either side. There were no visual disturbances upon examination.

3. Imaging and lab results

On his arrival, He had Normal serum sodium (139 meq/l) and potassium (3.5 meq/l) levels, as well as a complete blood count, calcium (8.6 mg/dl), magnesium levels (1.9 mg/dl) and creatinine levels (0.65 mg/dl) were noted. His serum phosphate was low (0.9 mg/dl, normal range 2.5–5) and his liver function tests were within normal limits except high levels of alkaline phosphatase 334 (iu/l, normal range 40–130).

The patient underwent a CT scan of his brain and a MRI which demonstrated an intracranial tumor, (Figs. 1,2), which was thought to be an olfactory groove meningioma with a tumor related hematoma with minor mass effect. This extra-axial hyperdense lesion measured 2.6 × 1.9 cm. The tumor itself appeared as an enhanced, bleeding tumor with an attachment in the anterior skull base at the olfactory groove. At first it was presumed that the patient had a meningioma or schwannoma per the radiology report.

4. Intraoperative notes, immediate postoperative and follow up

The patient was operated in our institution and a gross total resection was achieved. A frontal craniotomy was done avoiding opening of the frontal sinus. Tumor resection as well as hematoma removal was done. Thinking of a meningioma originating from the olfactory area, drilling of the cribriform bone was done in order to achieve a complete removal. Reconstruction was done using abdominal wall fat and a small pericranial flap. During surgery a pathology specimen was taken. The intraoperative frozen section pathology report came back as a meningioma.

At the end of surgery the patient was extubated, with a full recovery. His immediate postoperative course and hospital stay throughout were uneventful and the patient was discharged home. 16 days after discharge the patient was readmitted to our institution with general weakness. Upon second admission the patient was fully

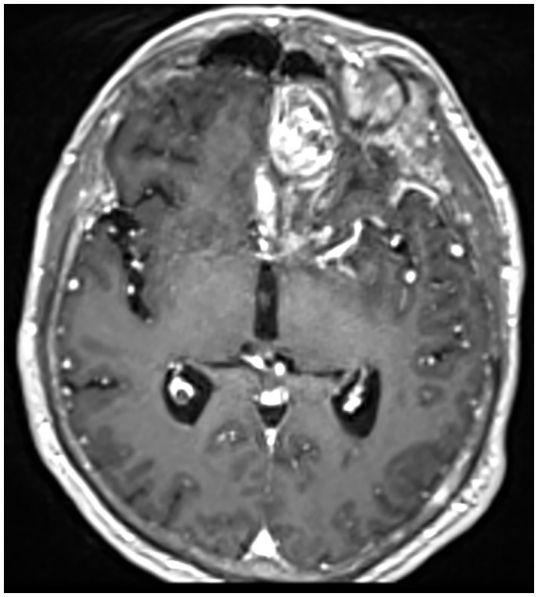

Fig. 2. An axial T1 contrast MRI displaying the tumor with the hematoma above it.

awake and oriented to time, place and situation. He was afebrile and hemodynamically stable. The patient's lab results showed a normal complete blood count, normal serum calcium (8.4 mg/dl), phosphorus (3.5 mg/dl) and magnesium (2.2 mg/dl). Vitamin D 25-OH was 37 nmol/l. The patient underwent a repeat CT scan of his brain which was very much similar to his postoperative CT scan albeit lower volume of free air within the skull (Figs. 3, 4, 5, 6). The patient was admitted to the neurosurgical ward for observation. A 24-h urine collection was obtained which showed hypocalciuria (< 15 mg) and urine phosphate within normal range (382 mg/24 h). The patient was recommended to stop his phosphate supplement.

In a detailed review of his past medical history, it was found that he had diffuse bone pain and gait disturbances with severe hypophosphatemia and hyperposphaturia for 6 years. A spine and pelvis CT scan was done 5 years before the surgery and showed many bone lesions at

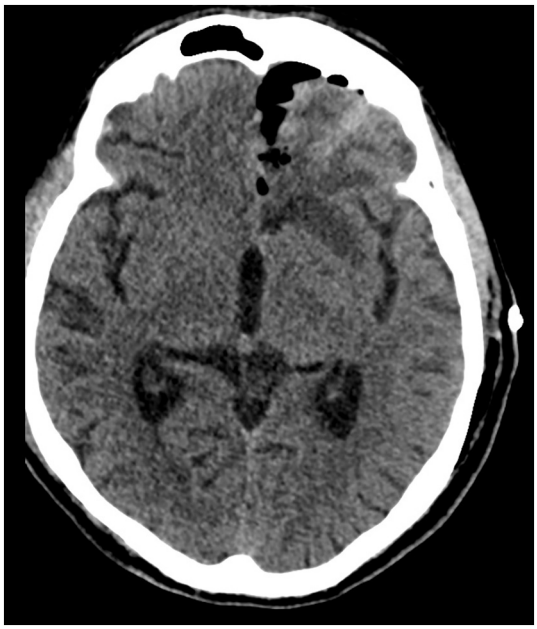

Fig. 3. An axial non-contrast brain CT demonstrating a gross total resection after surgical removal.

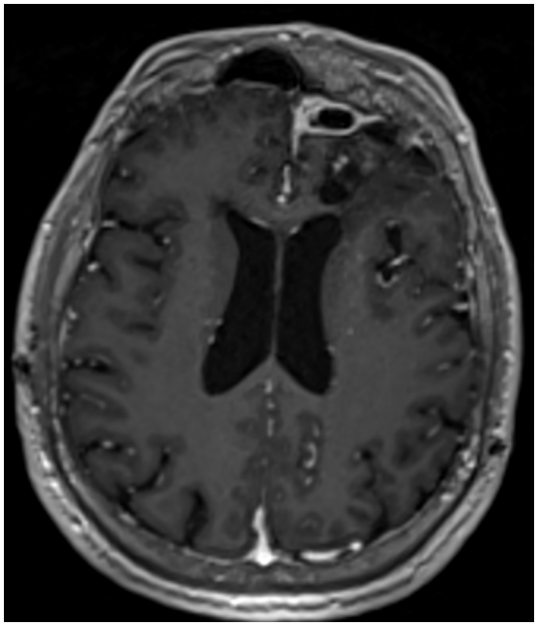

Fig. 4. An axial T1 contrast MRI displaying enhancement of the tumor cavity but no evidence of residual tumor.

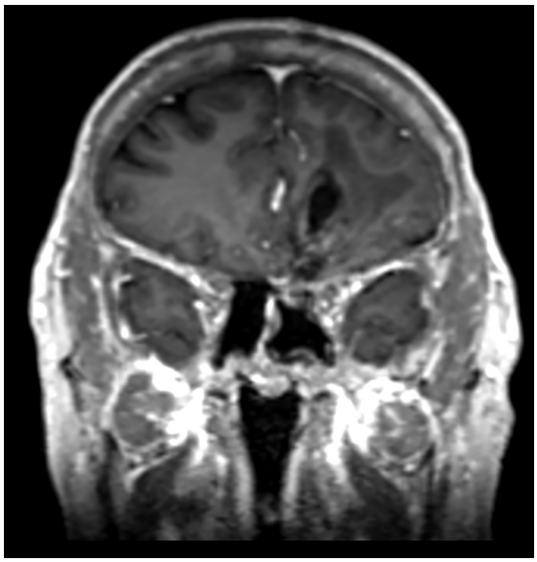

Fig. 5. A coronal T1 contrast MRI displaying gross total resection.

pelvis and vertebras (multiple myeloma work-up was carried-out and found to be negative). A bone scan 2 years later showed diffuse increased uptake and bone mineral density measured by dual-energy X-ray absorptiometry (DXA) was low (T score −3.5 at femoral neck and −3.6 at lumbar spine).

His second hospitalization was uneventful with resolution of his general weakness and he was discharged home.

This patient's final pathology report was noticeable for mesenchymal tumor components. Tumor cells were positive for vimentin, somatostatin receptor subtype 2A, CD56, SATN2, D2-40, BCL2 and cyclinD1, with a Ki67 proliferation index of 10%. Mitotic activity was very low (less than 1MF/10HPF).

5. Outcome

The patient was then followed up by his surgeon and an endocrinologist. At 2-months follow-up the patient reports improvement

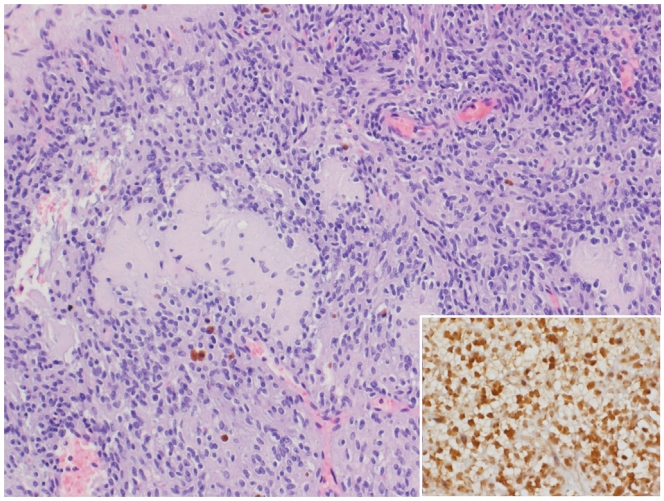

Fig. 6. Spindle/ovoid cell mesenchymal tumor with chondroid matrix production (H&E, original magnification X200). Inset: Tumor cells stain for nuclea isoform of fibroblast growth factor 23 (FGF23 polyclonal antibody, original magnification X400).

of his general weakness and gait disturbances, as well as bone pain. His neurological symptoms improved as well. The bone and muscle symptoms, that were active for years, almost disappeared during the follow up after the surgical resection of his tumor.

Follow up of his metabolic bone disease indicated excellent recovery. His serum calcium and phosphorus values are within normal limits and he needs only vitamin D supplement. There is no hyperphosphaturia. The patient is scheduled to undergo a CT scan of the bones in order to identify changes in his bones.

6. Discussion

We report on the treatment of a 58 year old male harboring a brain tumor with radiological features suggestive of a meningioma, however the pathology report concluded it was a phosphaturic mesenchymal tumor. There have been scant reports of intracranial lesions of PMTs. Reis-Filho et al. report of what was considered a cavernous meningioma in a 47 year old woman presenting with a 7 year history of muscle pain and diplopia [5]. Similar to our patient, this patient also presented with lab abnormalities, hypophosphatemia with normal serum calcium levels. During surgery, this was a highly vascularized tumor. The cells were strongly immunoreactive to vimentin. This patient had improved symptoms two weeks after surgery, which is a similar time frame of symptom improvement in our patient. Ellis et al. [6] report of an 8 year old presenting to the ER with severe headaches and inability to walk due to severe imbalance. A surgical removal of this tumor, which caused hydrocephalus in this patient, caused resolution of her symptoms with a tumor-free follow up of 42 months. This paper, in addition to others, displays the benign postoperative course after gross total tumor resection in these types of brain tumors [7]. The authors recommend follow up with serial imaging as well as 24 h urine phosphorus, serum phosphorus and calcium as well as 1-OH and 1,25-OH cholecalcifrol, alkaline phosphatase and serum FGF23 [6]. Fathalla et al. [8], report on a 49 year old female with developmental delay and a nonhealing ankle fracture requiring repeated surgery. Increased FGF23 subsequently lead to diagnosing an extra-axial space occupying lesion in the patient's right frontal lobe. Presenting with abnormalities similar to previous reports, (hypophosphatemia and normal calcium levels) this patient underwent a gross total resection with phosphate levels returning to normal and being able to ambulate on her own with a cast on her ankle. The authors mention the possibility of suspected meningiomas seen on imaging which are treated with conservative

management eventually turning out to be PMTs, therefore leading do misdiagnosis and a lower prevalence of these tumors [8].

Similarly to our patient, these above-mentioned papers advocate gross total resection which has led to recovery of the metabolic bone disease, complete resolution of symptoms with no recurrence seen on long term follow up periods. In addition, in exceedingly rare cases do PMTs present as a multifocal disease [9], decreasing the likelihood of complete remission after gross total resection.

Our patient presented with TIO due to mesenchymal tumor with a clinical and laboratory picture suggestive of a FGF23-secreting tumor. FGF23 is a known culprit in PMT associated TIO, and oversecretion of FGF23 is the cause of the metabolic bone disease in most of the cases (103–53,54,55,56,57) [10,11,12,13]. FGF23, located on chromosome 12p13.3 is a key player in the regulation of phosphorus. This peptide secreted by osteocytes and osteoblasts and it's primary function is reduction of phosphorus reabsorption in proximal renal tubules, as well as reduction of vitamin D 1α-hydroxylase expression that leads to reduced concentrations of $1\alpha,25(OH)_2D_3$(103–62,63). Oversecretion of FGF23 causes hyperphosphaturia, hypophosphatemia and vitamin D deficiency, with metabolic bone disease as a result. Surgical resection of the tumor reduces the FGF23 levels and enables recovery of the metabolic bone disease.

7. Conclusion

PMT tumors can cause laboratory changes which will alert the physician to their presence. Intracranial PMT tumors are an extremely rare entity however the treating physician must be aware to red lights such as muscle pain and laboratory abnormalities. This will alert the physician and direct him/her to the possibility of an intracranial PMT tumor. Gross total resection of these intracranial pathologies will most often times lead to complete resolution of symptoms with no recurrence reported hitherto. Further follow up and larger studies are needed in order to understand the natural history and postoperative course of these supposedly benign tumors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.inat.2018.12.010.

References

[1] J.M. Boland, P.J. Tebben, A.L. Folpe, Phosphaturic mesenchymal tumors: what an endocrinologist should know, J. Endocrinol. Investig. (February 2018), https://doi.org/10.1007/s40618-018-0849-5.

[2] W. Wu, C. Wang, J. Ruan, F. Chen, N. Li, F. Chen, A case report of phosphaturic mesenchymal tumor-induced osteomalacia, Medicine (Baltimore) 96 (51) (2017) e9470, , https://doi.org/10.1097/MD.0000000000009470.

[3] A.L. Folpe, J.C. Fanburg-Smith, S.D. Billings, et al., Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature, Am. J. Surg. Pathol. 28 (1) (2004) 1–30 http://www.ncbi.nlm.nih.gov/pubmed/14707860 , Accessed date: 13 May 2018.

[4] R.S. Bower, W.P. Daugherty, C. Giannini, I.F. Parney, Intracranial phosphaturic mesenchymal tumor, mixed connective tissue variant presenting without oncogenic osteomalacia, Surg. Neurol. Int. 3 (2012) 151, https://doi.org/10.4103/2152-7806.104745.

[5] J.S. Reis-Filho, M.E. Paiva, J.M. Lopes, August 2003: 47-year-old female with a 7-year history of osteomalacia and hypophosphatemia, Brain Pathol. 14 (1) (2004) 111–112 115 http://www.ncbi.nlm.nih.gov/pubmed/14997944 , Accessed date: 13 May 2018.

[6] M.B. Ellis, D. Gridley, S. Lal, G.R. Nair, I. Feiz-Erfan, Phosphaturic mesenchymal tumor of the brain without tumor-induced osteomalacia in an 8-year-old girl: case report, J. Neurosurg. Pediatr. 17 (5) (2016) 573–577, https://doi.org/10.3171/2015.9.PEDS14617.

[7] C.K. Ledford, N.A. Zelenski, D.M. Cardona, B.E. Brigman, W.C. Eward, The phosphaturic mesenchymal tumor: why is definitive diagnosis and curative surgery often delayed? Clin. Orthop. Relat. Res. 471 (11) (2013) 3618–3625, https://doi.org/10.1007/s11999-013-3178-1.

[8] H. Fathalla, M. Cusimano, A. Di Ieva, J. Karamchandani, R. Fung, K. Kovacs, Osteomalacia-inducing tumors of the brain: a case report, review and a hypothesis, World Neurosurg. 84 (1) (2015), https://doi.org/10.1016/j.wneu.2015.02.030 (189.e1–5).

[9] R. Arai, T. Onodera, M.A. Terkawi, T. Mitsuhashi, E. Kondo, N. Iwasaki, A rare case of multiple phosphaturic mesenchymal tumors along a tendon sheath inducing osteomalacia, BMC Musculoskelet. Disord. 18 (1) (2017) 79, https://doi.org/10.1186/s12891-017-1446-z.

[10] T. Shimada, S. Mizutani, T. Muto, et al., Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia, Proc. Natl. Acad. Sci. U. S. A. 98 (11) (2001) 6500–6505, https://doi.org/10.1073/pnas.101545198.

[11] R. Kumar, Tumor-induced osteomalacia and the regulation of phosphate homeostasis, Bone 27 (3) (2000) 333–338 http://www.ncbi.nlm.nih.gov/pubmed/10962341 , Accessed date: 14 May 2018.

[12] R. Kumar, J.D. Haugen, E.D. Wieben, J.M. Londowski, Q. Cai, Inhibitors of renal epithelial phosphate transport in tumor-induced osteomalacia and uremia, Proc. Assoc. Am. Physicians 107 (3) (1995) 296–305 http://www.ncbi.nlm.nih.gov/pubmed/8608414 , Accessed date: 14 May 2018.

[13] Q. Cai, S.F. Hodgson, P.C. Kao, et al., Brief report: inhibition of renal phosphate transport by a tumor product in a patient with oncogenic osteomalacia, N. Engl. J. Med. 330 (23) (1994) 1645–1649, https://doi.org/10.1056/NEJM199406093302304.