

# Phosphaturic mesenchymal tumor of the occipitocervical region: Report of two rare cases and literature review

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## Case report

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# Abstract

## Background

Tumor-induced osteomalacia (TIO) is regarded as a rare paraneoplastic syndrome mainly caused by phosphaturic mesenchymal tumor (PMT). To our known, only 5 occipitocervical PMTs have been described in the world's English literature. We reported two rare cases of occipitocervical PMT, and conducted a retrospective analysis of these 7 cases. The purpose of this study is to discuss the clinical characteristics and treatment of occipitocervical PMT.

## Case Presentation

Both patients were middle-aged females, and had a long-standing bone pain. In case 1, there were no abnormalities in biochemical indicators. The blood phosphorus was normal and alkaline phosphatase (ALP) was elevated in case 2. Magnetic resonance imaging (MRI) suggested that osteolytic bone destruction accompanied by a soft tissue mass in left C1-2 vertebra (case 1). In case 2, the bone destruction was located on the right C1-2 and the clivus. Then both patients underwent complete resection of tumor, and case 2 also received adjuvant radiotherapy, the histopathology revealed a PMT. Case 2 suffered recurrence during 5-year follow-up.

## Conclusions

Occipitocervical PMT is quite rare, and only 5 cases have been reported in the literature. Currently, complete resection of the tumor is the best option. The surgery is difficult, and requires delicate operation due to the complex anatomy of the occipitocervical region. Postoperative radiotherapy has little effect on local control. And further research is needed to confirm the effectiveness of the newly-emerged therapies.

# Background

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome characterized by severe hypophosphatemia and osteomalacia.[1] Most of the causative tumor is Phosphaturic mesenchymal tumor. PMT will overproduce fibroblast growth factor 23 (FGF23) which regulates serum phosphate concentrations.[2] Oversecretion of FGF23 can lead to increased renal phosphorus excretion and bone metabolism disorders. The clinical symptoms of PMT are not specific include bone pain, muscle weakness and pathologic fracture.[3] As far as we know, occipitocervical PMT was only described in 5 cases in the world's English literature. In this study, we report two rare cases of occipitocervical PMT treated in our hospital, and retrospectively analyzed these 7 cases to increase surgeons' understanding of this rare disease.

## Case Presentation

### Case 1

A 55-year-old woman was admitted to our spine tumor center, complaining dull pain throughout the body for 1 year and headache, a mass around her left mastoid process for 3 months. No significant medical history was found.

The laboratory tests showed no abnormality (blood routine test, serum phosphorus, calcium, ALP and tumor markers were normal). Physical examinations performed on admission revealed a 2 × 3 × 4 cm mass in the left mastoid process with poor mobility and no tenderness, restricted cervical spine movement. Muscle weakness of grades 4 for bilateral upper and lower extremities.

Computed tomography angiography (CTA) of vertebral artery indicated the internal density of lesion was not uniform with obvious enhancement (Fig. 1A). The left vertebral artery suffered from serious compression and stenosis (Fig. 1B). The cervical MRI revealed a large soft tissue mass in C1-2 and occipital bone. The atlas and axis were expansive bony

destruction, uneven enhancement was observed (Fig. 1C,D). Based on the laboratory tests and images, the diagnosis was unclear. An open biopsy was conducted and the preliminary diagnosis was suspected to be a PMT. To relieve her pain and avoid further compression, an operation of tumor completely removal by two separate stages was planned. However, the patient refused to undergo surgery after being informed of the risks and prognosis. She was treated with bisphosphonates to suppress osteolysis. One year later, patient came to our hospital for treatment with symptoms worsened. MRI revealed rapid progression of the lesion and much larger than before (Fig. 1E). The mass was about 80 mm in the longest diameter.

The posterior tumor resection and reconstruction were conducted first. During the operation, destruction of the left C1/2 appendix, occipital bone and part of the temporal bone were detected and resected through the piecemeal method with adoption of the computer assisted navigation system and 3D hawk eye technology. The tumor was sand-like, without intact capsule and clear boundary. The left vertebral artery was ligated due to the severe compression according to the preoperative blocking test. To guarantee the local solid reconstruction, an occipital-cervical fusion was performed down to the lower cervical spine (Fig. 1F). One month later, we carried out the anterior tumor resection. Bone destruction occurred in the anterior arch of the atlas and clivus. No reconstruction was performed after removing the tumor. The postoperative histopathologic examination verified the diagnosis of PMT. The tissue contained amounts of spindle cells, accompanied by giant cells and distinctive “grungy” calcification (Fig. 2). Immunological staining was as follows: CD34(-), S100(-), satb2 (+), CD68 (+), Lysozyme (-), Ki67 (20–30%+), CD45 (partly+), CD163 (partly+), CDK4 (partly+), CK19 (+), D2-40 (Foci+), epithelial membrane antigen (EMA, partly+).

The postoperative recovery was uneventful without severe complications and the symptoms disappeared quickly. The postoperative chemical indicators were basically normal (Fig. 3).

## Case 2

A 41-year-old woman presented with a 3-year history of progressive pain that originated from her low back and developed to the whole body gradually. The patient complained of sublingual discomfort and the tip of the tongue deflection for 3 months. A mass had been found around the right mastoid process for 1 week. No significant medical history was found.

Physical examinations revealed an approximately 2 × 2 × 2 cm mass in the right mastoid process with poor mobility and no tenderness. Movement of cervical spine was limited. And the muscle strength of bilateral upper and lower extremities was grade 4.

Laboratory findings showed normal serum phosphorous, increased alkaline phosphatase (141 U/L) and normal serum calcium.

CTA of the vertebral artery indicated that branches of the external carotid artery supplied blood for the mass, and the right vertebral artery and internal carotid artery were compressed and pushed away (Fig. 4A). The cervical MRI revealed bony destructions in the right C1-2 and clivus with a soft tissue mass. The lesion showed uneven enhancement (Fig. 4B,C). Both the MRI and CTA revealed a possible malignant tumor.

The biopsy was carried out and results revealed a PMT. A single posterior approach was planned to get the tumor resection and local reconstruction (Fig. 4D). Intraoperatively, the tumor was just like the sand, with sticky feature and unclear boundary. Same as the images, part of the upper cervical spine suffered from erosion. The occipito-cervical fusion was adopted to ensure the local stability. The tumor was a lesion composed of amounts of spindle cells, accompanied by “grungy” calcified and sticky matrix.

Immunohistochemical staining found positivity in CD31, CD34, Ki67(5%) and Fli-1, while other indicators such as EMA, AE1/AE3, S-100, SMA were negative. Combining her higher level of alkaline phosphatase, the final diagnosis was considered as PMT. Postoperative blood indexes were basically normal. One month later, she was advised to receive

gamma knife as an adjuvant therapy. 5 years after the initial operation, she came to our hospital again due to the local recurrence.

## Discussion

Phosphaturic mesenchymal tumor is first proposed by Weidner and Santa Cruz,[4] which is the common cause of tumor induced osteomalacia. In general, it is a benign, small lesion, which is difficult to detect, and malignant ones were less than 10% cases.[3] Primary site of PMT can be anywhere throughout the body, with 53% occurring in bone, 45% in soft tissue, and 2% in skin.[5–7] However, spinal PMT was rarely reported, especially Occipitocervical region.

In our review, totally 7 occipitocervical cases have been described in the English literature, including two cases we reported. Clinical data for these 7 patients are shown in Table 1. The mean age of these patients was 52.57 years (range 32–87 years) with a female predominance (all were female). Everyone suffered a long period of osteomalacia (mean time 2.86 years) before being ultimately diagnosed as PMT. In addition, all the patients underwent surgery, two of them were partial resection and both suffered recurrence. 2 patients received adjuvant radiotherapy. A total of 4 cases (57.14%) had recurrence during the follow-up.

Table 1  
Clinical features of 7 cases with occipitocervical PMT published in English and our current study.

| Author                    | Age (y) | Sex    | Location                         | Recurrence/metastasis   | Treatment                                                                     | Duration of Osteomalacia | Follow-up |
|---------------------------|---------|--------|----------------------------------|-------------------------|-------------------------------------------------------------------------------|--------------------------|-----------|
| Mulani M et al, 2017[8]   | 48      | Female | left occipitotemporal bone       | No                      | left retromastoid craniotomy and resection of tumor                           | 2 years                  | 1 months  |
| Folpe A et al, 2004[17]   | 32      | Female | C1 vertebra                      | unresectable recurrence | surgery and radiotherapy                                                      | 4 years                  | 3 years   |
| Basu S et al, 2016[25]    | 53      | Female | skull base and left basi-occiput | Multiple recurrence     | Partial resection of tumor and retromastoid craniotomy                        | 2 years                  | 13 months |
| Mishra T et al, 2019[26]  | 52      | Female | left occipital bone              | No                      | complete resection of the tumor and left retromastoid craniotomy              | 2 years                  | 3 months  |
| Fatani HA et al, 2013[27] | 87      | Female | C2 vertebra                      | Multiple recurrence     | Partial resection of tumor and C2 laminectomy                                 | 6 years                  | unknown   |
| Our case 1                | 55      | Female | left occipitocervical region     | No                      | anterior and posterior complete resection of tumor; occipital-cervical fusion | 1 years                  | 2 years   |
| Our case 2                | 41      | Female | Right C1-2 vertebra and clivus   | local recurrence        | posterior resection of tumor and radiotherapy                                 | 3 years                  | 5 years   |

Diagnosis of occipitocervical PMT is usually difficult in clinical practice, and the nonspecific symptoms such as a long-standing bone pain, muscle weakness or limited activity often interfere with the doctor's judgment. Then patients are often treated with calcium and phosphorus supplements. The lesion is not detected in the occipitocervical region until symptoms of nerve compression such as tinnitus[8] or a large mass occur. Our cases presented with a long-standing bone pain, headache and tongue deflection. And both patients could feel a large mass at the back of neck.

Biochemical indicators are mainly low serum phosphate, high ALP, low serum 1,25(OH)2D3, normal or slightly low serum calcium and high FGF-23. While there is also a few patients with normal lab findings.[6, 9, 10] In our study, the biochemical indicators of case 1 showed no abnormalities which made diagnosis difficult.

In the early stage of PMT, the tumor is usually small and in obscure locations. Thus locating PMT is challenging, and the lesion often remained undetected by conventional tests. Many studies have confirmed the value of octreotide scan and PET/CT in early diagnosis.[1, 3, 11, 12] Technetium-99m octreotide scintigraphy can detect the expression of somatostatin receptors (SSTRs) and the accuracy rate is appropriately 60%.[1, 13] Jain A et al conducted a prospective study and used

contrast-enhanced 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) to locate the tumor. The result showed the sensitivity of PET-CT was 87.5%, and positive predictive value was 100%.[14] CT and MRI are valuable in analyzing the degree of bone destruction and the size of soft tissue mass. On CT scans, bone lesions are typically osteolytic, show a narrow zone of transition, and commonly contain internal matrix. On MRI examination, PMTs are usually T1 hyperintense, T2 mixed intensity, and uneven enhancement. Our two cases were detected easily through MRI and CT, because the tumor had grown too large which could be observed easily.

Histologically, majority of the PMT are benign and rich in spindle cells. The matrix demonstrates cartilaginous or myxomatous areas, abundant blood vessels, and metaplastic bone. And the tumor often lacks nuclear atypia and mitotic figures with low nuclear grade. Rarely, malignant PMT presented with increased cellularity, a high nuclear grade and excessive mitotic activity.[3, 15, 16] On immunohistochemical analysis, PMT has been scarce except for complementary studies performed to exclude other differential diagnoses. Folpe A et al[17] reported that desmin, S100 protein, CD34, and cytokeratins were usually negative. Recent studies showed a high sensitivity but limited specificity of FGF23 expression. Other newly-discovered markers such as SSTR2A, ERG, CD56, and DOG1 may be useful for diagnosis and differential diagnosis of PMT.[18]

At present, the treatment of PMT mainly includes medical therapy, surgical therapy, chemoradiotherapy and octreotide therapy. While surgical resection remains the main treatment option which can improve the abnormality of the biochemical indicators, and relieve the symptoms. The anatomy of the occipitocervical region is complex and contains many important structures such as vertebral arteries, nerve roots and spinal cord. Therefore, the operation on this site is difficult and delicate. In our cases, vertebral artery was enveloped by the mass and the surrounding normal tissue was severely compressed. We used 3D hawk-eye technology and computer-assisted navigation system to carefully isolate and completely resect the tumor lesion. However, sometimes complete excision is not possible because the boundaries of the tumor are not well identified, and the surgeon had to perform partial resection. Sun Z et al reported about 5% patients experienced recurrence due to incomplete resection.[19] In our review, two patients of occipitocervical PMT undertook partial resection and both had recurrence (Table 1). Radiotherapy as a common adjuvant therapy has been shown to be effective in many cancers. One patient of our cases received postoperative radiotherapy, but had a local recurrence during follow-up. Folpe A et al[17] also reported a case of PMT in atlas. The patient undertook adjuvant radiotherapy, and suffered recurrence 3 years after surgery. Therefore, the effect of adjuvant radiotherapy was limited in occipitocervical PMT. In addition, calcium and phosphorus supplements may slightly relieve symptoms but cannot correct abnormal biochemical markers (hypophosphatemia).[20, 21] In our study, case 1 was initially treated with bisphosphonates to inhibit bone destruction, but the results showed that bisphosphonates had little control over tumor progression. Octreotide therapy is controversial now. Elston M et al[20] used preoperative octreotide therapy to treat oncogenic osteomalacia. The results showed a reduction in the serum FGF23, the serum phosphate initially increased but did not normalize. While Ovejero D et al reported that octreotide therapy is ineffective in treating tumor-induced osteomalacia in a short term.[22] Furthermore, other new therapies were also used to treat inoperable or recurrent PMTs including human monoclonal anti-FGF23 antibody,[23, 24] somatostatin analogues and peptide receptor radionuclide therapy (PRRT). Basu S et al used <sup>177</sup>Lu-DOTATATE PRRT for the first time to treat patients with multiple recurrence. 3 months after treatment, the symptoms and indicators improved.[25] However, the long-term efficacy and safety of these therapies are unknown, and requires further research.

## Conclusions

Occipitocervical PMT is quite rare, and only 5 cases have been reported in the literature. Currently, complete resection of the tumor is the best option. The surgery is difficult, and requires delicate operation due to the complex anatomy of the occipitocervical region. Postoperative radiotherapy has little effect on local control. And further research is needed to confirm the effectiveness of the newly-emerged therapies.

## Abbreviations

TIO, tumor-induced osteomalacia; PMT, phosphaturic mesenchymal tumor; ALP, alkaline phosphatase; MRI, Magnetic resonance imaging; FGF, fibroblast growth factor; CTA, computed tomography angiography; SSTRs, somatostatin receptors; PRRT, peptide receptor radionuclide therapy

## Declarations

## Availability of data and materials

We respect the patient's rights to privacy and to protect his identity, so we do not wish to share our patient data. We presented, in the manuscript, all the necessary information about the case report. Raw data regarding our patient is in his admission file, a file that is strictly confidential, without the possibility of publishing raw data from it.

## Competing interests

The authors declare that they have no competing interests.

### Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

### Ethics approval and consent to participate

This clinical study of the abovementioned case report was waived by the institutional review board at our center.

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We declare that we have not received any kind of fund from any source and do not have any conflict of interest in this present study.

## Authors' contributions

Author LXZ is mainly responsible for Conceptualization, Methodology, Writing - Review and Editing. Author YWH is mainly responsible for Data curation and investigation. Author JJY is mainly responsible for Writing - Original Draft and software. Authors JY, GJB, LJJ, KG and XH is mainly responsible for data collection and analysis. Corresponding author TLL is mainly responsible for validation, supervision and project administration. All authors read and approve the final manuscript.

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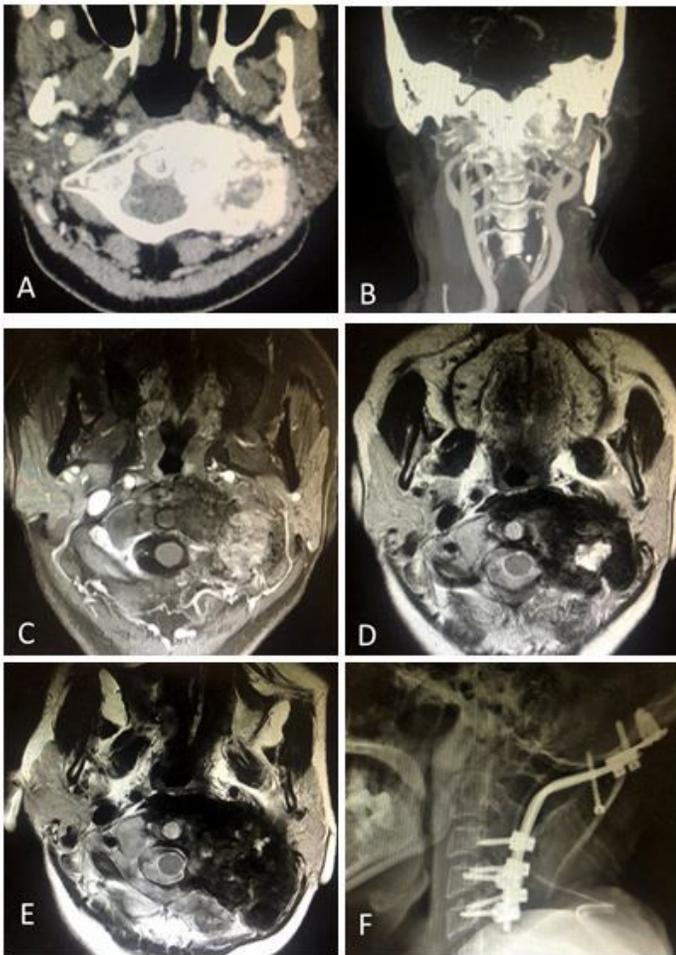
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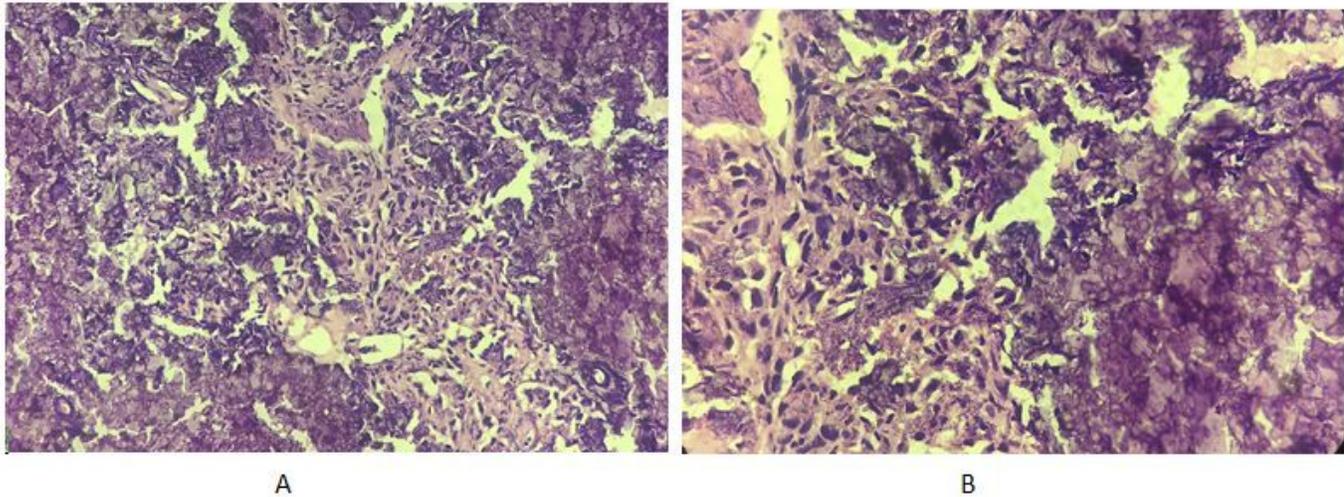
## Figures



**Figure 1**

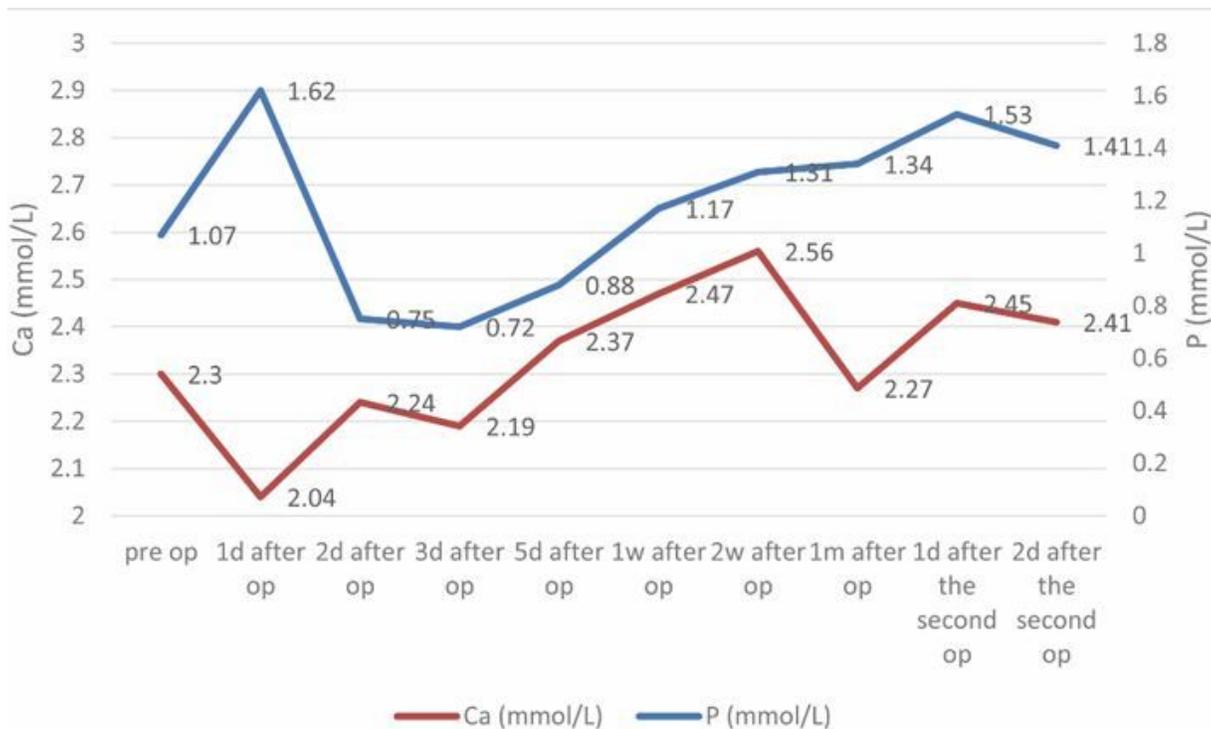
The preoperative and postoperative images of PMT in case 1. A, the transverse section CT scan, showing the atlas was expansive bony destruction, and the internal density of lesion was not uniform with obvious enhancement. B, the coronal CTA scan, revealing the mass surrounded and invaded the left vertebral artery. C, the transverse section of T1-weighted MRI,

showing a large soft tissue mass involving the left upper cervical spine and occipital bone. D, transverse section of T2-weighted MRI in 2017, showing the left side of atlas was destructed with uneven internal signals. E, transverse section of T2-weighted MRI in 2018, showing rapid progression of the lesion and much larger than before. F, the image of the postoperative X-ray.



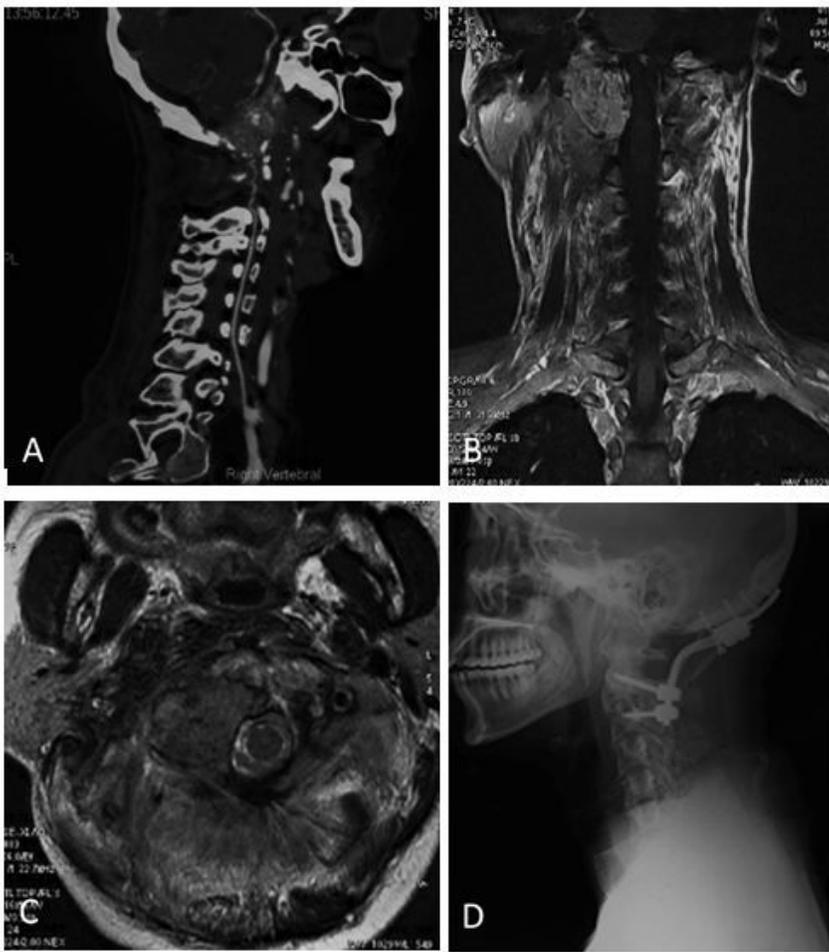
**Figure 2**

Histopathology of the tumor in Case 1. A, showed the tumor cells were mainly elongated spindle shaped, with round or oval nuclei, diffuse or fascicular growth, and some were braided or hemangioperiderma shaped around thick-walled vessels, with scattered osteoclast-like giant cells (hematoxylin-eosin stain, original magnification  $\times 100$ ). B, showed that adipocytes, mucinous chondroid cells, stellate cells and other cells can be seen in the matrix, and osteoid matrix can be seen, with partial calcification, which is scattered in the form of clouds and masses of granular particles (hematoxylin-eosin stain, original magnification  $\times 200$ ).



**Figure 3**

Results of blood analysis of Serum phosphorus levels and calcium level in case 1.



**Figure 4**

The preoperative and postoperative images of PMT in case 2. A, the right vertebral artery is surrounded by a mass and compressed. B, C, the coronal and transverse section of T2-weighted MRI, revealing a soft tissue mass involving the C1-2 vertebra and clivus with uneven enhancement. D, the image of postoperative X-ray.