The Laryngoscope

Case Report

Malignant Phosphaturic Mesenchymal Tumor of the Larynx

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Phosphaturic mesenchymal tumors are rare neoplasms predominantly originating in the trunk and extremities. Malignant variants are exceedingly rare, and can present significant diagnostic challenges to the pathologist and otolaryngologist alike. This report describes the first case of malignant phosphaturic mesenchymal tumor involving the larynx, and emphasizes the importance of vigilance in both histopathologic and clinical actions so that appropriate treatment can be provided in a timely manner. The clinical presentation, radiologic and histologic features, and management are discussed.

Key Words: Phosphaturic mesenchymal tumor, osteomalacia, larynx.

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INTRODUCTION

Phosphaturic mesenchymal tumors are rare neoplasms with the potential to incite osteomalacia from paraneoplastic processes. Malignant variants are exceedingly rare and often share several histologic characteristics with giant cell tumors. Despite these similarities, malignant phosphaturic mesenchymal tumors have several unique characteristics; failure to recognize this neoplasm as distinct entity may have significant treatment implications. We present the first reported case involving the larynx, and emphasize the importance of vigilance in both histopathologic and clinical actions so that appropriate treatment can be provided in a timely manner.

CASE REPORT

A 24-year-old female presented to another hospital with acute airway obstruction and underwent urgent tracheostomy. Direct laryngoscopy at that time demonstrated a large glottic mass. Initial biopsy reports were suggestive of low-grade chondrosarcoma. She was then referred to our institution where transoral laser surgery revealed a mass arising at the posterior cricoid plate with transglottic extension to the left paraglottic space. Contrast-enhanced computed tomography demonstrated a heterogeneous mass extending from the aryepiglottic folds to the level of the tracheostomy cannula. There was evidence of thyroid and cricoid cartilage erosion (Fig. 1). The tumor was debulked and histologic sections showed a lesion comprised of round to spindled cells with vesicular nuclei, variably prominent nucleoli, and eosinophilic cytoplasm set within a myxoid to collagenous stroma containing irregularly shaped pseudovascular spaces. Scattered osteoclast-like multinucleated giant cells were seen throughout the lesion. The patient was diagnosed with a giant cell tumor of soft tissue. Less than 1 month later, there was aggressive regrowth of the lesion and a repeat endoscopic resection was attempted. The mass was found to completely occlude the subglottis, glottis, and supraglottis. Further CO_2 laser debulking was performed and additional biopsies were again taken. Similar to the prior biopsy, the lesion consisted of a cellular proliferation of stellate to spindled-shaped cells with scattered osteoclast-type multinucleated giant cells embedded within a myxoid to hyalinized, collagenous stroma (Figs. 2 and 3) There were several areas exhibiting hypercellularity, high nuclear grade, and mitotic activity of more than 5 mitoses per 10 high-power fields. In addition, characteristic foci of "grungy" calcification and osteoid were present (Fig. 4) Also noted were irregularly shaped pseudovascular spaces creating a "sieve-like" appearance. After careful review by several head and neck pathologists at two institutions, the histomorphologic features of the lesion were determined to be most consistent with

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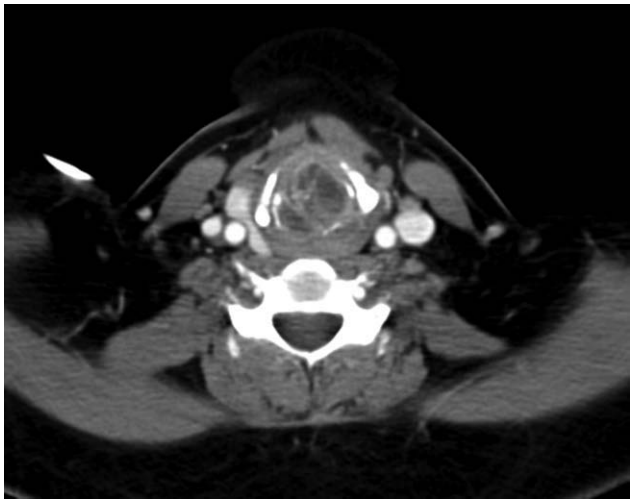

Fig. 1. Axial, contrast-enhanced computed tomography demonstrating a mass at the level of the cricoid, with evidence of thyroid and cricoid cartilage erosion.

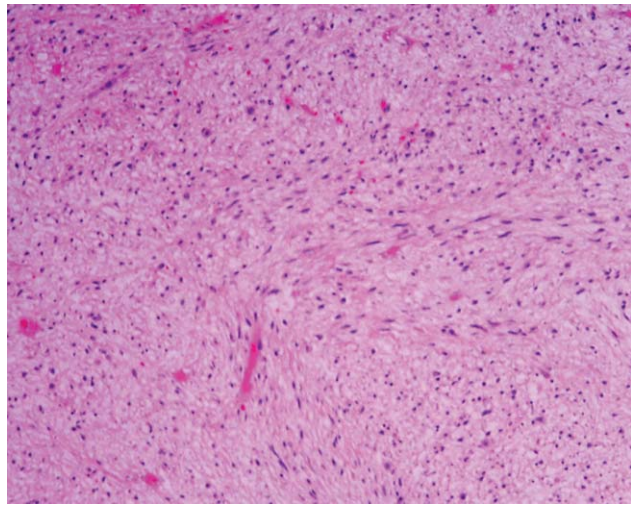

Fig. 3. Loose myxoid stroma. H&E stain. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

a malignant phosphaturic mesenchymal tumor, mixed connective tissue (PMTMCT) type. The differential diagnosis included giant cell tumor of larynx, spindle cell carcinoma with heterologous elements, and high-grade osteosarcoma. The presence of large areas of spindle cells devoid of osteoclast-like giant cells and "grungy" calcified matrix (characteristics of PMTMCT) argued against a giant cell tumor of larynx. Moreover, the young age of the patient as well as negative stains for numerous cytokeratins (cytokeratin [CK] AE1/AE3, panCK, CK903, CK5/6, and CAM 5.2) did not support a diagnosis of spindle cell carcinoma with heterologous elements. A high-grade osteosarcoma was excluded based on the characteristic features of PMTMCT. The patient did not demonstrate evidence of phosphaturia, hyperphosphatemia, decreased 1,25-dihydroxyvitamin D, or clinical osteomalacia. After a multidisciplinary tumor board evaluation the patient underwent several courses of neoadjuvant chemotherapy, including doxorubicin, docetaxel, and gemcitabine. There was only limited response to chemotherapy and the patient subsequently underwent a total laryngectomy at which time residual tumor extended from the posterior cricoid cartilage to the arytenoids and aryepiglottic folds. Pathology was consistent with residual phosphaturic mesenchymal tumor. Infiltration into cricoid cartilage and osseous metaplasia were noted, and tumor necrosis was estimated at 80%. She remains free of disease at four months follow-up.

DISCUSSION

Phosphaturic mesenchymal tumors (PMT) are rare neoplasms that are associated with decreased serum 1,25-

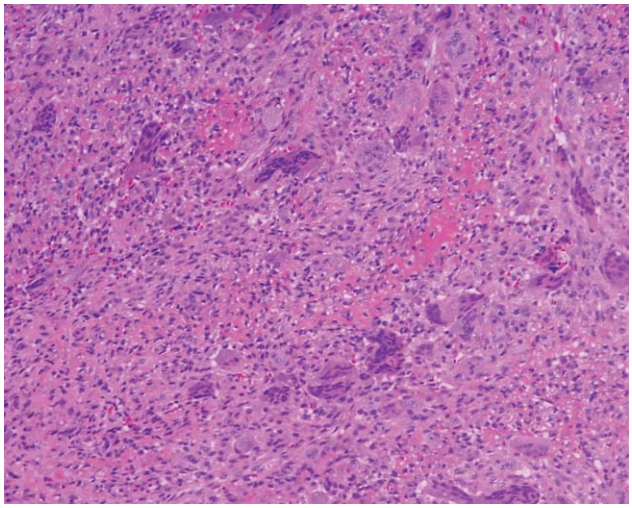

Fig. 2. Cellular spindle cell region with osteoclast-like multinucleated giant cells and osteoid-like matrix. H&E stain. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

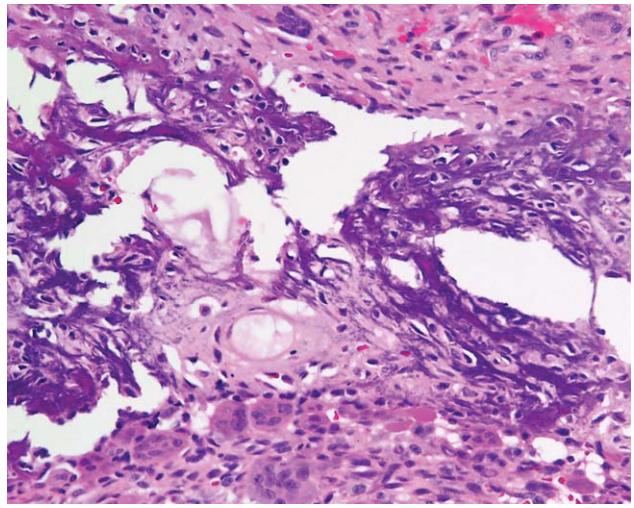

Fig. 4. Cartilage-like stroma with "grungy" calcification and osteoclast like giant cells (in the lower half). H&E stain. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

dihydroxyvitamin D_3 levels, vitamin D resistance, and renal phosphate wasting.[1,2] This entity was initially described as part of a group of soft tissue neoplasms with the potential to incite osteomalacia by virtue of a paraneoplastic process.[1,3] Included in this initial characterization of tumors causing "oncogeneous osteomalacia" were hemangiopericytomas, giant cell tumors, osteoblastomas, and hemangiomas.[1,2,4] Despite similarities between these neoplasms, PMT are now thought by many to share specific histologic characteristics, which together make them a morphologic entity distinct from these other soft tissue tumors.[1,4]

Clinically, patients often present with evidence of renal phosphaturia and osseous changes, including pathologic fractures, bone pain, and generalized fatigue. This owes in large part to the location of the primary lesion being frequently limited to the extremities and trunk, which allow the tumor to remain physically elusive yet pathologically active.[1–3]

Histologically, PMT demonstrate spindle cells with granular chromatin and elongated nuclei in a mixture of giant cells, cartilaginous, or myxomatous areas, prominent blood vessels, and metaplastic bone. The vast majority of specimen lack nuclear atypia, necrosis, or mitotic figures.[1,2,5] Interestingly, despite the low nuclear grade, many lesions have been shown to invade surrounding tissue. Rarely, these lesions demonstrate evidence of malignancy, including increased cellularity, a high nuclear grade and excessive mitotic activity.[1] This histologic description shares similarities with giant cell neoplasms, and these tumors can therefore be mistaken as such. In addition, the immunohistochemical profile of PMTs may also resemble that of malignant hemangiopericytomas, having the potential to stain positive for vimentin and factor XIIIa.[2]

The effort to isolate PMTs from other similar lesions has stimulated the genetic analysis of several proteins upregulated in this neoplasm. Genetic analysis of PMTs demonstrates the modulation of matrix extracellular phosphoglycoprotein, osteopontin, and heat-shock protein 90. Importantly, PMT have also been demonstrated to produce an excessive quantity of fibroblast growth factor-23 (FGF-23), a specific protein that affects renal phosphate handling and results in the phosphate wasting seen with these tumors.[1,3] In a 2004 study by Toyosawa et al.[5] the expression of an acidic phosphoprotein, Dentin matrix protein 1 (DMP1), has been shown to be unique to PMT. The authors conclude that immunohistochemical evidence of DMP1 expression could prove useful in the diagnosis of these lesions.

As suggested, it is highly likely that the unique classification of these lesions has been underutilized since the benchmark writings of Weidner and Santa Cruz in 1987.[1,4] As a result, the true incidence of PMT is unknown. The focus of many nonpathologic reports on treatment and clinical management, rather than histopathologic diagnosis, has been cited as a cause for underrecognition of PMT. The absence of a histologic focus by most journal articles thereby leaves broad, nonspecific labels in the place of precise and accurate diagnoses for these neoplasms.[1,6]

In one of the most extensive reviews to date, Folpe and colleagues[1] attempt to address this issue of misdiagnosis by performing a retrospective analysis of mesenchymal tumors causing osteomalacia, or with histologic features felt to be identical to those of PMT. In this report, 29 tumors causing oncogeneous osteomalacia and 3 tumors determined to be PMT without oncogeneous osteomalacia were reviewed. Of the 32 specimens, a total of 28 lesions were determined to be PMT, 12 of which received a revised diagnosis as such. Four of the 28 specimens had clinicopathologic characteristics of malignancy, and 3 existed without evidence of oncogeneous osteomalacia. No lesions were located in the head and neck. Despite a seemingly broad differential diagnosis that may accompany this lesion, recognition of the specific features of this neoplasm should allow for an accurate diagnosis and appropriate treatment. These features, eloquently described by Folpe et al., allow for the distinction of PMT from soft tissue hemangiopericytoma, giant cell tumors of bone and soft tissue, chondroma of soft parts, mesenchymal chondrosarcoma, sclerosing hemangioma, osteosarcoma, and pleomorphic sarcoma.

Treatment of benign PMT involves management of underlying osteomalacia, in addition to management of the primary lesion. The reversal of abnormal bone metabolism, if present, is common after surgical excision of the primary lesion. Lack of this normalization has been cited as a reliable predictor of incomplete excision, or lesion recurrence.[4,5] Lesions without evidence of oncogenic osteomalacia may be encountered incidentally, as they are frequently limited to the trunk or extremities and produce limited early symptomatology. When arising in other locations, PMT are often more conspicuous, and herald symptoms associated with their particular site of origin. As discussed, lesions arising in the head and neck are considered uncommon, and malignant lesions of the head and neck are indeed rare.[3,6,7] The location of the neoplasm described in this report, spanning the glottis with extension from the supraglottis to the subglottic trachea, has not been documented in the literature to date. Fortunately, the patient's localizing symptoms contributed to a vigilant workup and punctual diagnosis, possibly contributing to the absence of the paraneoplastic processes often seen in more advanced lesions.

Although other phosphaturic tumors have been described in the head and neck, the vast majority of reports discuss benign, noninvasive neoplasms. One other malignant lesion of the head and neck was reported in a patient at the Kanazawa University in Japan. This lesion involved the tongue and was treated with both radiation and surgery. The authors describe a successful reduction in tumor size with radiation; however, gross tumor remained after radiotherapy.[8] Although external beam radiation was not utilized preoperatively in our patient, she received postoperative radiotherapy and remains free of disease at early follow-up.

Finally, despite our limited success in reducing gross tumor burden with the use of neoadjuvant chemotherapy, significant tumor destruction was noted on histologic evaluation. Although this may merely reflect rapid growth of the neoplasm, it may also be attributable to a more pronounced chemotherapeutic effect than was first appreciated.

CONCLUSION

Malignant PMT are uncommon neoplasms that share several histologic characteristics with other lesions, and are likely an underdiagnosed entity. We describe the first reported malignant PMT to involve the larynx, and highlight the importance of a committed, multidisciplinary approach to this challenging diagnosis. Although a successful chemoradiation protocol has not been established for this rare neoplasm, the best treatment of malignant PMT is surgical.

BIBLIOGRAPHY

1. Folpe A, Fanburg-Smith J, Billings SD, 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* 2004;28:1–30.
2. Toyosawa S, Tomita Y, Kishino M, et al. Expression of dentin matrix protein 1 in tumors causing oncogenic osteomalacia. *Mod Pathol* 2004;17: 573–578.
3. Yun KI, Kim DH, Pyo SW. A phosphaturic mesenchymal tumor of the floor of the mouth with oncogenic osteomalacia: report of a case. *J Oral Maxillofac Surg* 2009;67:402–405.
4. Weidner N, Santa Cruz D. Phosphaturic mesenchymal tumors. A polymorphous group causing osteomalacia or rickets. *Cancer* 1987;59: 1442–1454.
5. Policarpio-Nicolas ML, Abbott TE, Dalkin AC, Bennett-Wick J, Frierson HF Jr. Phosphaturic mesenchymal tumor diagnosed by fine-needle aspiration and core biopsy: a case report and review of literature. *Diagn Cytopathol* 2008;36:115–119.
6. Woo VL, Landesberg R, Imel EA, et al. Phosphaturic mesenchymal tumor, mixed connective tissue variant, of the mandible: report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;108:925–932.
7. Shelekhova KV, Kazakov DV, Michal M. Sinonasal phosphaturic mesenchymal tumor (mixed connective tissue variant): report of 2 cases. *Am J Surg Pathol* 2010;34:596–597.
8. Uramoto N, Furukawa M, Yoshizaki T. Malignant phosphaturic mesenchymal tumor, mixed connective tissue variant of the tongue. *Auris Nasus Larynx* 2009;36:104–105.