AT THE FOREFRONT
UChicago Medicine

University of Chicago Department of Pathology
IRAP Case Presentations Handout
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Case #1: Drs. Manisha Goel and Jennifer Bennett

Diagnosis: *STK11* adnexal tumor

Clinical History: A 46-year-old female without any significant medical history presented to an outside hospital with abdominal pain. Imaging studies revealed a complex right adnexal cyst. Serum CA-125 was within normal limits. She underwent exploratory laparoscopy which revealed a right fallopian tube mass that ruptured intraoperatively. Right salpingectomy was performed.

Gross and Microscopic Findings: Gross examination revealed a 6 cm mass involving the ampullary portion of the fallopian tube with unremarkable tubal fimbriae. Microscopically, the tumor was cellular and paratubal with focal extension into the wall of the fallopian tube. The tumor showed diverse architectural patterns with cords and trabeculae being the predominant patterns. Other patterns mimicking tubular, glandular, and cribriform formations were also evident. Intervening fibrous stroma was prominent in addition to a striking myxoid matrix in the background. Individual cells were columnar to cuboidal, with ovoid nuclei that often showed irregular and angulated contours. Nuclei were uniformly atypical with vesicular chromatin and prominent nucleoli. Nuclear grooves were also not infrequent. The tumor had readily identifiable mitotic figures, present at a count of greater than 10 per 10 high-power fields.

Differential Diagnosis:

- Female adnexal tumor of probable Wolffian origin (FATWO)
- Sex-cord stromal tumor, NOS
- Mesonephric-like adenocarcinoma
- Endometrioid carcinoma
- Mesothelioma

Ancillary studies:

- IHC: The tumor was positive for CAM5.2, AE1/AE3, inhibin, WT1, D2-40, calretinin (focal), CD10 (focal), and AR (rare cells), but cells were negative for EMA, SF1, FOXL2, CK7, CK20, Claudin-4, GATA-3, TTF-1, ER, PR, PAX8, SALL-4, and OCT-3/4. BRG-1 and INI-1 showed retained expression in tumor cells.

- Molecular: *STK11* splice site mutation (c.598-2A>G) (VAF-83%); *STK11* deletion (copy number loss) resulting in loss of heterozygosity; other copy number alterations: 1p loss, 1q gain.

Discussion: While morphology and immunohistochemistry, in this case, were not distinctive enough to categorize this tumor initially, similar tumors were recently compiled into a novel diagnostic entity described by Bennett et al. These are called *STK11* adnexal tumors since they are characterized by pathogenic mutations, variants of uncertain significance, or deletions in *STK11* gene, which is a well-known tumor suppressor gene. This tumor has a predilection for paratubal location and consists of an

assortment of epithelial patterns in a distinct myxoid matrix. Interanastomosing cords and trabeculae are the most commonly observed patterns. Although there is substantial diversity with multiple histologic patterns present in almost all of these tumors, individual cells are uniformly atypical with prominent nucleoli and frequent nuclear grooves. Immunohistochemically, these tumors show variable expression for epithelial and most sex cord markers, with the exception of SF1 often negative (rarely focally positive) and FOXL2 consistently negative. This morphological and immunohistochemical profile closely resembles the above-mentioned differentials, which led to many of these cases being diagnosed previously as FATWO or unclassified or extraovarian/fallopian tube sex cord tumors before the diagnostic *STK11* gene alterations were detected. The majority of cases described behaved aggressively with recurrences in 80% and metastatic disease reported in 50%. Of particular interest, is the association of this tumor with Peutz-Jeghers syndrome (PJS) in a significant number of cases scoring the underlying importance of genetic counseling in these cases. The diagnosis of this tumor requires the detection of recurrent *STK11* alterations for which employing a next-generation sequencing panel reporting both mutations and copy number alterations is essential in the diagnostic workup.

In summary, tumors arising in paratubal location with these unique morphologic features including a myxoid matrix should prompt molecular testing to detect diagnostic alterations in the *STK11* gene. Establishing a diagnosis of *STK11* adnexal tumor in turn can lead to genetic testing to detect patients with associated PJS.

References:

1. Bennett JA, Young RH, Howitt BE et al. A distinctive adnexal (usually paratubal) neoplasm often associated with Peutz– Jeghers syndrome and characterized by STK11 alterations (STK11 adnexal tumor): a report of 22 cases. Am. J. Surg. Pathol. 2021; 45; 1061–1074.

2. Simpson JL, Michael H, Roth LM. Unclassified sex cord-stromal tumors of the ovary: a report of eight cases. Arch Pathol Lab Med. 1998;122:52–55.

3. Barker D, Sharma R, McIndoe A, et al. An unusual case of sex cord tumor with annular tubules with malignant transformation in a patient with Peutz-Jeghers syndrome. Int J Gynecol Pathol. 2010;29:27–32.

4. Mirkovic J, Dong F, Sholl LM, et al. Targeted Genomic Profiling of Female Adnexal Tumors of Probable Wolffian Origin (FATWO). Int J Gynecol Pathol. 2019;38:543–551.

5. Bennett JA, Ritterhouse LL, Furtado LV, et al. Female adnexal tumors of probable Wolffian origin: morphological, immunohistochemical, and molecular analysis of 15 cases. Mod Pathol. 2020;33:734–747.

6. Taxy JB, Battifora H. Female adnexal tumor of probable Wolffian origin: evidence of a low grade malignancy. Cancer. 1976;37:2349–2354.

7. Shah R, McCluggage WG. Unclassifiable Malignant Extraovarian Sex Cord-Stromal Tumors: Report of 3 Cases and Review of Extraovarian Sex Cord-Stromal Tumors. Int J Gynecol Pathol. 2017;36:438–446.

8. Moore M, Boyde A, Rowlands GL, et al. Primary fallopian tube sex cord tumour: tubal counterpart of uterine tumour resembling ovarian sex cord tumour. Histopathology. 2018;73:175–178.

Case #2: Drs. Jung Woo Kwon and Tatjana Antic

Diagnosis: Low grade oncocytic tumor

Clinical history: The patient is a 59-year-old with an incidentally found left exophytic renal mass measuring 6.7 cm. He underwent left partial nephrectomy.

Gross findings: A 6.7 cm well-circumscribed, unencapsulated, hemorrhagic, yellow-tan solid mass. No central scar is present.

Microscopic findings: Well-circumscribed, solid, eosinophilic tumor with tightly packed nests of monomorphic cytologically-bland cells with occasional tubule formation. Tumor cells have ample eosinophilic granular cytoplasm and smooth round nuclei with coarse chromatin. Perinuclear clearing is focally present.

Differential diagnosis:
- Renal oncocytoma
- Eosinophilic variant of chromophobe renal cell carcinoma
- Papillary renal cell carcinoma with solid morphology (formerly known as type II)
- Eosinophilic solid and cystic renal cell carcinoma
- Succinate dehydrogenase deficient renal cell carcinoma
- Other oncocytic tumors of kidney
    - Eosinophilic vacuolated tumor
    - Low grade oncocytic tumor

Ancillary studies:

1) Immunohistochemistry:
    - Vimentin: Negative
    - CK7: Diffusely positive
    - CD117: Negative

2) Molecular studies:
    - No copy number variation or pathogenic variant identified.

Discussion: Groups of solid eosinophilic tumors in tuberous sclerosis patients that had similar morphology to renal oncocytoma and eosinophilic variant of chromophobe renal cell carcinoma were first described in 2014. Studies revealed that these groups of solid eosinophilic tumors could also occur sporadically in non-tuberous sclerosis patients via *TSC/MTOR* mutations. Based on morphology and immunohistochemical profile, these solid eosinophilic renal tumors were further classified into 3 distinct groups:

1) Eosinophilic solid and cystic renal cell carcinoma: Combination of solid and cystic architecture with cells containing abundant eosinophilic cytoplasm. CK20 and vimentin are positive while CK7 and CD117 are negative. It usually presents at low stage and has good prognosis, but there are reported cases of metastases (hence the name renal cell carcinoma).

2) Eosinophilic vacuolated tumor (formerly described as high grade oncocytic tumor): Predominantly solid nests of eosinophilic cells in the background hypocellular or edematous stroma. Many tumor cells are

variably vacuolated. CD117 is positive while CK7 and vimentin are negative. There is only limited data on its malignant potential and additional studies are underway.

3) Low grade oncocytic tumor: Solid nests of eosinophilic cells with occasional tubule formation. Often contains focal hypocellular or edematous stroma. Tumor cells have ample eosinophilic cytoplasm with minimal nuclear membrane irregularity. Perinuclear clearing is often present, but only focally. CK7 is diffusely positive while CD117 and vimentin are negative. There is only limited data on its malignant potential but it is generally thought to have low malignant potential.

All three groups are now recognized in the 2022 WHO classifications of urinary and male genital tumours. Diagnosis of our case of solid eosinophilic tumor is low grade oncocytic tumor as its morphology and immunohistochemical profile of diffuse CK7 positivity and CD117/vimentin negativity fit perfectly. Renal oncocytoma is ruled out as CK7 should be negative. Chromophobe renal cell carcinoma is ruled out as CD117 should be positive. Solid type of papillary renal cell carcinoma (formerly known as type II) is ruled out as vimentin should be positive. Small subset of low grade oncocytic tumor is known to have no pathogenic variant, and our tumor belongs to the subset.

References:

1. Guo J, Tretiakova MS, Troxell ML, Osunkoya AO, Fadare O, Sangoi AR, Shen SS, Lopez-Beltran A, Mehra R, Heider A, Higgins JP, Harik LR, Leroy X, Gill AJ, Trpkov K, Campbell SC, Przybycin C, Magi-Galluzzi C, McKenney JK. Tuberous sclerosis-associated renal cell carcinoma: a clinicopathologic study of 57 separate carcinomas in 18 patients. Am J Surg Pathol. 2014 Nov;38(11):1457-67. doi: 10.1097/PAS.0000000000000248. PMID: 25093518.

2. Tjota M, Chen H, Parilla M, Wanjari P, Segal J, Antic T. Eosinophilic Renal Cell Tumors With a TSC and MTOR Gene Mutations Are Morphologically and Immunohistochemically Heterogenous: Clinicopathologic and Molecular Study. Am J Surg Pathol. 2020 Jul;44(7):943-954. doi: 10.1097/PAS.0000000000001457. PMID: 32091432.

3. Tjota MY, Wanjari P, Segal J, Antic T. TSC/MTOR-mutated eosinophilic renal tumors are a distinct entity that is CK7+/CK20-/vimentin-: a validation study. Hum Pathol. 2021 Sep;115:84-95. doi: 10.1016/j.humpath.2020.12.006. Epub 2020 Dec 22. PMID: 33352195.

4. WHO Classification of Tumours, 5th edition, Urinary and Male Genital Tumours

5. Yang P, Cornejo KM, Sadow PM, Cheng L, Wang M, Xiao Y, Jiang Z, Oliva E, Jozwiak S, Nussbaum RL, Feldman AS, Paul E, Thiele EA, Yu JJ, Henske EP, Kwiatkowski DJ, Young RH, Wu CL. Renal cell carcinoma in tuberous sclerosis complex. Am J Surg Pathol. 2014 Jul;38(7):895-909. doi: 10.1097/PAS.0000000000000237. PMID: 24832166; PMCID: PMC4139167.

Case #3: Drs. James Paik, Andrea Olivas, and Tatjana Antic

Diagnosis: Embryonal Rhabdomyosarcoma

Clinical History: A 67-year-old male presented with a 7-month history of lower urinary tract symptoms that progressed to gross hematuria with acute urinary retention 1 month prior to resection. His PSA was not elevated and cystoscopy was unremarkable. Pelvic MRI revealed a solid and cystic mass arising from the prostate. He underwent an open radical prostatectomy with bilateral pelvic lymph node dissection.

Gross and Microscopic Findings: Gross examination revealed a 7 x 6.5 x 3 cm cystic lesion along the posterolateral peri-urethral aspect that arrived disrupted. It had a ragged, red-tan lining and was densely adherent to the rectum. Microscopically, the lesion exhibited both solid and cystic architecture. There were areas of stromal hypercellularity with round-to-oval, hyperchromatic blue cells and some myxoid areas. Lesional cells condensed around blood vessels and below portions of benign prostatic urethra with squamous metaplasia. Cells with eosinophilic cytoplasm and eccentric nuclei were also observed. More than 20 mitotic figures were observed per 10 high power fields.

Differential Diagnosis:

- Benign prostatic hyperplastic nodules
    - Benign stromal nodules
- Prostatic stromal tumors
    - Phyllodes
    - STUMP
    - Sarcoma
- Sarcomatoid carcinoma
- Other
    - Hematologic malignancies
    - Leiomyosarcoma
    - Rhabdomyosarcoma

Ancillary studies:

- **IHC:** Lesional cells were positive for Desmin and Myogenin and negative for Androgen receptor and CK7.
- **FISH:** FISH was negative for the characteristic *PAX3/FOXO1* and *PAX7/FOXO1* fusion products found in alveolar rhabdomyosarcomas.
- **NGS:** Pathologic mutations were detected in *ARID1A*, *KRAS*, *PIK3CA*, and *EP300.*

Discussion: Sarcomas arising from the prostate are exceedingly rare, accounting for 0.1-0.2% of all prostate neoplasms, and one study finds that rhabdomyosarcomas account for roughly one-third of these diagnoses. Most rhabdomyosarcomas occur in the first decade of life, and rhabdomyosarcoma has an aggressive clinical course and a poor prognosis in adults. Patients often present late stage with advanced disease. Important histologic features include hyperchromatic cells with varying morphology, myxoid stroma, perivascular condensation, and rhabomyoblastic cells. Embryonal rhabdomyosarcomas

exhibit a cambium layer. The differential diagnosis is broad, but can be narrowed using a few key immunohistochemical stains: Desmin, Myogenin, Androgen receptor, and Keratins.

A wide variety of non-specific mutations have been documented in embryonal rhabdomyosarcomas, including gains in chromosomes 2, 8, and 12, as well as losses of heterozygosity at the 11p15 locus. This patient had pathologic mutations in ARID1A, KRAS, PIK3A, and EP300. About 6% of embryonal rhabdomyosarcomas exhibit PIK3A mutations, and 6% of cases exhibit KRAS mutations.

The patient's post-operative course was complicated by hematuria and an anastomotic leak. Four months after their primary resection, imaging found a 14 cm recurrence, and the patient underwent a pelvic exenteration. Two months after this procedure, the patient was diagnosed with pulmonary metastases and scheduled for adjuvant chemotherapy.

References:

1. Hansel DE, Epstein JI. Sarcomatoid carcinoma of the prostate: a study of 42 cases. Am J Surg Pathol. 2006 Oct;30(10):1316-21.

2. Musser JE, Assel M, Mashni JW, Sjoberg DD, Russo P. Adult Prostate Sarcoma: the Memorial Sloan Kettering Experience. Urology. 2014 Sep;84(3):624-8.

3. Olivas AD, Antic T. Rhabdomyosarcoma of the Adult Prostate: A Case Report With Complete Molecular Profile. International Journal of Surgical Pathology. 2020;28(1):92-98.

4. Olivas AD, Taxy J, Wolsky R, Antic T. Phyllodes Tumor of the Prostate With Epithelial Intestinal Metaplasia. Am J Surg Pathol. 2018 Jun;42(6):836-839.

5. Park H, Park S, Kim KH, Cho MS, Sung SH, Ro JY. Stromal nodules in benign prostatic hyperplasia: morphologic and immunohistochemical characteristics. Prostate. 2014 Oct;74(14):1433-43.

Case #4: Drs. Raghad Kherallah and Aliya Husain

Diagnosis: Thymoma, AB type

Background: 72-year-old male smoker who presented as transfer from OSH for evaluation of a lung mass. Chest X-ray revealed a left upper lobe heterogenous mass encasing the central and peripheral pulmonary arteries with invasion into the mediastinum.

Morphology: The biopsy revealed round to oval epithelioid cells with vesicular chromatin and small nucleoli. Focally, spindled cells were identified. These tumor cells were arranged in nests and formed pseudorosettes. Multiple lymphocytes were scattered between the epithelioid cells.

Differential diagnosis: Lung adenocarcinoma, squamous cell carcinoma, neuroendocrine tumor, thymoma, and thymic carcinoma.

Ancillary Studies

IHC: The tumor cells were positive for CK5/6, CAM5.2, and p40 and were negative for TTF-1, CD117, synaptophysin, and chromogranin. The lymphocytes were positive for TdT.

Molecular: KRAS c. 176_178del, p.A59del and PIK3CA c.1624G>A, p.E542K

Discussion:

WHO type AB thymoma is comprised of both type A (bland spindle cells associated with few lymphocytes) and type B (small plump ovoid cells admixed with numerous lymphocytes) discrete components. These tumor cells can be arranged in a storiform pattern, hemangiopericytoma-like pattern, nested rosette-like pattern, solid sheet pattern, or no pattern at all. They can be associated with myasthenia gravis and rarely with paraneoplastic syndromes such as hypogammaglobulinemia and pure red cell aplasia.

The morphologic features seen in this biopsy (spindle-round epithelial cells, pseudorosette formation, and numerous lymphocytes) and the immunohistochemical pattern (TdT positive lymphocytes and p40/cytokeratin positive tumor cells) support the diagnosis of a thymoma AB type. The top differentials at the time included thymoma, thymic carcinoma, and poorly differentiated squamous cell carcinoma. However, the presence of immature TdT positive lymphocytes strongly favored the tumor to be from thymic origin over squamous cell carcinoma of the lung. Additionally, CD117 was negative which favored thymoma over thymic carcinoma.

Interestingly, the molecular studies revealed PIK3CA and KRAS mutations/deletions, which can only be found in <1% of thymomas. Thymomas more frequently exhibit mutations in *HRAS*, *NRAS, p53*, and *general transcription factor 2I* (*GTF2I*). For cases such as this, in which the molecular does not aid in making the diagnosis, it becomes imperative that the lymphocytes in the biopsy are not missed and that a TdT stain is performed for diagnostic confirmation.

References

1. Christopher D.M. *Diagnostic Histopathology of Tumors*. Philadelphia: Elsevier Saunders, 2013. 1558-1614. Print.
2. Husain, Aliya N. *Thoracic Pathology*. Philadelphia: Elsevier , 2012. Print.

3. Marx, Alexander et al. “The 2021 WHO Classification of Tumors of the Thymus and Mediastinum: What Is New in Thymic Epithelial, Germ Cell, and Mesenchymal Tumors?.” *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* vol. 17,2 (2022): 200-213. doi:10.1016/j.jtho.2021.10.010
4. Radovich, Milan et al. “The Integrated Genomic Landscape of Thymic Epithelial Tumors.” *Cancer cell* vol. 33,2 (2018): 244-258.e10. doi:10.1016/j.ccell.2018.01.003
5. Sakane, Tadashi et al. “A mutation analysis of the EGFR pathway genes, RAS, EGFR, PIK3CA, AKT1 and BRAF, and TP53 gene in thymic carcinoma and thymoma type A/B3.” *Histopathology* vol. 75,5 (2019): 755-766. doi:10.1111/his.13936
6. Tateo, Valentina et al. “An Overview on Molecular Characterization of Thymic Tumors: Old and New Targets for Clinical Advances.” *Pharmaceuticals (Basel, Switzerland)* vol. 14,4 316. 1 Apr. 2021, doi:10.3390/ph14040316

Case #5: Drs. Emily Symes and Sandeep Gurbuxani

Diagnosis: EBV-positive inflammatory follicular dendritic cell/fibroblastic reticular cell (FDC/FRC) tumor

Clinical History: The patient is a 78-year-old female with history of bilateral papillary renal cell carcinoma status post bilateral partial nephrectomies in 2017. New PET-avid splenic lesions were noted in 4/2022. The patient underwent splenectomy in 7/2022.

Gross and Microscopic Findings: Gross examination revealed partially morcellated spleen with one 1.2 cm white-tan, well-circumscribed nodule and four detached white-tan nodules with central necrosis, measuring from 1.8 to 3.8 cm in greatest dimension. H&E stain revealed spindle cell infiltrate with admixed small lymphocytes and plasma cells.

Differential Diagnosis:
- Metastatic carcinoma
- Melanoma
- Thymoma
- Mesenchymal tumors:
    - GIST
    - Leiomyoma
    - SFT

Ancillary Studies:
Immunohistochemistry:
- EBV in situ hybridization, SMA positive
- CD21, D2-40, clusterin negative, can be negative for all follicular dendritic cell markers
- CD3, CD20, CD68 highlighting background T-cells, B-cells, and macrophages

Discussion:
EBV-positive inflammatory follicular dendritic cell tumor is a rare tumor composed of a low-grade proliferation of mesenchymal dendritic cells. Malignancy is extranodal in 80% of cases, involving the spleen, liver, and GI tract and nodal in approximately 15%. The median age is 49 years with no gender predilection. Patients present with a slow-growing mass and may have fever and lymphadenopathy. Malignant cells may sparse and obscured by the inflammatory infiltrate, so diagnosis requires a high degree of suspicion.

Microscopically, the architectural pattern varies and may be fascicular, storiform, whorled, diffuse, or reticular. Spindled, oval, or epithelioid tumor cells with eosinophilic cytoplasm and indistinct cell borders (syncytial features) are characteristic. Multiple nuclei and/or pseudoinclusions may also be present. Tumor cells are positive for EBV in situ hybridization and for one or more follicular dendritic cell markers, including CD21, CD23, CD35, clusterin, CNA.42, CXCL13, and podoplanin.

Lineage of EBV-infected cells is uncertain and varies between nodal and extranodal cases. One case series demonstrated that spindle cells were positive for EBV in all extranodal cases with rare EBV-positive T- and B-cells. EBV-positive follicular dendritic cells and coexpression of SMA was also noted in extranodal cases.

No specific molecular alterations are associated with the tumor. However, mutations in genes in the NF-κB pathway and involving cell cycle regulation may be seen.

First line treatment is complete surgical excision. Chemotherapy or radiotherapy may also be required. Poor prognosis is associated with tumor size ≥ 6 cm, necrosis, high mitotic count (≥ 5 mitoses / 10 hpf), and atypia. Local recurrence occurs in 28% of cases, and metastasis in 27%, most commonly involving lung, liver, bone, or lymph nodes.

References:

1. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: A Report from the Clinical Advisory Committee. *Blood*. 2022 Jun 2:blood.2022015851. doi: 10.1182/blood.2022015851. Epub ahead of print. PMID: 35653592.
2. Facchetti F, Simbeni M, Lorenzi L. Follicular dendritic cell sarcoma. *Pathologica*. 2021;113(5):316-329. doi:10.32074/1591-951X-331. PMID: 34837090.
3. Arber DA, Kamel OW, van de Rijn M, et al. Frequent presence of the Epstein-Barr virus in inflammatory pseudotumor. *Hum Pathol*. 1995;26(10):1093-1098. doi:10.1016/0046-8177(95)90271-6. PMID: 7557942.
4. Kutok JL, Pinkus GS, Dorfman DM, Fletcher CD. Inflammatory pseudotumor of lymph node and spleen: an entity biologically distinct from inflammatory myofibroblastic tumor. *Hum Pathol*. 2001;32(12):1382-1387. doi:10.1053/hupa.2001.29679. PMID: 11774173.

Case #6: Drs. Chandni Desai and Nicole Cipriani

Diagnosis: Phosphaturic mesenchymal tumor

Clinical History: The patient is a 43-year-old male with hypophosphatemia and osteomalacia who presented with an expansile, lytic, right maxillary mass. Serum FGF23 was elevated. The patient subsequently underwent a right partial maxillectomy.

Gross and Microscopic Findings: Gross examination revealed expansion of the right maxillary alveolus and involvement of the roots of the maxillary teeth by a well-circumscribed, tan-yellow mass. Microscopy revealed a proliferation of spindle cells interspersed within a moderately cellular stroma that was associated with indistinct islands and nests of plump epithelioid cells. Abundant perivascular and stromal eosinophilic to basophilic matrix with patchy coarse calcification was present. There was no necrosis, increased mitoses, perineural, or lymphovascular invasion.

Differential Diagnosis:

- Solitary Fibrous Tumor
- Mesenchymal Chondrosarcoma
- Osteosarcoma
- Central giant cell granuloma
- Ameloblastic fibrosarcoma
- Phosphaturic mesenchymal tumor

Ancillary Studies: The epithelial islands were positive for AE1/AE3, p63, p40, and CAM5.2 and likely represented odontogenic rests. Both spindle and epithelial cells were negative for SMA, desmin, CD34, and S100. STAT6, beta-catenin, ERG and FLI1 were also negative. FGF23 CISH showed positivity in the spindle cells but not in the epithelial islands.

Discussion: Phosphaturic mesenchymal tumor (PMT) is a common cause of tumor induced osteomalacia (TIO), a rare paraneoplastic syndrome wherein tumor cells secrete FGF23. FGF23 is involved in phosphate homeostasis and is normally secreted by osteocytes in response to increased calcitriol. However, in the presence of tumor cells, the normal feedback loop of FGF23 is disrupted and secretion of this growth factor leads to decreased renal phosphate reabsorption, decreased renal 1, 25-dihydroxyvitamin D production, and ultimately decreased bone mineralization, or osteomalacia. Symptoms include bone pain, muscle weakness, and an increased propensity to fractures. Although a rare cause of osteomalacia, TIO, often caused by PMT, is an important consideration in patients exhibiting these symptoms, especially if FGF23 is inappropriately normal or high and there is no improvement with vitamin D supplementation. Studies have shown that a diagnosis of PMT has sometimes preceded the diagnosis of TIO. Thus, although it is of utmost importance to consider the entirety of the patient's clinical profile when making histopathologic diagnoses, there sometimes may be no clinical context that suggests a diagnosis of PMT. In this case, a high index of suspicion,

radiographic correlation, and the judicious use of immunohistochemistry is paramount in confirming a diagnosis of PMT.

The differential diagnosis of a proliferating, cellular spindle cell neoplasm in the craniofacial skeleton is vast and can include solitary fibrous tumor, mesenchymal chondrosarcoma, osteosarcoma, central giant cell granuloma, ameloblastic fibrosarcoma (AFS), and PMT. The presence of grungy, bluish matrix with coarse calcification surrounding moderately cellular spindle cells may resemble malignant chondroid and osteoid neoplasms, but the cells of PMT are not markedly atypical or pleomorphic and mitoses are infrequent. Imaging of PMT typically reveals a lytic lesion as opposed to the sunburst pattern seen with osteosarcoma. In addition, immunohistochemistry is invaluable in eliminating other spindle cell neoplasms such as solitary fibrous tumor.

Entrapped, proliferating epithelial islands seen in tumors of the maxilla and mandible are most likely odontogenic rests that, when coupled with a cellular, spindle cell stroma, may resemble a biphasic odontogenic tumor such as AFS. However, the stroma of PMT, though sometimes cellular, is not frankly sarcomatous and ameloblastic islands are not present thus helping to eliminate AFS as a diagnosis. Lastly, FGF23 CISH may be used to confirm the diagnosis if any doubt remains.

PMT is treated with complete surgical resection and lab values as well as symptoms are expected to normalize rapidly. Recurrence and metastasis is rare but can be seen when there is increased nuclear pleomorphism, greater than 5 mitoses/HPF, and necrosis.

References:

1. Agaimy, A, Skalova, A, Franchi, A, Alshagroud, R, Gill, A J, Stoehr, R, Baumhoer, D & Bauer, S (2020) Histopathology 76, 814– 821. https://doi.org/10.1111/his.14053 Ameloblastic fibrosarcoma: clinicopathological and molecular analysis of seven cases highlighting frequent BRAF and occasional NRAS mutations
2. Akinyamoju AO, Olusanya AA, Adeyemi BF, Kolude B. Ameloblastic fibrosarcoma: Report of a case. J Oral Maxillofac Pathol. 2013 Sep;17(3):424-6. doi: 10.4103/0973-029X.125212. PMID: 24574665; PMCID: PMC3927348.
3. Bocchialini G, Salvagni L, Guerini A, Castellani A. Central giant cell granuloma of the mandibular condyle: A rare case and a literature review. *Heliyon*. 2019;6(1):e03085. Published 2019 Dec 28. doi:10.1016/j.heliyon.2019.e03085
4. Brandi ML, Clunie GPR, Houillier P, et al. Challenges in the management of tumor-induced osteomalacia (TIO). *Bone*. 2021;152:116064. doi:10.1016/j.bone.2021.116064
5. Daram SP, Timmons C, Mitchell RB, Shah G. Desmoid Fibromatosis of the Maxilla. *Ear, Nose & Throat Journal*. 2020;99(1):NP6-NP8. doi:10.1177/0145561318824239
6. Folpe AL. Phosphaturic mesenchymal tumors: A review and update. Semin Diagn Pathol. 2019;36(4):260-268. doi:10.1053/j.semdp.2019.07.002
7. Ghorbani-Aghbolaghi A, Darrow MA, Wang T. Phosphaturic mesenchymal tumor (PMT): exceptionally rare disease, yet crucial not to miss. Autops Case Rep. 2017;7(3):32-37. Published 2017 Sep 30. doi:10.4322/acr.2017.031
8. Majumdar S, Boddepalli R, Uppala D, Rao AK. Mesenchymal chondrosarcoma of mandible. J Oral Maxillofac Pathol. 2016 Sep-Dec;20(3):545. doi: 10.4103/0973-029X.190963. PMID: 27721626; PMCID: PMC5051309.

9. Paparella M L, Olvi L G, Brandizzi D, Keszler A, Santini-Araujo E & Cabrini R L (2013) Histopathology 63, 551–557 Osteosarcoma of the jaw: an analysis of a series of 74 cases
10. Patil PG. Surgical obturator duplicating original tissue-form restores esthetics and function in oral cancer. World J Stomatol 2013; 2(4): 97-102
11. Qari, H., Hamao-Sakamoto, A., Fuselier, C. *et al.* Phosphaturic Mesenchymal Tumor: 2 New Oral Cases and Review of 53 Cases in the Head and Neck. *Head and Neck Pathol* 10, 192–200 (2016). https://doi.org/10.1007/s12105-015-0668-3
12. Qin H, Zeng H, Li H, Yuan S, Yang J. Malignant phosphaturic mesenchymal tumor-ossifying fibroma-like subtype: a case report and literature review. BMC Musculoskelet Disord. 2021;22(1):677. Published 2021 Aug 10. doi:10.1186/s12891-021-04558-1
13. 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(6):925-932. doi:10.1016/j.tripleo.2009.07.005
14. Wu H, Bui MM, Zhou L, Li D, Zhang H, Zhong D. Phosphaturic mesenchymal tumor with an admixture of epithelial and mesenchymal elements in the jaws: clinicopathological and immunohistochemical analysis of 22 cases with literature review. Mod Pathol. 2019;32(2):189-204. doi:10.1038/s41379-018-0100-0