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**IRAP 2021, October 25**

**CASE #1**

**PRESENTER:** Ansa Mehreen, MBBS.

**ATTENDINGS:** Ajit Paintal, M.D. and William Watkin M.D.

**CASE HISTORY:**

A 52-year-old female with a past medical history of multiple sclerosis presented with a slowly growing mass in the left parotid gland for which she underwent left parotidectomy. The mass measured 1.8 x 1.7 x 1.4 cm. Prior FNA per outside institution report showed Warthin’s tumor.

**FINAL DIAGNOSIS:** Oncocytic variant of mucoepidermoid carcinoma.

**DIFFERENTIAL DIAGNOSIS:**

* Oncocytoma,
* Oncocytic pleomorphic adenoma and,
* Oncocytic variant of mucoepidermoid carcinoma.

**DISCUSSION:**

Mucoepidermoid carcinoma (MEC) is a malignant epithelial neoplasm with variable components of mucinous, epidermoid, and intermediate cells forming solid and cystic patterns. The presence of mucin-containing cells, mucinous cyst formation, and foci of extravasated mucin are considered a hallmark of MEC, while intracellular mucicarmine staining is considered a diagnostic criterion. In majority of cases, tumor cells strongly express p63. There are many histologic variants of MEC, including oncocytic, clear cell, sclerosing, solid, Warthin-like, ciliated, and sarcomatoid. 60-80% of these tumors show *CRTC1*-*MAML2 or CRTC3-MAML2* fusion.

MEC is often difficult to diagnose due to the histologic mimickers and rarity or even the absence of intracellular mucicarmine staining in a large number of these tumors, which is considered a diagnostic criterion. In such instances, a more objective diagnostic ancillary test is warranted. We are reporting a parotid gland with a well-circumscribed nodular mass. Microscopically, the mass was predominantly eosinophilic with areas of lymphoid proliferation in the background. On high power, the neoplastic areas demonstrated variable histology but mainly composed of oncocytic cells with cystic spaces containing dense eosinophilic secretions. The oncocytes show centrally placed nuclei with abundant granular eosinophilic cytoplasm, a low nuclear:cytoplasmic ratio and minimal to no mitotic activity. The tumor had some other areas with duct formation and eosinophilic secretions in the duct lumens. Areas of lymphoid stroma with vague germinal center formation were also seen. Lastly, there were a few areas showing squamoid proliferation with fibrotic stroma around but given the patient’s history of FNA, a possible reaction to the FNA was debatable. On IHC tumor cells were positive for p63 and CK8/18. Special mucicarmine stain highlighted the abundant luminal and extracellular mucin, but intracellular mucin was not identified. However, the lesion had many other features of MEC and given the high suspicion, FISH analysis was performed which showed *CRTC1-MAML2* fusion.

Recently, a European group published a study in which 30 cases within the spectrum of oncocytic neoplasm including low-grade/uncertain oncocytic tumor,” “oncocytoma,” and “oncocytic carcinoma were tested for *MAML2* fusion irrespective of p63 and mucicarmine staining. 22 out of the 30 cases showed *MAML2* fusion and the diagnoses were revised to oncocytic variant of MEC. In their study, 5 cases were totally devoid of intracellular mucin and in 15 cases mucin containing cells were scarce and hardly discernable on H&E. Another study published by a Chinese group also highlights the importance of *MAML2* fusion for diagnosing Warthin-like variant of MEC. Their study included 16 cases that were diagnosed as lymphadenoma. These were tested for *MAML2* fusion and 9 of them harbored *MAML2* fusion.

We believe that the literature in this particular area is rapidly evolving, and there should be a low threshold for ordering ancillary tests like molecular diagnostics such as FISH analysis in cases with scarce goblet cells or other ambiguous histologic features to accurately classify these salivary gland tumors with overlapping histologic features.

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**CASE #2**

**PRESENTER:** Robert Toelke, M.D.

**ATTENDING:** William Watkin, M.D.

**CASE HISTORY:**

This patient is a 77-year-old female who presented to the emergency department complaining of abrupt onset bloody diarrhea associated with dull abdominal pain. This followed two months of rectal bleeding.

**FINAL DIAGNOSIS:** Enterocolic lymphocytic phlebitis.

**DIFFERENTIAL DIAGNOSIS:**

* Medium vessel vasculitis (polyarteritis nodosa),
* Small vessel vasculitis (ANCA vasculitides),
* Variable vessel vasculitis (Behçet’s disease) and,
* Vasculitis with associated systemic disease (Systemic Lupus Erythematosus).

**KEY FEATURES:**

* Rare form of vasculitis characterized by a lymphocytic infiltrate involving veins of bowel wall and mesentery. Arteries are spared.
* Restricted to gastrointestinal tract. Not associated with systemic vasculitis.
* Risk factors:
  + No definitive causes have been identified.
  + Possible association with medications, including flutamide.
  + Possible association with IgG4 disease.
* Patients present with abdominal pain, diarrhea and rectal bleeding. Some cases associated with intussusception.
* Surgery is only definitive treatment and is typically curative. Not responsive to medical therapy.

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**CASE #3**

**PRESENTER:** Aibek Akmatbekov M.D.

**ATTENDING:** Ajit Paintal M.D.

**CASE HISTORY:**

* 62-year-old female smoker.
* Medical History: breast lumpectomy – unspecified.
* Family History: lung, breast, colon, skin cancer.
* Chief complaint: postmenopausal bleeding.
* Endometrial biopsy: uterine cancer.
* Hysterectomy and staging.

**FINAL DIAGNOSIS:** High-grade Endometrial Adenocarcinoma, *POLE* Mutated.

**DIFFERENTIAL DIAGNOSIS:**

* Cervical Adenocarcinoma: high-grade glandular pattern, location of the cervix.
* Serous Adenocarcinoma: high-grade glandular pattern with few solid areas.
* High-Grade Endometrioid Adenocarcinoma: high grade glandular pattern with few solid areas.
  + Immunohistochemistry:
    - MMR protein expression: MLH1, PMS2, MSH2 – heterogeneous pattern with areas of loss and areas with intact expression, MSH6 intact.
    - p53 wild type pattern.

**DISCUSSION:**

* Histology:
* Glandular growth pattern with slit–like spaces with smooth luminal borders with superficial myometrial invasion,
* Solid areas are seen,
* Peri-tumor lymphoplasmacytic infiltration is present,
* High grade cytology with pleomorphic vesicular nuclei with prominent nucleoli and loss of polarity. No mucinous or squamous differentiation identified and,
* Mitotic figures are plentiful.
* One of seven lymph nodes is positive.
* Immunochemistry:
* p53 wild type expression, MLH1, PMS2, MSH2 – heterogeneous pattern with areas of loss and areas intact expression and MSH6 intact.
* NGS expanded panel:
* *POLE* hotspot mutation (P286R),
* Very high tumor mutation burden 253/MB,
* Other mutations like *TP53*, *MMR* etc.
* What is *POLE* Mutation?
* Catalytic subunit of DNA polymerase epsilon, which has a proofreading exonuclease domain responsible for maintaining fidelity during DNA replication.
* TCGA classification of endometrial adenocarcinoma (EC):
* *POLE* (ultramutated) subtype.
* MSI (hypermutated) subtype.
* Copy Number (CN) high subtype.
* Copy Number (CN) low subtype.
* Mutation spectra of the TCGA subgroups of EC:
* *POLE*-mutant subgroup: high tumor mutation burden, *POLE* mutation.
* MSI subgroup: MSI instability, intermediate mutation burden.
* Copy number high subgroup: high tumor aberration, low tumor mutation burden, recurrent *TP53* mutation.
* Copy number low subgroup: low tumor mutation burden, low grade, ER positive.
* Prognoses:
* *POLE-*mutant tumor: excellent prognosis (98% survival rate).
* CN high tumors: poor prognosis (48% survival rate).
* MSI and CN low tumors: intermediate prognosis (70-80% survival rate).
* Clinico-morphological features of *POLE*-mutant EC:
* Low stage, low frequency of LVI.
* High grade with bizarre cytological atypia and peri-tumor lymphoplasmacytic infiltrate.
* TransPORTEC RAINBO trial, consists of multiple subtrials:
* GREEN/MMRd trial: radiotherapy followed PD-L1 inhibitors,
* RED/ p53abn trial: chemoradiation followed by DNA damage response-targeting drugs,
* ORANGE/NSMP trial - chemoradiotherapy or radiation followed by hormonal therapy and,
* BLUE/*POLE* trial – observation only after surgery.
* Treatment of *POLE*-deficient tumor:
* Observation only after surgery due to excellent prognosis.

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**CASE #4**

**PRESENTER:** Joshua Wodskow, D.O.

**ATTENDING:** Mir Alikhan, M.D.

**CASE HISTORY:** A 69-year-old female with a past medical history of polycythemia vera, COPD, and hypertension. She presented complaining of dizziness, nausea, and diplopia. A non-contrast CT scan showed an enhancing soft tissue mass in the left sphenoid sinus invading the cavernous sinus. A biopsy of the sinus mass was obtained.

**FINAL DIAGNOSIS:** Myeloid Sarcoma with megaloblastic differentiation in a patient with polycythemia vera.

**DIFFERENTIAL DIAGNOSIS:**

* Acute lymphoblastic lymphoma,
* Diffuse large B-cell lymphoma and,
* High grade carcinoma.

**DISCUSSION:**

Polycythemia vera (PV), a myeloproliferative neoplasm, is normally an indolent disease with a relatively small (15-20%) progression rate to myelofibrosis (MF) over seven to fifteen years. This post-polycythemia vera, or “spent phase”, may then progress again to acute myeloid leukemia (AML). Rarely (2-10%), AML forms an extramedullary mass known as a myeloid sarcoma which may have the same or different differentiation from the medullary leukemia. In our case, the patient had typical disease progression from PV to MF over ten years and then three months later rapidly and unexpectedly progressed again to AML and myeloid sarcoma. Molecular and immunophenotypic features identified three possible explanations for the patient’s rapid progression.

The first feature is the highly unusual megakaryocytic differentiation exhibited by the patient’s AML. Leukemia with megakaryocytic differentiation and acute megakaryoblastic leukemias are known to be poor prognostic indicators with decreased survival rates compared to leukemias with other differentiations. The second and third features were discovered by Next Generation Sequencing performed on the patient’s bone marrow. The leukemia displayed the expected *JAK2* V617F mutation -nearly ubiquitous in PV patients- however, the allelic burden suggested a loss of heterozygosity. This loss of heterozygosity in *JAK2* leads to an accelerated disease course as the wild-type *JAK2* acts as competitive inhibitor for the oncogenic mutated *JAK2*. The third feature is the presence of two *TP53* mutations, R248W and R248Q. This is indicative of compound heterozygosity and a lack of a functional *TP53*. It is well known that *TP53* mutations contribute to poor prognoses in many malignancies and leukemia is no exception. Additionally, loss of heterozygosity of *TP53* has been found to have a worse prognostic impact.

With these three features the rapid progression seen in our patient can be understood. Recently many researchers have begun to advocate molecular phenotyping of newly diagnosed myeloproliferative neoplasms for this very reason.

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**CASE #5**

**PRESENTER:** Adesola Akinyemi, M.D., MPH.

**ATTENDING:** John Groth, M.D.

**CASE HISTORY:** 70-year-old male with a history of bladder urothelial carcinoma. He presented with right lower extremity pain and had a duplex which was positive for venous thromboembolus. A subsequent chest CT scan revealed showed a suspicious nodule in the right upper lung. Further workup with a PET scan showed mild activity in the lung; however, a hypermetabolic indistinct right pelvic sidewall mass was revealed.

**FINAL DIAGNOSIS**: *TFCP2*-rearranged spindle cell/sclerosing rhabdomyosarcoma.

**DIFFERENTIAL DIAGNOSIS:**

1. Sarcomatoid carcinoma,
2. Rhabdomyosarcoma, spindle cell/sclerosing variant and,
3. Dedifferentiated liposarcoma.

**DISCUSSION:**

* Classification of rhabdomyosarcomas, traditionally:
  + Alveolar,
  + Embryonal,
  + Pleomorphic and,
  + Spindle cell/sclerosing. Recently described subtypes of spindle cell/sclerosing rhabdomyosarcoma:
    - *NCOA2* and/or *VGLL2*-rearranged (infantile),
    - *MYOD1* mutations (mostly seen in young adults) and,
    - *TFCP2*-rearranged (mostly seen in adults).
    - These subtypes differ from traditional spindle cell/sclerosing rhabdomyosarcoma in clinicopathologic behavior, molecular alteration and prognosis.
* Transcription Factor Cellular Promoter 2 (*TFCP2)* gene:
  + Located on chromosome 12q13.
  + Encodes a transcription factor which binds the alpha-globin promoter and activates transcription of the alpha-globin gene.
    - Encoded protein regulates erythroid gene expression.
  + Also activates many other cellular and viral gene promoters.
* *TFCP2* rearrangement rhabdomyosarcoma:
  + First identified in 2018 following search for gene fusions combined with unsupervised expression analysis of a series of 184 sarcomas.
  + Epidemiology and clinical features:
    - Wide age spectrum, 11-86 years, (median age = 31 years).
    - Slight female preponderance.
    - Most cases are intraosseous, with craniofacial preponderance. Other sites include the sacrum, peritoneum, femur and inguinal region.
  + Morphology:
    - Most tumors show hybrid of spindle cell and epithelioid cells. Few cases show pure epithelioid and spindle cell morphologies while some cases exhibit round cell morphology.
    - In most cases, malignant cells are arranged in sheets, short fascicles (usually spindle cell areas).
    - Some cases have trabecular pattern and some show more sclerosis, fibrous and myxoid areas.
    - In most cases, cells have abundant eosinophilic cytoplasm.
    - Nuclei are mostly monomorphic with mid-sized and vesicular with distinct nucleoli. However, some cases depict nuclear pleomorphism with hyperchromasia and anisokaryosis. Some nuclei lack distinct nucleoli.
  + Immunohistochemistry:
    - Tumor cells depict myogenic expression with myogenin and/or MyoD1 expression.
    - Tumor cells also show epithelial expression with positive pancytokeratin.
    - Most cases also express ALK by immunohistochemistry.
    - MDM2 and CDK4 expression is also seen in rare cases.
  + Some molecular alterations:
    - In all cases, *TFCP2* is fused to *EWSR1* or *FUS.*
    - Genomic amplifications of *MDM2* in 12q15 reported.
    - *ALK* alterations present in some cases with hemizygous internal deletion, hemizygous deletion and homozygous internal deletion.
  + Prognosis and treatment:
    - Although the presence of spindle cell morphology in rhabdomyosarcoma is associated with better prognosis than cases lacking spindle cell, prognosis in *TFCP2* fusion rhabdomyosarcoma is poor regardless of morphology. Death occurs within 15 months in most cases.
    - Currently, no definitive treatment is available but one patient responded to *ALK* inhibitors. However, further investigation is needed.

**KEY POINTS:**

* Not all spindle cell tumors with *MDM2* and *CDK4* amplification are dedifferentiated liposarcomas,
* *TFCP2* rhabdomyosarcomas should be considered in tumors with spindle cell and epithelioid neoplasms with positive keratins and ALK, and,
* Most cases of *TFCP2* rearranged rhabdomyosarcomas are intraosseous, but they may also be extraosseous.

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