**Case #1**

**PRESENTER:** Kiran Manjee, MBBS

**ATTENDING:** Ajit Paintal, MD; William Watkin, MD

**CASE HISTORY:**

The patient is a 38-year-old female with a past medical history of bilateral low-grade serous ovarian carcinoma. She now presents with two new abdominal masses.

**FINAL DIAGNOSIS:**

**HIGH-GRADE OVARIAN CARCINOMA ARISING FROM LOW-GRADE SEROUS OVARIAN CARCINOMA**

**DIFFERENTIAL DIAGNOSIS:**

* High-grade endometrioid adenocarcinoma
* High-grade serous carcinoma
* Mucinous adenocarcinoma
* Clear cell carcinoma
* Carcinosarcoma
* High-grade carcinoma arising from low-grade serous ovarian carcinoma

**DISCUSSION:**

Low-grade serous ovarian carcinoma (LGSC) often, but not always arise from serous borderline tumors (SBT) and are commonly associated with a high frequency of *KRAS*, *NRAS*, *BRAF*, *ERBB2*, *CTNNB1* and *PIK3CA* mutations. While high-grade serous ovarian carcinoma (HGSC) are thought to originate from fallopian tube, arising from serous tubal intraepithelial carcinoma and has a high frequency of TP53 mutations as well as a high number of chromosomal copy number alterations. Based on molecular findings, both these lesions are usually unrelated and are considered two separate entities. However, the coexistence of LGSCA or SBT with HGSCA, undifferentiated and sarcomatoid carcinoma of the ovary at the time of presentation or in the recurrent tumor has been previously reported in a few case reports and small series.

Recent studies have identified a small subset of HGSC which show no *TP53* mutations. The most frequent somatic mutations in the cohort of *TP53-*wildtype HGSC involved genes implicated in RAS/MAPK signaling and it can be hypothesized that these HGSC arise from low-grade serous precursors.

It is possible that progression from low-grade to high-grade tumors would be observed more frequently over time in women with untreated low-grade serous tumors, but the natural course of disease is interrupted in the vast majority of individuals by diagnosis and treatment prior to the occurrence of the transformative genetic events. Alternative possibilities are that some women diagnosed with high-grade tumor may have had an antecedent or coexisting low-grade carcinoma which: 1) was either not recognized due to its being present only focally and/or sampling bias; 2) was overgrown by the high-grade tumor. And/or 3) underwent early rapid clonal evolution and progression to the high-grade tumor that subsequently dominated the tumor burden.

**References**:

1. Chui MH, Momeni Boroujeni A, Mandelker D, Ladanyi M, Soslow RA. Characterization of TP53-wildtype tubo-ovarian high-grade serous carcinomas: rare exceptions to the binary classification of ovarian serous carcinoma. Modern Pathology. 2020 Aug.
2. Murali R, Selenica P, Brown DN, Cheetham RK, Chandramohan R, Claros NL, Bouvier N, Cheng DT, Soslow RA, Weigelt B, McCluggage WG. Somatic genetic alterations in synchronous and metachronous low-grade serous tumours and high-grade carcinomas of the adnexa. Histopathology. 2019 Mar;74(4):638-650.
3. Zarei S, Wang Y, Jenkins SM, Voss JS, Kerr SE, Bell DA. Clinicopathologic, Immunohistochemical, and Molecular Characteristics of Ovarian Serous Carcinoma with Mixed Morphologic Features of High-grade and Low-grade Serous Carcinoma. Am J Surg Pathol. 2020 Mar;44(3):316-328.
4. Boyd C, McCluggage WG. Low-grade ovarian serous neoplasms (low-grade serous carcinoma and serous borderline tumor) associated with high-grade serous carcinoma or undifferentiated carcinoma: report of a series of cases of an unusual phenomenon. Am J Surg Pathol. 2012;36:368–375.
5. Chui MH, Xing D, Zeppernick F, et al. Clinicopathologic and molecular features of paired cases of metachronous ovarian serous borderline tumor and subsequent serous carcinoma. Am J Surg Pathol. 2019;43:1462–1472.
6. Dehari R, Kurman RJ, Logani S, et al. The development of highgrade serous carcinoma from atypical proliferative (borderline) serous tumors and low-grade micropapillary serous carcinoma: a morphologic and molecular geneticanalysis. Am J Surg Pathol. 2007;31:1007–1012.
7. Quddus MR, Rashid LB, Hansen K, et al. High-grade serous carcinoma arising in a low-grade serous carcinoma and micropapillary serous borderline tumour of the ovary in a 23-year-old woman. Histopathology. 2009;54:771–773.

**Case #2**

**PRESENTER:** Adesola Akinyemi, MD, MPH

**ATTENDING:** John Groth, MD

**CASE HISTORY:**

The patient is a 62-year-old female with a history of thyroid nodule, pulmonary nodule, vocal cord polyp and recurrent squamous cell carcinoma of the tongue, status post partial glossectomy and chemotherapy presented with pelvic pain. Laboratory investigations showed elevated Cancer Antigen 125 (CA125) and normal Carcinoembryonic Antigen (CEA) levels. Magnetic Resonance Imaging (MRI) revealed a multilobulated heterogeneous, predominantly solid 10.2 cm mass in the right adrenal region extending to the left adnexal region and abutting the rectosigmoid. She had omentectomy, hysterectomy with bilateral salpingo-oophorectomy and pelvic wall excision. The bulk of the tumor was in the omentum.

**FINAL DIAGNOSIS**:

**PRIMARY PERITONEAL SARCOMA, *DICER1* MUTANT**

**DIFFERENTIAL DIAGNOSIS:**

* Recurrent/metastatic squamous cell carcinoma
* Carcinosarcoma
* Sex cord stromal tumor
* Desmoplastic small round cell tumor (DSRCT)
* Biphasic mesothelioma
* Extrarenal Wilms and
* Neuroectodermal tumor: Embryonal tumor with multilayered rosettes-like tumor.

**DISCUSSION:**

* *DICER1* gene:
  + Located on chromosome 14, q32.13.
  + Encodes the endoribonuclease Dicer protein of the ribonuclease III family.
  + Dicer endoribonuclease plays a role in protein translation by controlling miRNA splicing.
  + May act as:
    - Tumor suppressor – due to loss-of-function in genes that normally contribute to the prevention of cancer.
    - Oncogene – due to gain of function in genes that contribute to the onset of cancer.
* *DICER1* associated diseases are encountered in various organ systems, including:
  + Genitourinary/gynecologic systems: Cystic nephroma, Wilms tumor, sex cord stromal tumors.
  + Nervous system: Pituitary blastoma, pinealoblastoma, embryonal tumor with multilayered rosettes (EMTR)-like infantile cerebellar tumor, primary *DICER1*-associated CNS sarcoma.
  + Respiratory system: Pulmonary cysts/nodules, pleuropulmonary blastoma (PPB).
  + Endocrine system: Multinodular goiter, thyroid adenoma, differentiated thyroid cancers.
* *DICER1* associated sarcomas:
  + Relatively rare but have also been described in various organ-systems, including the peritoneum.
  + Regardless of site, they show a mixture of heterologous components including:
    - Undifferentiated small round blue cells,
    - Pleomorphic spindle cells,
    - Anaplasia,
    - Chondroid differentiation,
    - Rhabdomyosarcomatous differentiation and,
    - Myxoid differentiations.
  + Peritoneal sarcoma was recently described and called “pleuropulmonary blastoma-like peritoneal sarcoma”.
  + Central nervous system sarcomas show rosette-like structures and described as “Embryonal tumor with multilayered rosettes-like infantile cerebellar tumor”.
  + *DICER1* associated sarcomas resemble types I, Ir, II and III pleuropulmonary blastoma due to the presence of sub-epithelial mesenchymal proliferation.
* Proposed unifying nomenclature for *DICER1* associated sarcomas:
  + Not all components are seen in every case.
  + A lack of awareness of this has, and may lead to diagnosing *DICER1* associated sarcomas of the same origin differently, based on the predominant feature seen.
  + Current lack of awareness of the disease and variation in nomenclature may lead to confusion for patients, clinicians, researchers and others.
  + Recently proposed nomenclature emphasizes location and presence of *DICER1* mutation. For example:
    - “Primary Intracranial Sarcoma, *DICER1* mutant” will replace “*DICER1*-associated central nervous system sarcoma” and “intracranial embryonal rhabdomyosarcomas”, both of which likely refer to the same disease.

**KEY POINTS:**

1. When the following components are present in a tumor of any location, consider a *DICER1* related sarcoma:
   1. Biphasic, pleuropulmonary blastoma/Wilms tumor-like appearance.
   2. Embryonal tumor with multilayered rosettes-like appearance.
   3. Heterologous rhabdomyoblastic differentiation, myxoid/chondroid or chondrosarcomatous differentiation.
2. When biallelic *DICER1* mutations are present, germline testing should be performed.

**References**:

1. Chiang, S., Snuderl, M., Kojiro-Sanada, S., Pi-Sunyer, A. Q., Daya, D., Hayashi, T., ... & Wang, L. (2017). Primitive Neuroectodermal Tumors of the Female Genital Tract: A Morphologic, Immunohistochemical and Molecular Study of 19 Cases. *The American journal of surgical pathology*, *41*(6), 761.
2. Choong, C. S., Priest, J. R., & Foulkes, W. D. (2012). Exploring the endocrine manifestations of DICER1 mutations. *Trends in molecular medicine*, *18*(9), 503-505.
3. de Kock, L., Priest, J. R., Foulkes, W. D., & Alexandrescu, S. (2019). An update on the central nervous system manifestations of DICER1 syndrome. *Acta Neuropathologica*, 1-13.
4. Doros, L. A., Rossi, C. T., Yang, J., Field, A., Williams, G. M., Messinger, Y., ... & Legallo, R. D. (2014). DICER1 mutations in childhood cystic nephroma and its relationship to DICER1-renal sarcoma. *Modern Pathology*, *27*(9), 1267-1280.
5. Foulkes, W. D., Priest, J. R., & Duchaine, T. F. (2014). DICER1: mutations, microRNAs and mechanisms. *Nature Reviews Cancer*, *14*(10), 662-672.
6. Kamihara, J., Paulson, V., Breen, M. A., Laetsch, T. W., Rakheja, D., Shulman, D. S., ... & Pinches, R. S. (2020). DICER1-associated central nervous system sarcoma in children: comprehensive clinicopathologic and genetic analysis of a newly described rare tumor. *Modern Pathology*, 1-12.
7. McCluggage, W. G., & Foulkes, W. D. (2020). DICER1-associated sarcomas: towards a unified nomenclature. *Modern Pathology*, 1-3.
8. Robertson, J. C., Jorcyk, C. L., & Oxford, J. T. (2018). DICER1 syndrome: DICER1 mutations in rare cancers. *Cancers*, *10*(5), 143.
9. Schultz, K. A. P., Nelson, A., Harris, A. K., Finch, M., Field, A., Jarzembowski, J. A., ... & Walter, A. (2020). Pleuropulmonary blastoma-like peritoneal sarcoma: a newly described malignancy associated with biallelic DICER1 pathogenic variation. *Modern Pathology*, 1-8.
10. Warren, M., Hiemenz, M. C., Schmidt, R., Shows, J., Cotter, J., Toll, S., ... & Shah, R. (2019). Expanding the spectrum of dicer1-associated sarcomas. *Modern Pathology*, 1-11.

**Case #3**

**PRESENTER:** Ansa Mehreen, PGY2

**ATTENDING:** Megan Sullivan, MD

**CASE HISTORY:**

The patient is an 86-year-old woman who presented with a palpable mass in her right breast. She had a prior benign right breast excision in the same area in 2015.

**FINAL DIAGNOSIS:**

**TALL CELL CARCINOMA WITH REVERSE POLARITY (TCCRP)**

**DIFFERENTIAL DIAGNOSIS:**

* Intraductal papilloma with florid UDH
* Solid papillary carcinoma
* Encapsulated papillary carcinoma
* Tall cell carcinoma with reverse polarity

**DISCUSSION:**

Tall Cell Carcinoma with Reverse Polarity (TCCRP) is a newly recognized breast malignancy characterized by circumscribed nests of epithelial cells distributed in dense fibrous stroma. Many of the nests have delicate fibrovascular cores, imparting a solid papillary pattern. Foamy histiocytes are often present within the cores. The tumor cells are tall and columnar with abundant eosinophilic cytoplasm. The most striking histological feature is the presence of nuclei at the apical rather than basal poles of columnar epithelial cells. Mitotic figures are rare. Although TCCRP shows some histological similarities to the tall cell variant of papillary thyroid carcinoma, immunohistochemical and molecular studies confirm the breast origin of this tumor. Most TCCRP have a triple negative phenotype, however, Ki-67 proliferation index is usually low (<20%). They characteristically express both low and high molecular weight cytokeratins. Myoepithelial cells are absent at the periphery of the tumor cell nests as well as within the fibrovascular cores.

Molecularly, TCCRP is characterized by *IDH2*p.Arg172 hotspot mutations (reported in 84% of cases). Hotspot mutations affecting *IDH2* have been described in AML, cholangiocarcinoma and gliomas, but first time being reported in breast carcinoma in TCCRP. *PIK3CA* missense mutations have also been identified in about 68% of these tumors, a more common mutation seen in 20 to 30 % of breast carcinomas. *RET* rearrangement and *BRAF* mutations, which are molecular features of papillary thyroid carcinoma have been negative in TCCRP.

TCCRP has usually an indolent clinical course, with a favorable prognosis. The majority of patients have been disease free during the follow up period. There are three reported cases of lymph node metastasis, both axillary and intra-mammary. Only one case with aggressive clinical behavior (bone metastasis) has been reported. Complete excision with negative margins and adjuvant radiation therapy is the treatment of care.

**References**:

1. Chiang S, Weigelt B, Wen HC, Pareja F, Raghavendra A, Martelotto LG, Burke KA, Basili T, Li A, Geyer FC, Piscuoglio S, Ng CK, Jungbluth AA, Balss J, Pusch S, Baker GM, Cole KS, von Deimling A, Batten JM, Marotti JD, Soh HC, McCalip BL, Serrano J, Lim RS, Siziopikou KP, Lu S, Liu X, Hammour T, Brogi E, Snuderl M, Iafrate AJ, Reis-Filho JS, Schnitt SJ. IDH2 Mutations Define a Unique Subtype of Breast Cancer with Altered Nuclear Polarity. Cancer Res. 2016 Dec 15;76(24):7118-7129.
2. Zhong, E., Scognamiglio, T., D’Alfonso, T., Song, W., Tran, H., Baek, I., & Hoda, S. A. (2019). Breast tumor resembling the tall cell variant of papillary thyroid carcinoma: molecular characterization by next-generation sequencing and histopathological comparison with tall cell papillary carcinoma of thyroid. *International Journal of Surgical Pathology*, *27*(2), 134-141.
3. Lozada, J. R., Basili, T., Pareja, F., Alemar, B., Paula, A. D. C., Gularte‐Merida, R., ... & Foschini, M. P. (2018). Solid papillary breast carcinomas resembling the tall cell variant of papillary thyroid neoplasms (solid papillary carcinomas with reverse polarity) harbour recurrent mutations affecting IDH 2 and PIK 3 CA: a validation cohort. *Histopathology*, *73*(2), 339-344.
4. Eusebi, V., Damiani, S., Ellis, I. O., Azzopardi, J. G., & Rosai, J. (2003). Breast tumor resembling the tall cell variant of papillary thyroid carcinoma: report of 5 cases. *The American journal of surgical pathology*, *27*(8), 1114-1118.
5. Pareja, F., da Silva, E. M., Frosina, D., Geyer, F. C., Lozada, J. R., Basili, T., ... & Wen, H. Y. (2020). Immunohistochemical analysis of IDH2 R172 hotspot mutations in breast papillary neoplasms: applications in the diagnosis of tall cell carcinoma with reverse polarity. *Modern Pathology*, 1-9.

**Case #4**

**PRESENTER:** Aibek Akmatbekov M.D

**ATTENDING:** Ajit Paintal M.D, Mark Dietriech M.D

**CASE HISTORY:**

The patient is a 57-year-old male with no past medical history who presents with shortness of breath, cough, dysphagia and fatigue. He patient is a heavy smoker, smoking half a pack a day for 30 years. The patient underwent chest CT which showed a 9.5cm hilar mass.

**FINAL DIAGNOSIS:**

**SMARCA4-DEFICIENT THORACIC SARCOMATOID CARCINOMA**

**DIFFERENTIAL DIAGNOSIS:**

* Lymphoma
* Melanoma
* Primary thoracic sarcoma
* Non-small cell carcinoma
* Sarcomatoid Carcinoma

**DISCUSSION:**

* Cytology: cellular and discohesive, arranged in single and loose clusters
* Cells: large, round to oval with eosinophilic cytoplasm with rhabdoid features, pleomorphic nuclei bulging cytoplasmic border
* Mitotic figures are plentiful
* Background: Necrosis is abundant
* Characterized by loss of SMARCA4/SMARCA2 genes
* Loss of SMARCA4/ SMARCA2 and Claudin-4 by IHC and NGS panel
* Epidemiology of SMARCA4 deficiency tumor
* Large primary size
* Heavy smoking history
* Genomic relationship to the tumor
* Smoking has G>T transverse mutation with dominant smoking signature
* Mutational profile by NGS panel
* Pathogenesis of thoracic SMARCA4-deficiency tumor
* Stepwise inactivation of SMARCA4/SMARCA2 genes
* Co-inactivation of SMARCA4/SMARCA2 genes
* Sarcoma vs Carcinoma
* Genomic alterations including a dominant smoking signature,
* High TMB with smoking-associated NSCC-type mutations
* Focal expression of markers, TTF1 or p40, in subset of cases
* Documentation of a NSCC component in a some of the cases
* Pattern of metastatic spread for SD-TSTs was more typical of carcinoma than sarcoma
* Treatment of SMARCA4-deficient tumor
* Should be treated like NSCLC, not sarcoma
* Some respond well to checkpoint inhibitors, maybe b/c of high TMB
* FDA approved drug for the treatment of this tumors

**References**:

1. Sauter JL, Graham RP, Larsen BT, Jenkins SM, Roden AC, Boland JM. SMARCA4-deficient thoracic sarcoma: a distinctive clinicopathological entity with undifferentiated rhabdoid morphology and aggressive behavior. Mod Pathol. 2017 Oct;30(10)
2. Perret R, Chalabreysse L, Watson S, Serre I, Garcia S, Forest F et al. SMARCA4-deficient Thoracic Sarcomas: Clinicopathologic Study of 30 Cases With an Emphasis on Their Nosology and Differential Diagnoses. Am J Surg Pathol. 2019 Apr;43(4):455-465.
3. Le Loarer F, Watson S, Pierron G, de Montpreville VT, Ballet S et al. SMARCA4 inactivation defines a group of undifferentiated thoracic malignancies transcriptionally related to BAF-deficient sarcomas. Nat Genet. 2015 Oct;47(10):1200-5.
4. Yoshida A, Kobayashi E, Kubo T, Kodaira M, Motoi T, Motoi N et al. and molecular characterization of SMARCA4-deficient thoracic sarcomas with comparison to potentially related entities. Mod Pathol. 2017 Jun;30(6):797-809.
5. Rekhtman N, Montecalvo J, Chang JC, Alex D, Ptashkin RN, Ai N et al. SMARCA4-Deficient Thoracic Sarcomatoid Tumors Represent Primarily Smoking-Related Undifferentiated Carcinomas Rather Than Primary Thoracic Sarcomas. J Thorac Oncol. 2020 Feb;15(2):231-247.
6. Schneppenheim R, Frühwald MC, Gesk S, Hasselblatt M et al. Germline nonsense mutation and somatic inactivation of SMARCA4/BRG1 in a family with rhabdoid tumor predisposition syndrome. Am J Hum Genet. 2010 Feb 12;86(2):279-84.
7. Hasselblatt M, Gesk S, Oyen F, Rossi S, Viscardi E, Giangaspero F, Giannini C, Judkins AR, Frühwald MC, Obser T, Schneppenheim R, Siebert R, Paulus W. Nonsense mutation and inactivation of SMARCA4 (BRG1) in an atypical teratoid/rhabdoid tumor showing retained SMARCB1 (INI1) expression. Am J Surg Pathol. 2011 Jun;35(6):933-5.
8. Witkowski L, Carrot-Zhang J, Albrecht S, Fahiminiya S, Hamel N et al. Germline and somatic SMARCA4 mutations characterize small cell carcinoma of the ovary, hypercalcemic type. Nat Genet. 2014 May;46(5):438-43.
9. Schoenfeld AJ, Bandlamudi C, Lavery JA, Montecalvo J et al. The Genomic Landscape of *SMARCA4* Alterations and Associations with Outcomes in Patients with Lung Cancer. Clin Cancer Res. 2020 Jul 24.

**Case #5**

**PRESENTER:** Sachie Ikegami, MD. PhD.

**ATTENDING:** Linda M Ernst, MD. MHS.

**CASE HISTORY:**

This is the placenta of a 31-year old G7P4 female who delivered a stillborn fetus at 33 weeks and 4 days gestational age. The pregnancy was unremarkable up until 30 weeks 5 days gestation when she developed fever and chills. Her symptoms resolved the following day. 8 days later, she presented with irregular contractions and decreased fetal movement. Ultrasound confirmed intrauterine fetal demise. She underwent induction of labor and delivered a macerated stillborn male fetus.

**FINAL DIAGNOSIS:**

**MASSIVE PERIVILLOUS FIBRIN DEPOSITION AND CHRONIC INTERVILLOSITIS**

**DIFFERENTIAL DIAGNOSIS:**

* Changes related to IUFD
* Villous infarction (ischemic); maternal malperfusion of the placental bed
* Avascular villi with abundant perivillous fibrin; fetal vascular malperfusion
* Chronic villitis/chronic intervillositis
* Massive perivillous fibrin deposition

**DISCUSSION:**

Massive perivillous fibrin deposition and chronic histiocytic intervillositis are rare and poorly understood placental lesions. Both are associated with poor fetal outcome and high risk of recurrence. Their co-occurrence has been described, but for most cases the cause remains unknown. Risk factors include: malaria or viral infection, autoimmune disorders such as anti-phospholipid antibody syndrome. In this case, the specific etiology is unknown, but the recent maternal infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) does raise the possibility of an infectious etiology. Although vertical transmission is uncommon, case report series and cohort studies and have suggested potential placental pathologic features associated with SARS-CoV-2 infection including massive perivillous fibrin deposition as well as chronic intervillous inflammation. In this case, while the immediate cause of death can be confidently attributed to placental insufficiency secondary to massive perivillous fibrin deposition and chronic histiocytic intervillositis, the underlying etiology of these placental pathologies is uncertain.

**KEYPOINTS:**

1. Massive perivillous fibrin deposition and chronic intervillositis are rare placental conditions with significant risk of recurrence, and associated with neonatal morbidity and mortality.
2. Although vertical transmission is uncommon, SARS-CoV-2 infection can be associated with variety of placental histopathology including chronic inflammation.
3. Our case suggests SARS-CoV-2 infection may contribute to the placental pathology including massive perivillous fibrin deposition and chronic intervillositis.

**References:**

1. Vivanti A.J. et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun 2020 Jul 14; 11(1):3572.
2. Baergen RN et al. Placental pathology in Covid-19 positive mothers: preliminary findings. Pediatr Dev Pathol. May-Jun 2020; 23(3):177-180.
3. Hecht JL et al. SARS-CoV-2 can infect the placenta and is not associated with specific placental histopathology: a series of 19 placentas from COVID-19-positive mothers. Mod Pathol. 2020 Nov; 33(11):2092-2103.
4. Shanes ED et al. Placental pathology in COVID-19. Am J Clin Pathol. 2020 Jun 8; 154(1):23-32.
5. Smithgall MC et al. Third trimester placentas of SARS‐CoV‐2‐positive women: histomorphology, including viral immunohistochemistry and in situ hybridization. Histopathology. 2020 Jul 21;10.1111
6. Zhang P et al. Detection of SARS-CoV-2 in placentas with pathology and vertical transmission. Am J Obstet Gynecol MFM. 2020 Nov; 2(4):100197.
7. Kotlyar AM et al. Vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis. Am J Obstet Gynecol. 2020
8. Menter T et al. Placental Pathology Findings during and after SARS-CoV-2 Infection: Features of Villitis and Malperfusion. Pathobiology. 2020 Sep 18;1-9
9. Mattuizzi A et al. Adverse perinatal outcomes of chronic intervillositis of unknown etiology: an observational retrospective study of 122 cases. Sci Rep. 2020; 10: 12611.
10. Weber MA et al. Co-occurrence of massive perivillous fibrin deposition and chronic intervillositis: case report. Pediatr Dev Pathol. 2006; 9(3):234-238.

**Case #6**

**PRESENTER:** Cory Gray, D.O.

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

**CASE HISTORY:**

The patient is a 41 years old male smoker with COPD and a family history significant for a father with bladder cancer and a maternal grandfather with duodenal cancer. He had surgery to remove a malignancy in 2017, But then presented with jaundice and abdominal pain in 2019, which resulted in an extensive workup. A CT scan was done which showed a 3.1 cm mass in the head of the pancreas and surrounding the common bile duct, with involvement of the portal vein and right hepatic artery. A Whipple procedure was subsequently performed.

**FINAL DIAGNOSIS:**

**METASTATIC/RECURRENT COLONIC ADENOCARCINOMA**

**DIFFERENTIAL DIAGNOSIS:**

* Pancreatic adenocarcinoma
* Metastatic gastrointestinal
* Invasive breast carcinoma

**DISCUSSION:**

* The Cancer Genome Atlas molecular classification of colorectal carcinomas:
  + Hypermutated
  + Ultramutated
  + Chromosomal Instability
* DNA polymerases epsilon and delta1 (POLE/POLD1):
  + Copy over approximately 3 X 109 bases during DNA replication
  + Proofreading exonuclease function – improves replication fidelity 100 fold
  + Other polymerases have a high error rate
* DNA damage and repair:
  + Damage caused by many agents:
    - X-rays
    - Ultraviolet light
    - Non-enzymatic methylation
  + Many types of lesions are created:
    - Abasic sites
    - Double stranded breaks
  + Many repair processes exist:
    - Base excision
    - Nucleotide excision
    - Recombinational
    - Mismatch
    - Direct reversal
    - All require POLE and POLD1 for completion
* Exonuclease domain mutations:
  + Renders the domain inactive
  + Decreases replication fidelity dramatically
  + Most common somatic mutation is P286R
* POLE L424V and POLD1 S478N
  + Pack together at the interface between two helices that form the base of the exonuclease active site
  + Mutations distort the packing of the helices by changes in amino acid size and charge signatures
* P286R:
  + Localizes to the DNA binding pocket adjacent to the exonuclease active site
  + Substitutions affect the structure of the DNA binding pocket as well as the exonuclease active site
  + Removes polymerase function altogether
* Ultramutated colonic carcinoma:
  + 5-7 mutations/Mb in conventional colonic adenocarcinoma, over 100 in ultramutated tumors
  + Occurs in younger population with a mean patient age of 39 years
  + More common in male
  + More common in left colon
  + More commonly moderately or well-differentiated
  + Mismatch repair proficient
* Tumor mutational burden:
  + Higher TMB is associated with good prognosis and response to immune checkpoint inhibitors
  + Enhanced progression-free and overall patient survival in cases with a high TMB, that receive checkpoint inhibitor therapy.

**References:**

1. Müller, M.F., Ibrahim, A.E.K. & Arends, M.J. Molecular pathological classification of colorectal cancer. Virchows Arch 469, 125–134 (2016).
2. Poulogiannis G, Ichimura K, Hamoudi RA, Luo F, Leung SY, Yuen ST, Harrison DJ, Wyllie AH, Arends MJ. Prognostic relevance of DNA copy number changes in colorectal cancer. J Pathol. 2010 Feb;220(3):338-47.
3. Briggs S, Tomlinson I. Germline and somatic polymerase ε and δ mutations define a new class of hypermutated colorectal and endometrial cancers. J Pathol. 2013 Jun;230(2):148-53.
4. Chatterjee N, Walker GC. Mechanisms of DNA damage, repair, and mutagenesis. Environ Mol Mutagen. 2017 Jun;58(5):235-263.
5. Temko D, Van Gool IC, Rayner E, Glaire M, Makino S, Brown M, Chegwidden L, Palles C, Depreeuw J, Beggs A, Stathopoulou C, Mason J, Baker AM, Williams M, Cerundolo V, Rei M, Taylor JC, Schuh A, Ahmed A, Amant F, Lambrechts D, Smit VT, Bosse T, Graham TA, Church DN, Tomlinson I. Somatic POLE exonuclease domain mutations are early events in sporadic endometrial and colorectal carcinogenesis, determining driver mutational landscape, clonal neoantigen burden and immune response. J Pathol. 2018 Jul;245(3):283-296.
6. Yarchoan M, Albacker LA, Hopkins AC, Montesion M, Murugesan K, Vithayathil TT, Zaidi N, Azad NS, Laheru DA, Frampton GM, Jaffee EM. PD-L1 expression and tumor mutational burden are independent biomarkers in most cancers. JCI Insight. 2019 Mar 21;4(6).
7. Gong J, Wang C, Lee PP, Chu P, Fakih M. Response to PD-1 Blockade in Microsatellite Stable Metastatic Colorectal Cancer Harboring a POLE Mutation. J Natl Compr Canc Netw. 2017 Feb;15(2):142-147.
8. Fedorova MS, Krasnov GS, Lukyanova EN, Zaretsky AR, Dmitriev AA, Melnikova NV, Moskalev AA, Kharitonov SL, Pudova EA, Guvatova ZG, Kobelyatskaya AA, Ishina IA, Slavnova EN, Lipatova AV, Chernichenko MA, Sidorov DV, Popov AY, Kiseleva MV, Kaprin AD, Snezhkina AV, Kudryavtseva AV. The CIMP-high phenotype is associated with energy metabolism alterations in colon adenocarcinoma. BMC Med Genet. 2019 Apr 9;20(Suppl 1):52.
9. Shia J, Schultz N, Kuk D, Vakiani E, Middha S, Segal NH, Hechtman JF, Berger MF, Stadler ZK, Weiser MR, Wolchok JD, Boland CR, Gönen M, Klimstra DS. Morphological characterization of colorectal cancers in The Cancer Genome Atlas reveals distinct morphology-molecular associations: clinical and biological implications. Mod Pathol. 2017 Apr;30(4):599-609.
10. Schrock AB, Ouyang C, Sandhu J, Sokol E, Jin D, Ross JS, Miller VA, Lim D, Amanam I, Chao J, Catenacci D, Cho M, Braiteh F, Klempner SJ, Ali SM, Fakih M. Tumor mutational burden is predictive of response to immune checkpoint inhibitors in MSI-high metastatic colorectal cancer. Ann Oncol. 2019 Jul 1;30(7):1096-1103.
11. Sharabi A, Kim SS, Kato S, Sanders PD, Patel SP, Sanghvi P, Weihe E, Kurzrock R. Exceptional Response to Nivolumab and Stereotactic Body Radiation Therapy (SBRT) in Neuroendocrine Cervical Carcinoma with High Tumor Mutational Burden: Management Considerations from the Center For Personalized Cancer Therapy at UC San Diego Moores Cancer Center. Oncologist. 2017 Jun;22(6):631-637.
12. Hino H, Shiomi A, Kusuhara M, Kagawa H, Yamakawa Y, Hatakeyama K, Kawabata T, Oishi T, Urakami K, Nagashima T, Kinugasa Y, Yamaguchi K. Clinicopathological and mutational analyses of colorectal cancer with mutations in the POLE gene. Cancer Med. 2019 Aug;8(10):4587-4597.