**Case #1**

**PRESENTER:** Kadir Isidan, MD

**ATTENDING:** John Groth, MD

**CASE HISTORY:** This patient is 34-year-old male presented to the hospital with 2cm mass on the left hand first webspace. The mass is slow growing and the patient states that it is there about 5 years. The mass is not painful and not causing any other symptoms. The patient does not have any other masses anywhere else. He works as a baggage checker at the airport. No pertinent family or social history.

**FINAL DIAGNOSIS:** Angiofibroma of soft tissue with *AHRR::NCOA3* fusion

**DIFFERENTIAL DIAGNOSIS:**

- Schwannoma
- Cutaneous myxoma (superficial angiomyxoma)
- Superficial acral fibromyxoma
- Solitary fibrous tumor
- Low grade fibromyxoid sarcoma
- Low grade myxofibrosarcoma
- Cellular angiofibroma
- Angiofibroma of soft tissue

**DISCUSSION:**

Angiofibroma of soft tissue (AFST) is a distinctive fibrovascular soft tissue tumor that pursues a benign clinical course, with rare local recurrences and no evident metastatic potential. It arises most commonly in the extremities of middle-aged adults but displays a broad anatomic and age distribution. Microscopically, it is characterized by bland, uniform, likely fibroblastic spindle cells set in an abundant fibromyxoid stroma, with a prominent and highly characteristic vascular pattern composed of innumerable branching, thin-walled blood vessels. Preliminary data suggest that these tumors also have a distinct and reproducible karyotype. Simple local excision seems to be adequate treatment.

AFST was found to harbor a recurrent translocation, t(5;8) (p15;q13), resulting in the expression of in-frame *AHRR-NCOA2* and *NCOA2-AHRR* fusion transcripts. Arbajian et al. reported an alternative gene fusion, *GTF2I-NCOA2*, demonstrating that different fusion partners could be associated with AFST, as well as the importance of NCOA2 in tumor pathogenesis. Other reported fusions include, *GAB1-ABL1*, *GTF21-NCOA2*, *AHRR-NCOA2*, *NCOA2-ETV4*, and *ETV4-AHRR*.

AHRR is a tumor suppressor gene that contributes to tumorigenesis when there are genetic alterations such as fusions, which has been seen in various leukemias and mesenchymal neoplasms. Recent examples are those of uterine tumor resembling an ovarian sex cord tumor with *ESR1-NCOA2* and *GREB1-NCOA2* fusions, intraosseous rhabdomyosarcoma with *MEIS-NCOA2* fusion, biphenotypic sinonasal sarcoma with *PAX3-NCOA2* fusion, and a uterine sarcoma with variable sex cord differentiation and a *GREB1-NCOA2* fusion.

By immunohistochemistry, AFST is variably positive for EMA, desmin, SMA, CD34, CD68, CD163 and ER. The *AHRR::NCOA2* fusion results in increased expression of cytochrome P450 1A1 (CYP1A1); a recent

study demonstrated CYP1A1 immunohistochemistry (IHC) to be moderately sensitive and highly specific for AFST.

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**QUESTIONS:**

1. Which of the following fusion is not related to angiofibroma of soft tissue?
    A. AHRR::NCOA2
    B. GAB1::ABL1
    C. ETV4::NCOA2
    D. ETV6::NCOA2

2. Which of the following staining pattern would be **most** consistent with angiofibroma of soft tissue?

A. S100(+), EMA(-), CYP1A1(-)
B. S100(-), EMA(-), CYP1A1(+)
C. S100(+), EMA(-), CYP1A1(+)
D. S100(-), EMA(+), CYP1A1(-)

**Answers:**

1. D
2. B

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**Case # 2**

**Presenter:** Ximena Wise, MD

**Attending:** Linda Ernst, MD

**Case History:** Our patient is a 25-year-old G1P0 female with no significant past medical history. A fetal anatomic assessment was performed in the second trimester which showed a large encephalocele, bilateral clubfeet, a left diaphragmatic hernia, and a single umbilical artery. The pregnancy was terminated at 19 weeks gestation, and a fetal autopsy was declined. Examination of the placenta showed no significant gross findings, except an umbilical cord with two vessels and a placenta that was small for gestational age.

**Final Diagnosis:** Small for gestation age placenta, with changes consistent of amnion disruption and chorion nodosum

**Differential Diagnosis:**

- Normal membranes with stripped amnion
- Chronic chorionitis
- Amnion nodosum
- Chorion nodosum

**Discussion:**

Chorion nodosum is a placental lesion composed of a deposition of fetal squamous which are buried within the chorionic mesenchyme. This lesion is not seen grossly, but may make the chorion appear dull and opaque. It differs microscopically from amnion nodosum, in which amnion nodosum consists of fetal squamous attached to the amniotic epithelium. Chorion nodosum is associated with amniotic band syndrome, limb-body wall complex, and extra-amniotic pregnancy and tends to occur in the early second trimester or in late pregnancy. It is a very rare lesion occurring in 0.1% of all placentas.

Chorion nodosum has been found to be highly associated with amniotic band syndrome, which comprises of various congenital anomalies, including disruption, deformation and malformation of organs that were intended to develop normally. Almost all cases reported occur sporadically. Different theories exist regarding its pathogenesis, with the vascular theory being accepted by most scientists today. Clinical manifestations of amniotic band syndrome include constrictive rings, limb/digit defects, neural or spinal defects, and craniofacial defects. The risk factors and guidelines for management of

amniotic band syndrome are not well defined. Both chorion nodosum and amniotic band syndrome should be kept in mind as potential causes of fetal deformations/malformation. Lastly, since almost all cases are sporadic, expectant mothers should focus on living a healthy lifestyle.

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**Questions:**

1. Chorion nodosum is characterized microscopically as:
    A. A small portion of detached, normal appearing amnion
    B. An infiltration of lymphocytes within the fibrous tissue of the chorion
    C. The deposition of fetal squamous attached to the amniotic epithelium
    D. The deposition of fetal squamous buried within the chorionic mesenchyme

2. Which pathogenic theory for amniotic band syndrome is most widely accepted today:
    A. Intrinsic theory
    B. Extrinsic theory
    C. Vascular theory
    D. None of the above

**Answers:**

1. D
2. C

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**Case #3**

**PRESENTER:** Stuart Hanviriyapunt, M.D.

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

**CASE HISTORY:** A 85-year-old male with leukocytosis since 2012, including WBC count of 13,500 cells/µL in 2022, after which he was found to be JAK2 V617F positive by PCR on peripheral blood and negative

for the p210 isoform of BCR-ABL1 by RT-PCR. He received external beam radiotherapy in March 2024 for his separate diagnosis of prostate cancer. In August 2024, his WBC count increased to 60,800 cells/µL.

**FINAL DIAGNOSIS:** Chronic Myeloid Leukemia with p190 isoform of BCR-ABL1 presenting in Blast Phase

**DIFFERENTIAL DIAGNOSIS:**

- Acute Myeloid Leukemia (AML) from Myeloproliferative Neoplasm (MPN)
- AML from Chronic Myelomonocytic Leukemia (CMML)
- AML from MDS/MPN with Thrombocytosis and SF3B1 Mutation
- AML from Myelodysplastic Syndrome (MDS)

**DISCUSSION:**

BCR-ABL1, a chimeric protein formed as a result of the chromosomal translocation t(9;22), also known as the Philadelphia chromosome, is responsible for almost all cases of chronic myeloid leukemia (CML) and some cases of acute lymphoblastic leukemia (ALL). Located on chromosome 22, the BCR, or breakpoint cluster region, gene encodes a protein product that regulates cell movement and function and is an example of a housekeeping gene, encoding a protein expressed in all cells of an organism because it is essential for maintaining cell function. On translocation, the ABL tyrosine kinase on chromosome 9 is thus rendered constitutively active, causing cytokine signal transduction pathways to stimulate growth and prevent apoptosis in hematopoietic cells. BCR-ABL1 exists in several different isoforms, depending on the precise position of the t(9;22)(q34;q11.2) genomic breakpoints. The most common BCR-ABL1 isoforms are p210 (major type; either e13a2 or e14a2) and p190 (minor type; e1a2). Other, less common BCR-ABL1 isoforms include e19a2 (minor type; encodes p230), as well as e1a3, e13a3, e14a3, e6a2, and e8a2. p210 is the hallmark of chronic myeloid leukemia (CML), and p190 occurs in the majority of B-cell acute lymphoblastic leukemia, but can be associated with CML (1-2%). p190 CML is associated with monocytosis, additional cytogenetic abnormalities (ACA), and vertiginous progression to blast phase, and often has a poor and/or short-lived response to the first-generation tyrosine kinase inhibitor, imatinib. Because of the treatment and prognostic implications, RT-PCR for the p210 transcript is insufficient for diagnosis p190 CML presenting in blast phase; it is crucial to employ multiple modalities, including FISH and conventional karyotyping, in BCR-ABL1 testing.

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**QUESTIONS:**

1. Which of the following is the most common isoform of BCR-ABL1?

   A. e14a3
   B. e13a3
   C. p230
   D. p210
   E. p190

2. Which of the following is most commonly associated with p190 isoform of BCR-ABL1?

   A. B-cell acute lymphoblastic leukemia (B-ALL)
   B. T-cell acute lymphoblastic leukemia (T-ALL)
   C. acute myeloid leukemia (AML)
   D. chronic lymphocytic leukemia (CLL)
   E. chronic myeloid leukemia (CML)

**Answers:**

1.D

2.A

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**Case #4**

**PRESENTER:** Priyanka Batra, M.D.

**ATTENDING:** Todd Kroll, M.D., Ph.D.

**CASE HISTORY:** A 34-year-old male who with pain in the right hip and thigh for a week after a twisting injury to his lower limb. CT scan revealed an oblique subcapital right femoral neck fracture and a large expansile lesion in the proximal right femur extending from the subcapital region through the femoral neck, intertrochanteric region and immediate subtrochanteric region, associated with cortical thinning and multiple cortical defects. MRI confirmed a lytic solid and cystic lesion, measuring 6.3 cm in greatest dimension. Fine needle aspiration and core needle biopsy were performed. On additional testing, his serum parathyroid hormone levels were found to be markedly elevated [1104 pg/ml (normal- 12-88)] with raised ALP and creatinine levels. He was clinically diagnosed to have hyperparathyroidism secondary to renal disease.

**FINAL DIAGNOSIS:** Brown tumor of hyperparathyroidism

**DIFFERENTIAL DIAGNOSIS:**

- Giant cell rich osteosarcoma (GCR-OS)
- Giant cell tumor of the bone (GCT)
- Aneurysmal bone cyst (ABC)
- Non ossifying fibroma (NOF)
- Brown tumor (BT)

**DISCUSSION:**

- Osteitis fibrosa cystica (OFC) was first described by Recklinghausen in 1891. Tumefactive form of OFC is called brown tumor (BT). It is referred to as “brown tumor” in the literature due to its color resulting from rich vascularity and deposits of hemosiderin. In older literature, the prevalence of brown tumors in hyperparathyroidism was reported as high as 58–69%, whereas in present times due to regular biochemical monitoring, this rate is observed to be under 5%. It is interesting to note that these brown tumors are known to regress spontaneously upon removal of the endocrine stimulus. BT have been well known to be endocrine driven lesions and are associated with hyperparathyroidism. Parathyroid hormone stimulates osteoblasts to release RANKL. RANKL binds to RANK on the surface of osteoclast precursors and promote maturation into active osteoclast that cause bone resorption. A 2020 study conducted by Guimares et al was the first one to suggest that brown tumors are associated with pathogenic mutations in KRAS. They were mainly an oral pathology department and studied 13 brown tumors of the jaw. *Pathogenic KRAS* mutations were detected in 7/13 cases. They also detected activation of the MAPK/ERK signaling pathway was present even in cases where no mutations were detected. In conclusion, KRAS mutation is one of the mechanisms of activation of MAPK/ERK signaling pathway that play a role in tumorigenesis of brown tumors. Another study conducted in 2022 by Turek et al, studied 16 brown tumors, in axial and peripheral skeleton, out of which 10 showed pathogenic KRAS mutations. They postulated that BT are true neoplasms driven by KRAS mutations and endocrine stimulation acts as a “second hit” for tumor development. They also hypothesized that in the cases that didn’t show KRAS mutation, an alternative, non-mutational based activation of the RAS-MAPK might be present. Mutations in KRAS and other MAPK activating genes are present in around 30% of malignant neoplasms. Interestingly, the same mutations have been identified in non-neoplastic conditions such as

endometriosis, arteriovenous malformations and even histologically normal endometrium, indicating that the sole presence of a driver mutation is not sufficient to cause cancer. RAS mutations by themselves are not enough for transformation of a benign cell. Other factors and additional mutations are required for the development of a neoplasm. That may be a reason for regression of the brown tumors upon correction of the parathyroid levels.

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**QUESTIONS:**

1. What is the primary pathological feature of a brown tumor?

    A. Osteoblastic activity
    B. Osteoclastic activity
    C. Fibrous tissue deposition
    D. Chondroid metaplasia

2. Which of the following conditions is most commonly associated with the development of brown tumors?

    A. Osteoporosis
    B. Paget's disease
    C. Hyperparathyroidism
    D. Osteosarcoma

**Answers:**

1-B

2-C

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**Case #5**

**PRESENTER:** Shruti Srikumar, M.D.

**ATTENDING:** Ajit Paintal, MD; Lin Liu M.D.

**CASE HISTORY:** A 70-year-old 20 pack year daily smoker with a remote history of fungal pneumonia who presented for routine screening CT scan, which showed a 1.7 cm right middle lobe lung nodule and "innumerable" sub-centimeter bilateral multifocal lung nodules. Follow up PET scan showed avidity within the main nodule (SUV 4.1), but no other extra-pulmonary lesions. Fine needle aspiration and subsequent resection of the main nodule were performed.

**FINAL DIAGNOSIS:**

Diffuse Idiopathic Neuroendocrine Cell Hyperplasia (DIPNECH)

**DIFFERENTIAL DIAGNOSIS:**

- Miliary Pattern of Metastatic Neuroendocrine Tumor
- Meningotheliomatosis

**DISCUSSION:**

DIPNECH was first described in 1953 by Felton et. al. in a case series of "adenomas of the carcinoid type" arising from bronchial lining in mostly middle aged to elderly women. In 1992 Aguayo et. al. reported similar *symptomatic* cases of the same disease; however, thereafter asymptomatic cases of DIPNECH emerged as well. In 2001 the WHO acknowledged DIPNECH. Overall DIPNECH is a very poorly defined and understudied entity. Per current literature, **DIPNECH is a *clinical-pathologic disease spectrum*** encompassing idiopathically occurring and diffuse pulmonary neuroendocrine cell hyperplasia (PNECH) which has *potential* downstream sequelae of airway obstruction and neoplasia. Briefly, PNECH is simply a proliferation of neuroendocrine cells that are native to the normal respiratory epithelium. PNECH by definition is a non-invasive lesion. Importantly, PNECH has the *potential* to result in two downstream effects as follows:

1. PNECH can give rise to invasive mass-forming tumor(s). Indeed, it is hypothesized to be a pre-invasive precursor lesion to neuroendocrine tumorlets and carcinoid tumors.
2. PNECH, due to its unique location in the respiratory epithelium of bronchioles, can result in airway obstruction. Obstruction can occur due to a nodular-shaped proliferation or interestingly due to the fact that pulmonary neuroendocrine cell hyperplasia results in supra-physiologic secretion of fibrosis-inducing hormone. Excess hormone then causes peribronchial fibrosis, which can also obstruct the airway lumen.

When PNECH is “diffuse” enough, generally considered to be both multifocal and bilateral, there is potential for multiple neuroendocrine tumorlets and/or carcinoid tumors to arise. This in turn results in overall increased risk of metastatic neuroendocrine disease. Simultaneously, “diffuse” PNECH has the potential to obstruct *many* airways. If severe, this would result in diminished pulmonary function, which would manifest on spirometry testing (obstructive pattern) and imaging (“air trapping,” “mosaic attenuation,” “constrictive bronchiolitis” etc.). Clinically, diminished PFTs would correlate with symptoms of cough and dyspnea, often mimicking asthma, and in extreme cases respiratory failure warranting lung transplant. Finally, the PNECH seen in DIPNECH is ultimately idiopathic with the current theory being that lung injury and/or toxic exposure may induce a “reactive” or “secondary” hyperplasia.

To reiterate, since DIPNECH is a clinical-pathologic disease spectrum that in the most extreme case would result in respiratory failure and metastatic neuroendocrine tumor(s), compared to a single sporadic carcinoid tumor, neuroendocrine lesions identified in the setting of DIPNECH will likely receive closer follow up in the form of serial PFTs and surveillance imaging. Thus it is an important entity for pathologists to recognize and either corroborate or suggest in the report.

In terms of the current WHO guidelines for diagnosis, there are two separate sets of criteria termed “Clinical DIPNECH Criteria” to be used for symptomatic patients and “Pathological DIPNECH Criteria” to be used for asymptomatic patients. Essential clinical criteria include obstructive symptoms and mosaic attenuation, while the only essential pathologic criteria is histologic evidence of PNECH and/or tumorlets. Importantly, since DIPNECH involves widespread in situ disease, if multiple carcinoids are seen in the setting of DIPNECH, they likely arose from distinct foci of PNECH; thus, logically the WHO recommends these carcinoids be staged as independent primaries rather than intrapulmonary metastasis.

Finally, because DIPNECH is poorly understood, the WHO criteria have several flaws. The two biggest issues stem from the fact that both the clinical and pathologic essential criteria are relatively non-specific for true DIPNECH, explained below:

1. Per the essential clinical criteria, a symptomatic patient can somehow be diagnosed with DIPNECH with no pathologic evidence of PNECH at all, and instead mosaic attenuation alone. However, in a 2021 study by Samhouri et. al. it was noted that in a cohort of 25 symptomatic patients with both bilateral pulmonary nodules and mosaic attenuation, DIPNECH was diagnosed <5% of the time, overall demonstrating that mosaic attenuation alone is non-specific for DIPNECH.
2. Per the essential pathologic criteria, an asymptomatic patient can be diagnosed with DIPNECH with evidence of histologic PNECH alone. However, in a 2018 study by Mengoli et. al. it was demonstrated that PNECH can be seen in the majority of asymptomatic sporadic carcinoid cases, overall indicating that PNECH alone is also very non-specific for DIPNECH.

Because of these issues with the current WHO criteria, it can be difficult for pathologists to know when to include DIPNECH in the differential diagnosis. Per a recent comprehensive review (Samhouri et. al. 2023), two features common to all reported cases of so-called DIPNECH were an initial finding of diffuse nodules on imaging and a subsequent histopathologic confirmation of PNECH. Thus, given the correct radiologic findings, the pathologist can then evaluate for DIPNECH.

Lastly, one remaining question regarding DIPNECH is whether differences exist between DIPNECH-associated carcinoids and solitary sporadic carcinoids. Prognostic studies show conflicting results, but overall DIPNECH-associated carcinoids appear indolent. Interestingly, a greater proportion of DIPNECH associated carcinoids express certain IHC markers (TTF-1, CD10, GRP, and OTP) than solitary sporadic carcinoids suggesting that there may be a biological difference between the two.

In summary, DIPNECH involves idiopathic and diffusely occurring pulmonary neuroendocrine cell hyperplasia that can potentially result in both airway obstruction and neoplasia. Pathologists can suspect this entity when there are radiologic findings of multifocal, bilateral pulmonary nodules on imaging and histopathologic evidence of pulmonary neuroendocrine cell hyperplasia further supported by multiple neuroendocrine tumorlets and/or carcinoids on histopathology. If multiple carcinoid tumorlets are seen in the setting of DIPNECH, they must be staged as independent primaries. Lastly, compared to diagnosis of a single sporadic carcinoid tumor, corroboration or suggestion of DIPNECH by the pathologist will likely prompt closer patient followup in the form of serial PFTs and surveillance imaging aimed at preventing progression to respiratory failure and metastatic neuroendocrine disease respectively.

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**QUESTIONS:**

1. PNECH can lead to
    A. Airway obstruction only
    B. Neuroendocrine neoplasms only
    C. Both airway obstruction and neuroendocrine neoplasms

2. DIPNECH is a:
    A. Clinical diagnosis
    B. Pathologic diagnosis
    C. Clinical-pathologic diagnosis

**ANSWERS:**

1. C
2. C

**Case #6**

**PRESENTER:** Sana Shah, M.D.

**ATTENDINGS:** John Lee, M.D., Ph.D., Ajit Paintal, M.D., Michael Paterakos, M.D.

**CASE HISTORY:** A 69-year-old male who presented with a rapidly enlarging sinonasal mass. An initial biopsy was performed. Based on the initial diagnosis, only chemoradiation was administered, and surgery was not performed. While partial tumor regression was achieved, a complete response was not observed. Approximately 1.5 years later, the mass recurred and extended to the skull base, although there was no evidence of intracranial involvement. Following the recurrence, a second biopsy was performed to reassess the lesion. The histological material submitted with this case includes two sets of slides: the first represents the initial biopsy, while the second corresponds to the biopsy performed after the recurrence

**FINAL DIAGNOSIS:** Sinonasal Teratocarcinosarcoma

**DIFFERENTIAL DIAGNOSIS:**

- SMARCA4 deficient sinonasal carcinoma
- SMARCB1 deficient sinonasal carcinoma
- High grade olfactory neuroblastoma/carcinoma
- Rhabdomyosarcoma
- Small cell carcinoma

**DISCUSSION:**

Sinonasal Teratocarcinosarcoma (TCS) is an exceptionally rare and highly aggressive neoplasm distinguished by its unique composition of epithelial, mesenchymal, and neuroepithelial elements. Initially described in 1966 as a malignant teratoma, the term "Teratocarcinosarcoma" was introduced in the 1980s and officially recognized as a distinct entity in the 2005 World Health Organization (WHO) classification. This tumor predominantly affects males, with a median age of presentation around 50 years, and most commonly arises in the sinonasal tract or skull base. The histopathology of sinonasal teratocarcinosarcoma (TCS) is characterized by its triphasic composition of epithelial, mesenchymal, and neuroepithelial elements. The epithelial components include squamous and glandular elements. Mesenchymal elements can exhibit differentiation into mature or immature cartilage, bone, and adipose tissue, while the neuroepithelial components frequently form primitive rosettes or neuroectodermal-like structures. Molecular analyses have identified frequent biallelic inactivation of the SMARCA4 gene, activating mutations in CTNNB1, and, less commonly, mutations in PIK3CA, all of which play significant roles in the tumor's pathogenesis.

The immunohistochemical (IHC) profile of TCS is crucial for diagnosis, as it reflects the tumor's histological heterogeneity. The epithelial elements are consistently positive for cytokeratins, including AE1/AE3 and CK5/6, confirming epithelial differentiation. Neuroepithelial components exhibit positivity for neuroendocrine markers such as synaptophysin, chromogranin, and neuron-specific enolase (NSE), indicative of neuroendocrine differentiation. Mesenchymal elements are characterized by desmin and myogenin expression, supporting skeletal muscle differentiation. Nuclear β-catenin staining is often observed, correlating with CTNNB1 mutations. These findings underscore the importance of employing a

broad panel of IHC markers to distinguish TCS from other sinonasal malignancies such as small cell carcinoma, olfactory neuroblastoma, or rhabdomyosarcoma.

Despite its rarity, TCS demands heightened awareness among otolaryngology and neurosurgical professionals due to its aggressive clinical behavior and significant therapeutic implications. Optimal management necessitates a multimodal approach, combining surgery, radiotherapy, and chemotherapy with trimodal treatment associated with improved survival outcomes. However, recurrence and disease progression remain common challenges, emphasizing the need for early diagnosis and a comprehensive treatment strategy to improve prognosis.

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**Questions:**

1. Which of the following histological features is most commonly observed in sinonasal teratocarcinosarcoma (TCS)?

    A. Triphasic composition with squamous and glandular epithelial elements, mesenchymal differentiation into cartilage or bone, and neuroepithelial rosette formation

    B. Spindle cell proliferation with necrosis and vascular invasion

    C. Sheets of small round blue cells with Homer Wright rosettes

    D. Glandular differentiation with extensive keratin pearl formation

2. Which of the following genetic mutations are most commonly associated with sinonasal teratocarcinosarcoma (TCS)?

    A. TP53 and EGFR mutations

    B. KRAS and MET mutations

    C. SMARCA4 inactivation and CTNNB1 mutations

    D. NRAS and BRAF mutations

**Answers:**

1. A

2. C