Illinois Registry of Anatomic Pathology
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Rush University Medical Center

<u>Case # 1</u>
Presenter: Arlen Brickman, MD
Attending: Ira Miller, MD, PhD

- **Diagnosis: Metastatic melanoma with heterologous differentiation**

Important Differential Diagnosis of Metastatic melanoma

- **Metaplastic breast (carcinosarcoma)**
- **Squamous cell carcinoma (spindle cell type)**
- **Malignant Peripheral Nerve Sheath Tumor (MPNST)**
- **Osteosarcoma**
- **Synovial sarcoma**
- **Collision tumor**

Discussion:
- **Malignant melanoma is a common and highly aggressive skin cancer that accounts for approximately 75% of skin cancer deaths.**
- **Diagnosis based on a combination of topographical, histomorphologic, and immunohistochemical features.**
- **Great phenotypic diversity of primary and metastatic malignant melanoma is well documented.**
- **Occasionally, melanoma cases may present with unexpected and unusual phenotypes that mimic a variety of non-melanocytic neoplasms and thus pose a great diagnostic confusion.**
- **Histology of metastases may mimic undifferentiated pleomorphic or spindle cell sarcoma, with immunohistochemistry negative for melanocytic markers including; S100, HMB45, Melan A, MITF, and SOX10. In these cases BRAF mutations can be used to differentiate between sarcoma and metastatic melanoma, as sarcomas are negative for BRAF mutations.**
- **Treatment can include BRAF targeted therapies when identified.**

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<u>Case # 2</u>
Presenter: Christine Rupcich, MD
Attending: Leonidas Arvanitis, MD

- **Diagnosis:** Primary Intracranial Ewing Sarcoma

Important Differential Diagnosis of primary intracranial Ewing sarcoma
- Anaplastic meningioma, WHO Grade III
- Hemangiopericytoma
- Poorly differentiated metastatic carcinoma
- Lymphoma/Leukemia
- High-grade glioma
    - GBM with PNET-like component
    - Anaplastic Oligodendroglioma
- Embryonal tumors
    - Medulloblastoma
    - Atypical teratoid/rhabdoid tumor
    - Central PNET/CNS Neuroblastoma

Discussion:
- It is exceedingly rare for Ewing sarcoma to occur primarily intracranially.
- The mean age at diagnosis is 19 years old (5 months-67 years).
- An equal ratio of men and women are affected.
- Patient's present with symptoms of a mass occupying intracranial lesion. The most common complains are headache, nausea/vomiting, and vertigo.
- Physical exam most commonly reveals papilledema and occasionally cranial nerve palsies.
- Radiologic findings are not specific; however, the most consistent findings are solitary, circumscribed, dural based masses with intense, diffuse enhancement. The masses can be variably cystic and have hemorrhage.
- Histologically the tumors look similar to other Ewing sarcomas. They are comprised of solid sheets of small-medium sized, round-oval, primitive appearing cells with fine chromatin and inconspicuous nucleoli. The cytoplasm is PAS positive and diastase sensitive. Mitotic figures can be readily identified and there are areas of necrosis. Homer-Wright rosettes are not generally seen.
- By immunohistochemistry the cells are at least focally positive for neuronal markers, are FLI-1 positive, and have membranous staining for CD99.
- As with other Ewing sarcomas, there is a t(11;22)(q24;q12) EWS:FLI1 fusion that can be detected with FISH studies.
- Treatment includes surgery, multiagent chemotherapy, and field radiation therapy.
- Because of its rarity, the exact outcome for primary intracranial Ewing sarcoma is not known. The 5 year survival of extraosseous Ewing's sarcoma of all sites is 60%. A study of 16 cases of primary intracranial Ewing sarcoma showed a 1 year survival of 91% and a 5 year survival of 50%.

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Case # 3
Presenter: Shenon Sethi, MD
Attending: Ira Miller, MD, PhD

Clinical history:
The patient is a 33 year old African American male who presented with a 6 year history of a gradually growing lesion on the right parieto-occipital region of his scalp that measured 10 x 8 x 5 cm and was tender, rubbery with focal rock hard areas, and normal overlying skin. MRI showed an extracranial mass with areas of calcification. There was no involvement of the underlying bone on CT.

Final Diagnosis: Myoepithelial predominant mixed tumor of skin/soft tissue with atypical features

Differential Diagnosis of Mixed chondro-epithelial/epithelioid tumor of skin/soft tissue in head and neck:

- Metastatic tumors
  - Metastasizing pleomorphic adenoma
  - Metaplastic carcinoma
- Melanoma
- Dedifferentiated chondrosarcoma
- Chondroid chordoma
- Extraskeletal myxoid chondrosarcoma
- Myoepithelial tumors
  - Myoepithelioma
  - Parachordoma
  - Mixed tumor

Discussion:

- Definition: Mixed tumors are well circumscribed lesions displaying epithelial and/or myoepithelial elements in varying proportions, within a hyalinized to chondromyxoid stroma.

- General features:
  - Mixed tumors in the skin are also known as chondroid syringomas, a term introduced in 1961, as it is characterized by the presence of sweat gland elements lying within a cartilage like stroma. These originate from both the secretory and ductal elements of the sweat glands.
  - Histogenesis of mixed tumors in the soft tissue is not well understood. The only distinction between a mixed tumor and myoepithelioma is the presence of ductal element which is seen in 10% of the cases.

- Epidemiology:
  - Mixed tumors in skin: They have been reported in patients aged 22 to 73 years with a mean age of occurrence of 50 years. Male to female ratios have varied among series, ranging from 1.3/1 to 5.0/1.
  - Mixed tumors in soft tissue: They affect all age groups but are most common before the age of 50 (average age 35 years). Slight male predominance is present.

- Sites of involvement:
  - Mixed tumors in skin: Generally occurs in the head and neck region. In the head and neck region, the tumor mostly affects the nose, cheek, and upper lip; but it may also occur on the scalp, forehead, brow, and upper eyelid. The tumor can also, rarely, involve the trunk, back, extremities, and genital organs, including penis, vulva, and scrotum.
  - Mixed tumors in soft tissue: Limbs (including hands and feet) are the commonest site and, and most cases are subcutaneous with up to 35% cases that are intramuscular or subfascial.

- Histopathology: Mixed tumors in the skin and soft tissue are morphologically similar to benign salivary gland pleomorphic adenomas and have an epithelial and/or myoepithelial and mesenchymal component. There is wide variability in their histologic appearance. The epithelial/myoepithelial component may appear as solid sheets, strands, single cells, glands, ducts. The surrounding stroma may be fibrous, myxoid, chondroid, hyaline, osseous or adipoid.
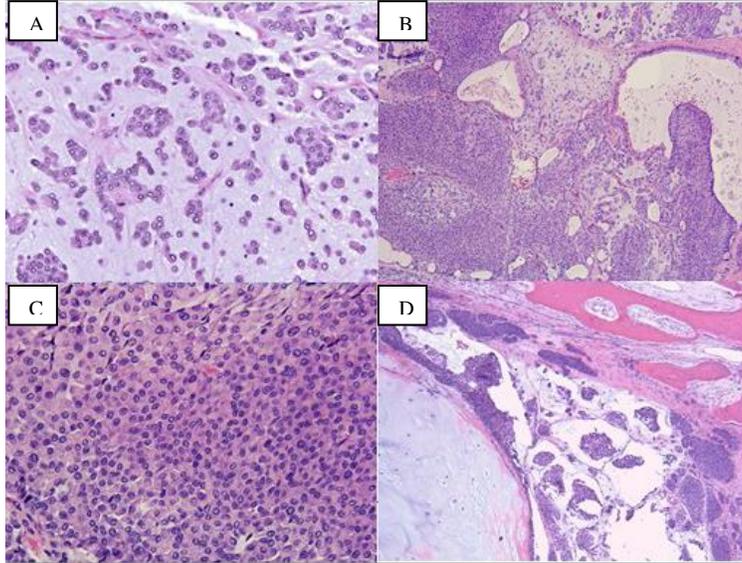

Fig1: H&E stained sections showing chondromyxoid areas with associated scattered single cells (A), ducts lined by single layer of epithelial cells (B), nests and sheets of plasmacytoid cells with eosinophilic hyaline cytoplasm (B&C) , metaplastic bone and cartilage (D).

- Immunophenotype:
  - Epithelial component: Keratin, EMA, CEA
  - Myoepithelial component: Vimentin, S100, Calponin, keratin, NSE; variable smooth muscle actin (20-25%), GFAP (45%).

- Prognostic factors:
  - Usually, mixed tumors are benign with a recurrence rate of 20%.
  - Malignant mixed tumors may arise de novo or from an incompletely excised benign mixed tumor. In contrast to the benign type, the de novo malignant variant occurs mostly on the extremities and trunk. Malignancy is characterized by cytologic atypia and increased mitotic figures. These may metastasize and the most common metastatic sites are lymph nodes, lung, and bone. Recurrence rate is 39-42%.
  - Tumors that show necrosis, infiltrative margins, or satellite nodules have been called atypical.

- Genetics:
  - Studies have shown up to 100% PLAG1 expression by immunohistochemistry.

- PLAG1 rearrangement by FISH was detected in 37% of skin and 58% of soft tissue mixed tumors in one study; however, all except one lacked the rearrangements seen in pleomorphic adenomas.

- Treatment:
  - Complete excision, including a rim of at least 3-4 mm of normal tissue surrounding the tumor.
  - Cases with atypical should be examined periodically because of the risk of undetected tumor left behind via satellite tumor nodules.
  - Cases with malignant histopathologic features, besides periodic follow up may also be considered for external beam radiotherapy.

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Case # 4
Presenter: Fatima Mir, MD
Attending: Paolo Gattuso, MD

Diagnosis: Reactive histiocytic proliferations

Important Differential Diagnosis of Reactive histiocytic proliferations
Reactive mesothelial cells
Signet ring cell mesothelioma
Metastatic signet ring cell adenocarcinoma of the GI tract
Metastatic breast carcinoma

Discussion:
- Extremely rare.
- Previously known as nodular mesothelial hyperplasia.
- Have been reported in mesothelial-lined locations such as the pleura, pericardium, peritoneum and hernia sac.
- Probably result from the irritation of mesothelial lining due to infection or trauma (surgery), which leads to aggregation of histiocytes.
- Histologically, can be nodular or diffuse.
- Contain variable proportions of histiocytes with vacuolated to clear cytoplasm and signet ring-like change, and could be misinterpreted as metastatic carcinoma.
- Occasionally, reactive histiocytes are known to show moderate nuclear pleomorphism and high mitotic activity.
- Immunohistochemical staining is critical for diagnosis to avoid false positive results.

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Case # 5
Presenter: Sara Javidiparsijani, MD
Attending: Shiram Jakate, MD

- **Diagnosis:** Combined hepatocellular and cholangiocarcinoma, classical type

Important Differential Diagnosis of Combined hepatocellular and cholangiocarcinoma, classical type
- Hepatocellular carcinoma, variants
- Intrahepatic cholangiocarcinoma
- Combined hepatocellular and cholangiocarcinoma with stem cell features subtypes

Key features:
- WHO definition: Unequivocal elements of both hepatocellular and cholangiocarcinoma that are intimately admixed
- Rare primary liver cancer with similar age, sex and liver back ground disease as HCC
- Radiology is not sensitive in diagnosing the tumor
- Pathology: Heterogeneous tumor with areas of adenocarcinoma (CK7, CK19 positive) and areas of hepatocellular carcinoma (Hep-Par-1 and Glyp-3 positive)
- Sub-categorized to 1) classical type and 2) subtypes with stem cell features based on the presence of cells with stem cell morphology (oval cells with high N:C) and immunohistochemistry (positive for EpCAM, NCAM, c-kit, CD133)
- Prognosis is determined by the proportion of adenocarcinoma component.

Discussion: These groups of rare primary liver cancers are believed to drive from "hepatic progenitor cells" which are normally present in all livers and at all ages. These cells become activated in chronic liver injuries like Hepatitis C or B and can differentiate to both hepatocytes and biliary epithelium.
Combined hepatocellular carcinomas are monoclonal tumors (based on loss of heterozygosity (LOH) studies) arising from these cells.
The radiologic features of these tumors are not specific and they are often mistaken with hepatocellular carcinomas. Pathology is the key diagnostic tool. The prognosis is determined by the cholangicarcinoma component, vascular invasion and lymph node metastasis. In one study, it was mentioned that the subtypes with stem cell features may have slightly better prognosis compared to the classical type.

Image 1: H&E image of combined hepatocellular and cholangiocarcinoma, classical type.
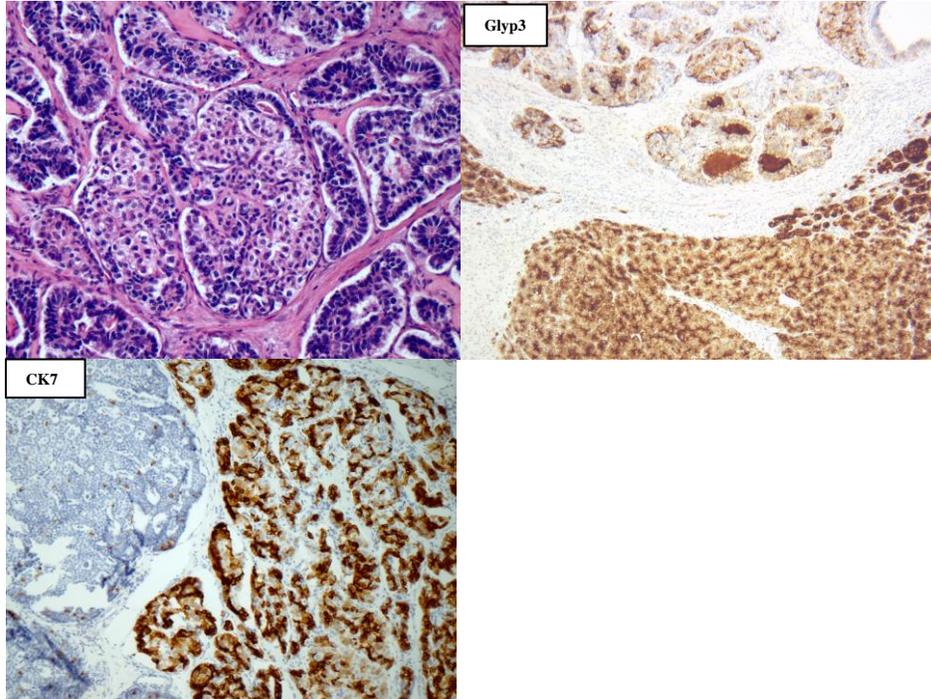
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Case # 6
Presenter: Yahya Al-Ghamdi, MD
Attending: Ira Miller, MD, PhD

- **Diagnosis:** Plexiform fibrohistiocytic tumor (PFT), histiocytoid type

Important Differential Diagnosis of plexiform fibrohistiocytic tumor, histiocytoid type

- Cellular neurothekeoma
- Reticulohistiocytoma
- Langerhans cell histiocytosis
- Non-necrotizing granuloma
- Juvenile xanthogranuloma
- Giant cell tumor of soft tissue

Key morphological/immunohistochemical features:

– The histiocytoid type of PFT is composed of clusters of epithelioid, histiocyte-like cells and multinucleated giant cells in a plexiform arrangement (positive for CD68)
– Negative for S100

Discussion:
- First described by Enzinger and Zhang, 1988
- Slow growing, painless soft tissue tumor that is situated in the dermis and subcutis
- The overlying skin is slightly raised and sometimes displays a central depression
- The largest reported lesion was 8.5 cm
- The median age of the largest reported series was 14.5 years (range: 2 months to 71 years)
- F>M
- There has been no evidence to suggest predilection for any particular race
- Preferentially involve the upper extremities followed by the lower extremities and head and neck
- Histopathology:
    - **Histiocytoid:** composed of clusters of epithelioid, histiocyte-like cells and multinucleated giant cells in a plexiform arrangement
    - **Fibroblastic:** composed mainly of elongated clusters and short fascicles of spindle fibroblast-like cells
    - **Mixed:** composed of both patterns in equal proportions
- Immunophenotyping:
    - CD68+ (Giant cells and histiocytoid cells)
    - SMA+ (spindle cells)
    - Negative for S100, desmin, and keratins
- Cytogenetics:
    - There has been no consistent chromosome change found yet
- Prognosis:
    - Unrelated to histologic type
    - Recurrence rate: 12.5%-50%
    - Metastasis: lymph node, lung, eyebrow
    - One patient died of metastatic disease
- Treatment:
    - Wide local excision and long-term follow-up

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