Northwestern University Post-
IRAP Discussion
September 28, 2020

<u>Case 1 (Dr. Ian Gelarden)</u>: Ewing Sarcoma with Myxoid Stroma

Clinical History: The patient is a 26-year-old female with a history of persistent headaches and "light headedness." Imaging of the head was obtained five years prior to presentation and showed no cranial abnormality. Physical examination revealed no external abnormalities and no neurological deficits. MRI of the brain revealed an expansile lesion of the right temporal bone with subtle thickening of the overlying dura. There was moderate mass effect on the right temporal lobe. Given the interval appearance and increase in size of this lesion, surgical excision was recommended.

Gross and microscopic findings: Grossly, the tumor was a lytic, expansile intraosseous lesion measuring 4.3 cm in greatest dimension. Microscopically, the tumor consisted of uniform spindled and rounded cells arranged in vague nodules and fascicles. Many areas showed prominent myxoid stroma with cells arranged in cords and reticular and pseudoacinar structures. These prominent myxoid areas accounted for more than 50% of the tumor volume. The tumor cells showed finely dispersed chromatin, small nucleoli, and pale eosinophilic to clear cytoplasm. The mitotic rate was 2 mitoses per 10 high power fields. No necrosis was identified.

Differential Diagnosis:
- Undifferentiated small round cell sarcoma
- Low-grade fibromyxoid sarcoma
- Meningioma
- Melanoma
- Myoepithelioma
- Rhabdomyosarcoma
- Solitary fibrous tumor
- Synovial sarcoma

Ancillary Studies:
- **IHC:** Tumor cells were positive for FLI1, CD56, and CD99, and negative for AE1/AE3, EMA, SSTR2A, desmin, MyoD1, MUC4, Melan-A, HMB45, S100, Sox10, STAT6, CD31, ERG, and WT1. Ki-67 proliferation index was <10%.
- **Molecular:** The tumor was positive for *EWSR1-FLI1* fusion transcript, confirmed by Sanger sequencing.

Discussion: Ewing sarcoma belongs to the WHO group of "undifferentiated small round cell sarcomas of bone and soft tissue". It is a small round cell sarcoma showing gene fusions involving one member of the FET family of genes and a member of the ETS family of transcription factors. Ewing sarcoma is the second most common bone malignancy in children and young adults, after osteosarcoma. There is a slight male predominance, with the majority of patients less than 20 years of age, and the tumor is more common in individuals of European ancestry. Ewing sarcoma arises most commonly in the diaphysis and diaphyseal-metaphyseal portions of long bones, pelvis, and ribs. Extraskeletal Ewing sarcoma occurs in about 12% of patients.

Grossly, Ewing sarcomas show a gray-to-white, soft cut surface, frequently with areas of necrosis or hemorrhage. Histologically, these tumors are composed of uniform small round cells with round nuclei showing fine chromatin and inconspicuous nucleoli with scant clear or eosinophilic cytoplasm. So called atypical Ewing sarcomas may show larger cells with irregular contours. Tumors previously deemed primitive neuroectodermal tumor may show rosette-type structures. Prominent myxoid stroma is extremely rare in Ewing sarcoma and more frequently seen in *BCOR* altered or *CIC-DUX* rearranged sarcomas.

Immunohistochemically, CD99 is an important marker for Ewing sarcoma, with diffuse membranous staining seen in approximately 95% of cases. NKX2-2 may have a higher specificity than CD99. Keratin expression is present in around 25% of cases and may be weak and patchy. FLI1 and ERG immunohistochemical stains are often positive in cases with these gene fusions. Genetic information is often required to diagnosis Ewing sarcoma. The most common translocation (~85%) results in the *EWSR1-FLI1* fusion, and the second most common results in the *EWSR1-ERG* fusion (~10%). The remaining cases have alternative fusions joining FET and ETS family members.

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Case 2 (Dr. Lucy Fu): Mast Cell Sarcoma

Clinical History: The patient is a 38-year-old male with history of T-cell lymphoblastic leukemia/lymphoma (T-ALL). He had refractory disease and achieved complete remission after chemotherapy and an HLA-matched sibling allogeneic HSCT. Nine months post-transplant, he presented with intractable vomiting, diarrhea, and fatigue. CT imaging showed significant upper abdomen and pelvic ascites; there was prominent mesenteric, omental, and peritoneal nodularity as well as scattered hepatic nodules; the proximal jejunum and distal duodenum showed marked mass-like bowel wall thickening. IR-guided biopsies were performed of the liver and omental nodules. Paracentesis of the ascites was also performed.

Gross and microscopic findings: Microscopically, tissue from the omental nodules showed sheets and vague nests of round to ovoid eosinophilic cells with scattered intervening fibrosis. On higher power, the cells show no obvious differentiation. Nuclei are pleomorphic with scattered mitoses. Cytoplasm is eosinophilic and granular with some areas showing prominent clear cell changes. Wright-Giemsa staining of the ascites showed scattered discohesive large cells which are quite pleomorphic, some with bi-lobed/multi-lobed nuclei. The tumor cells have ample, vacuolated cytoplasm with prominent metachromatic granules.

Differential Diagnosis:

- Clear cell sarcoma
- Epithelioid gastrointestinal stromal tumor (GIST)
- Metastatic carcinoma
- Metastatic melanoma
- Myoepithelioma of soft tissue
- Perivascular epithelioid cell tumor (PEComa)
- Hematologic malignancy
    - Lymphoma (T-ALL, DLBCL, ALCL)
    - Histiocytic sarcoma
    - Mast cell sarcoma
    - Myeloid sarcoma

Ancillary Studies:

- **Flow (ascites):** There is an abnormal dim CD45 cell population (90% of total cells) which is CD117+, CD33+, CD2+, CD25+, and CD123+; T-cells did not show evidence of phenotypic abnormality (CD3/CD5/CD7 positive and TdT negative).
- **IHC (biopsy):** Tumor cells were positive for CD45, CD25, CD68, tryptase, and CD117. Stains for epithelial, muscle, and melanocytic origin and DOG-1 were all negative.
- **Molecular:** The tumor showed multiple somatic mutations (*BRAF* p.G464V, *TP53* p.R282W, *ASXL1* p.Q768*, *RNX1* p.V164fs, *PHF6* p.C283fs) which were identical to mutations in the patient's original T-ALL (with the exception of *TP53*). Furthermore, clonal T-cell receptor (TCR) gene rearrangement revealed identical clonal bands in both the mast cell sarcoma and previous T-ALL.

Discussion: Mast cell sarcoma belongs to the spectrum of mastocytosis which is characterized by clonal, neoplastic proliferations of abnormal mast cells that accumulate in one/more organ systems. Localized to just the skin and on the more benign end of the spectrum is cutaneous mastocytosis which is further classified as urticaria pigmentosa, mastocytoma of skin, or diffuse cutaneous mastocytosis depending on degree of involvement. Systemic mastocytosis shows multifocal dense infiltrates of mast cells in bone marrow and/or other extracutaneous organs with at least one of the minor criteria (>25% atypical mast cells, activating *KIT* D816V mutation, CD25+, serum total tryptase >20 ng/mL). Systemic mastocytosis exists in indolent, smoldering, and aggressive subtypes, culminating in mast cell leukemia, which is highly malignant. Patients clinically present as an acute leukemia, and atypical mast cells comprise >20% total marrow cellularity and >10% of circulating leukocytes. Mast cell sarcoma is an aggressive solid tumor

variant characterized by localized destructive growth of highly atypical mast cells. It is reported to occur in the larynx, large bowel, meninges, bone, and skin. Disease is initially localized but quickly distantly metastasizes, ending in a terminal phase resembling mast cell leukemia. Prognosis is dismal and often fatal within a few months.

In an extensive literature review of 23 cases, Monnier et al showed that mast cell sarcoma is rare, accounting for fewer than 0.5% of all mastocytosis cases. The median patient age at diagnosis is 41 years with a range from 1 to 77 (including 5 pediatric cases). There is a slight predominance of females (13:10). The disease appears sporadic, with only one described familial case. De novo is the most frequent presentation; only 2 of the described 23 patients had a history of cutaneous mastocytosis.

Next generation sequencing and TCR gene rearrangement showed shared and retained genetic alternations between this case of mast cell sarcoma and our patient's previous T-ALL (see ancillary studies above). These genetic findings, especially the TCR gene rearrangement, suggest that this mast cell sarcoma represents a rare form of transdifferentiation—direct lineage reprogramming from the patient's original lymphoid neoplasm to this mast cell neoplasm. This phenomenon has previously been described in mature B-cell neoplasms and B-ALL transdifferentiating to histiocytic, dendritic cell, and Langerhans cell sarcomas; but this is the first reported case of transdifferentiation from T-ALL to mast cell sarcoma.

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Case 3 (Dr. Lukas Streich): Hibernoma

Clinical History: The patient is a 64-year-old female with a history of bilateral hip replacements several years prior. She had experienced chest pain, nausea and tingling of the extremities while shoveling snow during a Chicago winter storm. A cardiovascular workup was performed, including a CT scan of the chest and abdomen, which demonstrated an incidental 6.0 x 5.8 cm mass within the lower pole of the right kidney. The mass was heterogeneously enhancing on contrast MRI. The differential based on the imaging findings was clear cell renal cell carcinoma, liposarcoma, metanephric adenoma, and angiomyolipoma. The patient subsequently underwent a right radical nephrectomy.

Gross and microscopic findings: Grossly, there was a 7.5 x 6.5 x 6.0 cm circumscribed, bulging mass apparently arising in the perinephric fat, which was pushing against but not invading the lower renal pole. The cut surface was gelatinous to yellow-orange. Microscopically, the mass showed multivacuolated cells with central nuclei, variably eosinophilic granular cytoplasm, and no nuclear atypia, consistent with hibernoma cells. The tumor was well-demarcated from the adjacent renal parenchyma. There were occasional mature adipocytes without atypia, with a roughly equal ratio of adipocytes to hibernoma cells. Interspersed among these cells was a dense chronic inflammatory infiltrate, consisting predominantly of lymphocytes, with scattered plasma cells. Occasional lymphoid follicles were present. Other inflammatory cells, including eosinophils and neutrophils, were not present. The background was variably collagenous, with some sclerotic vessels. No lipoblasts, atypical adipocytes, or hematopoietic elements were found.

Differential Diagnosis:

- Well-differentiated liposarcoma/atypical lipomatous tumor (WDS/ALT)
- Myelolipoma
- Hibernoma
- IgG4-related disease
- Angiomyolipoma

Ancillary Studies:

- **IHC:** S100 (+), p16 (-), HMB-45 (-), MDM2 (-), Ki-67 proliferative index <1%, IgG4 (-)
- **Molecular:** MDM2 amplification (-)

Discussion: The hibernoma, a benign tumor of brown fat, is an uncommon lesion. It is named after its morphologic similarity to the brown fat glands which are most well-known in hibernating mammals. The existence of brown fat glands in adult *H. sapiens* was demonstrated as early as 1670 by one G.H. Velsch, and the first definitive morphologic description was given by Shinkishi Hatai in 1902, with further anatomic and histologic details published by Edward Bonnot in 1908. Bonnot in particular noted the extent of this tissue from the side of the neck, anteriorly to the clavicle, and posteriorly into the intrascapular region. Based on post-mortem studies, he named it the interscapular gland and postulated an endocrine function. A large post-mortem series by Heaton demonstrated the location and extent of brown adipose tissue in humans from infancy to old age. Tumors of brown fat were first described by H. Merkel in 1906 as a pseudolipoma, and were given the name, hibernoma, by Gery in 1914, and further elucidated in the subsequent decades. Further studies have shown the common anatomic sites of hibernomas are, in order of frequency, the thigh, shoulder, neck, upper back, chest, arm and retroperitoneum. It has additionally been rarely reported as an intraosseous lesion, and in the spermatic cord. These sites square rather well with Bonnot's original description, with rare exceptions. In the modern era, hibernomas have been characterized by rearrangements at 11q13, with resultant deletions of *MEN1* and *AIP*, and it has been shown that loss of AIP drives growth of these lesions. It is well established that these are benign tumors; there are no reports of metastasis in the literature. There are rare case reports of atypical hibernomas, one of which documents hyperchromatic and enlarged nuclei in the multivacuolated cells. The authors of that report comment that there are other benign tumors that can display cellular atypia (for example, uterine leiomyoma with bizarre nuclei), and that their case may in fact belong in this category, as the patient showed no evidence of metastases or recurrence during four years of monitoring.

A large review from the Armed Forces Institute of Pathology separated hibernomas into four morphologic variants: typical, spindle cell, lipoma-like, and myxoid. The typical hibernoma shows varying numbers of the characteristic brown fat cells, with multivacuolated, finely granular eosinophilic cytoplasm and centrally located nuclei, and interspersed univacuolate mature adipocytes. The AFIP authors subdivided typical hibernomas into three groups, according to degree of cytoplasmic eosinophilia, nature of the stroma, and the presence of spindled cells. The second variant, the lipoma-like, consists of predominantly mature adipocytes with rare hibernoma cells. The myxoid variant shows scattered classic hibernoma cells in an acellular myxoid stroma. The final and rarest variant, spindle cell, shows typical hibernoma cells with interspersed dense collagen bundles, mast cells, and bland spindled cells in a myxoid stroma. On immunohistochemical staining, the brown fat cells in hibernomas are positive for UCP1, S100, and vimentin; of these, UCP1 appears to be the most specific. UCP1, otherwise known as mitochondrial uncoupling protein 1, is a protein expressed specifically in brown adipose tissue which uncouples the electron transport chain in mitochondria; this mechanism is responsible for the thermogenic activity inherent to that tissue type. Recently, Al Hmada and colleagues reported a large case series of hibernomas mimicking atypical lipomatous tumors/well-differentiated liposarcoma (ALT/WDS). Their cases were composed of predominantly lipoblast-like cells, suggestive of a liposarcoma, but were negative when tested for the *MDM2* amplification which is the diagnostic hallmark of ALT/WDS.

In summary, hibernomas are uncommon benign tumors arising from brown fat. Their histologic appearance and immunoprofile reflect this origin. Given their overlap with ALT/WDS, it is prudent to rule out that diagnosis with FISH for *MDM2* amplification.

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Case 4 (Dr. Jessica Nguyen): Peutz-Jeghers Syndrome

Clinical History: The patient is a 54-year-old man with recurrent episodes of bowel obstruction status post prior small bowel resections who presented to the emergency department for abdominal pain. CT of the abdomen showed an ileoileal intussusception with large small bowel polyps serving as a lead point. Upper and lower GI endoscopy showed numerous gastric, small bowel, and colonic polyps. He subsequently underwent a small bowel resection.

Gross and microscopic findings: Grossly, the segment of small bowel showed innumerable pedunculated and sessile polyps with a multinodular, bosselated appearance. Microscopically, one of the representative polyps demonstrated a central core of branching smooth muscle bundles separating lobules of disorganized small bowel mucosa. There are cystically dilated glands and areas of inspissated mucin within the submucosa and muscularis propria. These displaced glands are partially lined by bland small bowel epithelium and an attenuated low cuboidal to columnar epithelium with free floating cells and eosinophilic granular debris in the mucin. No dysplasia is identified.

Differential diagnosis: Cases in which patients present with numerous gastrointestinal polyps should make one think of various polyposis syndromes such as the following:

- Juvenile polyposis syndrome
- Peutz-Jeghers syndrome
- Cowden/*PTEN* hamartoma syndrome
- Familial adenomatous polyposis

Discussion: Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by germline mutation in *STK11* in up to 70-80% of patients. The estimated prevalence is 1 in 50,000-200,000 births. Patients typically present with abdominal pain secondary to intussusception as seen in our case. Classically, patients will have mucocutaneous pigmentation around the mouth, eyes, nostrils, fingers, oral mucosa and perianal area. This pigmentation can appear as early as the first year of life, but can tend to fade away with age and might completely disappear in puberty or adulthood. Hamartomatous polyps most often develop in the small intestine (60-90%) especially in the jejunum, but also can arise in the large bowel (50-64%) and stomach (15-30%).

The diagnostic criteria for PJS is as follows:

- At least three histologically confirmed Peutz-Jeghers polyps *or*
- Any number of Peutz-Jeghers polyps with family history of PJS *or*
- Characteristic prominent mucocutaneous pigmentation with family history of PJS *or*
- Any number of Peutz-Jeghers polyps and characteristic prominent mucocutaneous pigmentation

Grossly, Peutz-Jeghers polyps typically are pedunculated with a multinodular, bosselated polyp head and thick stalk. Microscopically, Peutz-Jeghers polyps are hamartomatous polyps with a central core of arborizing smooth muscle branches that separate lobules of disorganized mucosa native to the site of origin. Dysplasia or adenocarcinoma may be seen arising in these polyps. Epithelial misplacement or pseudoinvasion may be seen, in which glands are entrapped in the submucosa, muscularis propria, and occasionally subserosa. This phenomenon is thought to be secondary to prolapse and can be a mimicker of invasive adenocarcinoma. Prior case reports have also described pseudoinvasion with enteritis cystica profunda like morphology, as seen in our case, in which the misplaced glands become cystically dilated and contain free floating benign epithelium, mucin, eosinophilic granular debris and necrotic cells. Examination of deeper sections may be helpful in these cases to rule out an invasive process.

Patients with PJS are at increased risk of gastrointestinal and extraintestinal malignancies including colorectal, breast, stomach, small bowel and pancreas cancers. Other notable tumors that can be associated with PJS are minimal deviation adenocarcinoma of the cervix, sex cord tumor with annular

tubules of the ovary (SCTAT), and large-cell calcifying Sertoli cell tumor of the testis. Therefore, periodic surveillance is important in these patients.

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<u>Case 5 (Dr. Matthew McCord)</u>: Extracranial Metastatic Anaplastic Pleomorphic Xanthoastrocytoma, WHO grade 3

Clinical History: The patient is a 50-year-old male with a history of a left temporal brain tumor. On resection, pathology was called glioblastoma, *IDH*-wildtype, WHO grade 4. The tumor was negative for *MGMT* promoter methylation. After surgical resection of the tumor, he completed chemotherapy with temozolomide and radiation therapy. Two years post-therapy, serial brain imaging showed no evidence of tumor recurrence. Just after two years post completion of therapy, he presented to the emergency department with acutely worsening back and shoulder pain. Imaging showed multiple bony tumors in the thoracic vertebrae, and a chest wall mass involving the 2nd and 3rd ribs, all concerning for metastatic malignancy. Biopsies of one vertebral mass and of the chest wall mass were taken.

Microscopic findings: Sections from the vertebral and chest wall masses showed hypercellular tumors, invading and destroying bone. Architecture was nodular and fascicular. Cytology showed epithelioid cells with vacuolated cytoplasm, with focal areas of clear cell cytology. Frequent mitotic figures were found (up to 15 per 10 high power fields).

Differential diagnosis:

- Malignant myoepithelioma of bone
- Meningioma
- Metastatic melanoma
- Clear cell sarcoma
- Epithelioid sarcoma
- Metastatic poorly differentiated carcinoma (including clear cell RCC)
- Extracranial metastatic glioma

Ancillary Studies:

- **IHC:** Tumor cells were negative for AE1/AE3, SSTR2A, EMA, SOX-10, Melan-A, and HMB-45. Tumor cells were positive for S100, Olig2, and GFAP
- **Next generation sequencing:** The original temporal lobe tumor, chest wall mass, and vertebral mass showed mutations in *BRAF* V600E, *TERT* promoter, and *SETD2*. The chest wall and vertebral tumors also showed *TP53* mutation.
- **DNA methylation-based tumor classification:** The chest wall mass fit best with methylation classes pleomorphic xanthoastrocytoma (PXA) and anaplastic pleomorphic xanthoastrocytoma.

Discussion: Pleomorphic xanthoastrocytoma (PXA) is a rare malignant glioma most frequently seen in children and young adults. The driver mutation usually affects a MAP kinase, often *BRAF* V600E. The tumors are usually well-circumscribed and have a predilection for the temporal lobe. The morphology is somewhat variable, but these tumors usually have fascicular or nested architecture with epithelioid cytology, often with lipidized cells and pleomorphic giant cell. Most PXAs are WHO grade 2. Anaplastic features (corresponding to WHO grade 3 designation) include hypercellularity, high mitotic activity, microvascular proliferation, and tumor necrosis. These tumors are positive for glial markers, including GFAP and Olig2, along with synaptophysin. In addition to *BRAF* V600E mutation, PXA may show loss of chromosome 9. Anaplastic PXA may show bi-allelic loss of *CDKN2A*.

There have been reports of anaplastic PXA metastasizing to bone. The diagnosis was quite challenging due to the rarity of extracranial metastasis in gliomas in general. Neither the morphology of the patient's original brain tumor (originally diagnosed as GBM) nor the bony metastases strongly suggested PXA. Initial impressions of the morphology suggested a sarcomatous or poorly differentiated carcinomatous entity. Immunohistochemical staining was initially non-contributory. Positive glial markers were diagnostic of an extracranial metastatic glioma. Re-review of the morphology of the original brain tumor cast doubt on the previous diagnosis of glioblastoma. Next generation sequencing of the primary brain tumor and metastases

showed *BRAF* V600E mutation, *TERT* promoter mutation, and *SETD2* mutation. The metastases also had *TP53* mutation.

For definitive classification of the glioma, tissue from the chest wall mass was sent for DNA methylation-based tumor classification. This technique relies on computer algorithm-based matching of DNA methylation patterns in an unknown sample to an established library of known entities belonging to different tumor classes. This method yields highly reliable and reproducible results for classifying CNS tumors with scant or poor-quality tissue. The tumor matched best with methylation classes for PXA and anaplastic PXA. These results fit well with the molecular genetic features. Based on a combination of morphologic, molecular genetics, and DNA methylation results, a final diagnosis of metastatic anaplastic pleomorphic xanthoastrocytoma, WHO grade 3, was yielded. With this diagnosis, the patient was treated with BRAF and MEK inhibitors, and initially responded favorably, although he subsequently developed additional metastases.

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Case 6 (Dr. Michael Swete): Langerhans Cell Histiocytosis

Clinical History: The patient is a 22-year-old woman with a history of diabetes insipidus and hypothyroidism who presented with pruritic labial ulcers that have waxed and waned over the past year.

Microscopic findings: The dermis showed large cells with eccentrically placed, reniform nuclei and abundant eosinophilic cytoplasm with a mixed inflammatory background.

Differential Diagnosis:

- Syphilis
- Primary cutaneous anaplastic large cell lymphoma
- Lymphomatoid papulosis
- Langerhans cell histiocytosis
- Rosai-Dorfman disease
- Histiocytic sarcoma

Ancillary studies:

- **IHC:** Tumor cells were positive for CD1a, S100, and CD207 (langerin), and negative for CD3, CD20, CD68, and CD30. HSV and *Treponema pallidum* IHC did not reveal any organisms. *BRAF* V600E was negative.

Discussion: Langerhans cell histiocytosis is an inflammatory myeloid neoplasm of Langerhans cells. It is most common in children, but can also affect adults, with a slight male predominance. It can affect any part of the body, most commonly the bone. Endocrine involvement is common with anterior pituitary dysfunction present in up to 62% of cases, with diabetes insipidus and growth hormone deficiency being most common. Prognosis depends on the organ(s) involved, with increased mortality in patients with high-risk organ (bone marrow, spleen, and liver) involvement and those with circulating *BRAF* V600E mutated cells.

Langerhans cells are dendritic, antigen-presenting cells that are present in all stratified squamous epithelia in the body. They derive from yolk sac and fetal liver but can be replenished by bone marrow progenitors following activation or injury. Electron microscopy shows tennis racket-shaped Birbeck granules. Langerhans cells stain positive for CD1a, S100, CD45, HLA-DR, and langerin. Histology for Langerhans cell histiocytosis shows large cells with eccentrically placed, reniform nuclei and voluminous cytoplasm. The background often shows a mixed inflammatory background, often showing many eosinophils.

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