the morphologic spectrum and etiology of DAD encountered during adult autopsy in an inner city teaching hospital. The diagnostic utility of post mortem lung culture was also evaluated.

**Design:** A retrospective study was performed on all adult autopsies from July 2010 to July 2011. Histopathologic diagnosis of DAD and the histopathologic characteristics of DAD were re-evaluated by one autopsy pathologist and one pathology resident, based on a duration (exudative or proliferative phase), severity (bilateral/unilateral; focal/exclusive) and pattern (classical vs. acute fibrosus and organizing pneumonia aka AFOP). Clinical history, pre and post mortem laboratory investigations, including post mortem lung culture (for bacteria, mycobacteria, fungi and virus) were reviewed to elucidate etiology.

**Results:** 120 adult autopsies were performed from July 2010 to July 2011. A significant subset of these cases had acute interstitial lung disease (28 cases and 77.8%). The majority of these cases demonstrated histologic features of DAD. The histopathological features of DAD were re-evaluated by one autopsy pathologist and one pathology resident. Morphologically, 23 of these cases (57.5%) demonstrated the features of organizing pneumonia, with no etiology identified. Post-mortem lung cultures were performed in 16 cases of which 9 cases (56.3%) were positive (5 bacterial, 2 fungal and 2 viral infections).

**Conclusions:** Our study highlights the morphologic spectrum of DAD encountered in adult hospital autopsy in an inner city teaching hospital, infection being the most common triggering factor, especially during acute exacerbation of chronic interstitial lung disease. A significant subset of these cases had acute interstitial lung disease with no etiology identified. Post-mortem lung culture was a valuable diagnostic tool.

### Bone and Soft Tissue Pathology

#### 20 Giant Cell Reparative Granuloma of Hands and Feet Show USP6 Gene Rearrangement: Are They Truly Solid Aneurysmal Bone Cyts?

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**Background:** Giant cell reparative granulomas (GCRG) are lytic lesions of the bone that can occur in the gnathic bones but have also been described in the small bones of the hands and feet. Morphologically, they are indistinguishable from the so-called ‘solid variant’ of Aneurysmal Bone Cysts (ABC) in extra-gnathic sites. The neoplastic nature of primary ABCs has been established with the identification of USP6 rearrangement in 70% of the cases. USP6 gene alterations in giant-cell rich lesions (GCRG/ABC) of the small bones of the hands and feet has not been previously studied.

**Design:** We investigated a group of 8 giant-cell rich lesions of the hands and feet by FISH for USP6 gene rearrangement, and further, compared the findings with other morphologically similar lesions including 9 giant cell GRCGs, 22 primary ABCs, 8 giant cell tumors of bone and 2 brown tumors of hyperparathyroidism.

**Results:** Overall, there were 49 samples from 48 patients including 26 females and 22 males. Radiologic imaging of the 8 lesions of the hands and feet showed 2 purely cystic, 1 purely solid and 4 mixed cystic and solid lesions. FISH for USP6 was performed on all of the 49 lesions in the study. Seven of the 8 (88%) lesions of the hands and feet showed rearrangement of the USP6 gene. No USP6 gene rearrangements were identified in the 9 cases of gnathic GCRGs, 2 cases of brown tumor or the 8 cases of GCT of bone. Thirteen of the 22 (59%) primary ABCs from the long bones and flat bones showed rearrangements of the USP6 gene rearrangement.

**Conclusions:** Our results suggest that the majority of the GCRGs of the hands and feet represent true ABCs and should be reclassified as such. The terminology of GCRG should be restricted only to lesions in the gnathic location. FISH for USP6 is a useful ancillary tool in the diagnosis of primary ABCs, and can be extremely helpful in distinguishing them from GCRGs and other morphologically similar lesions.

#### 30Extraskeletal Myxoid Chondrosarcoma with Non-EWSR1-NR4A3 Variant Fusions Correlate with Rhabdoid Phenotype and High Grade Morphology

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**Background:** Extraskeletal myxoid chondrosarcoma (EMC) is a rare soft tissue sarcoma with distinctive histology and uncertain histogenesis, characterized by EWSR1-NR4A3 fusion in 75% of the cases. A smaller proportion of cases show NR4A3 fused to other gene partners including TAF15, TCF12 and TFG. The impact of various gene fusions has not been previously evaluated.

**Design:** We investigated a group of 26 consecutive EMCs with adequate material for FISH and/or RT-PCR analysis and correlated the genetic findings with morphology and clinical outcome.

**Results:** There were 5 females and 21 males, with a median age of 49.5 years. The mean size of the tumors was 11.1 cm. FISH analysis showed that 16 (62%) of the 26 cases had EWSR1-NR4A3 fusion gene, 7 (27%) cases showed TAF15-NR4A3 gene fusion and 1 (4%) case showed TCF12-NR4A3 gene fusion. No rearrangements of the TFG or FUS genes were identified. Upon correlation, the morphology of most EWSR1-rearranged tumors (10 of 16) showed low cellularity, minimal cytologic atypia and low mitotic counts. In contrast, a predominant number of cases (80%) with variant (non-EWSR1) NR4A3 gene fusions (TAF15, TCF12) showed distinctive plasmacytoid / rhabdoid morphology, with increased cellularity, cytologic atypia and high mitotic counts. Follow-up showed that only 1 of 16 patients with EWSR1-rearranged tumors died of disease, in contrast to 3 of 7 (43%) patients with TAF15-rearranged tumors.

**Conclusions:** In conclusion, EMCs with variant NR4A3 gene fusions show a higher incidence of rhabdoid phenotype, high grade morphology and a more aggressive outcome compared to the more common EWSR1-NR4A3 positive tumors. Furthermore, as EWSR1 FISH break-apart assay is the preferred ancillary test to confirm diagnosis of EMC, tumors with variant NR4A3 gene fusions remain under-recognized and often misdiagnosed. FISH assay for USP6 in rearranged tumors recognizes >95% of EMCs and should be an additional tool in EWSR1-negative tumors.

### 31 Solitary Fibrous Tumor “Hemangiopericytoma” of Skin Is Rare; Other Differentials Should Be Considered

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**Background:** Solitary fibrous tumor (SFT), formerly hemangiopericytoma (HPC), is a rare neoplasm that can arise anywhere in the body. The majority of cases are benign; however, it can be of borderline or frank malignancy. Histologically it’s composed of fibroblast-like spindled cells with variable cellularity, infiltrating collagen bundles and staghorn-like vasculature. Although the majority of SFT arise in the deep soft tissue, and body cavities, they can also be located superficially. In fact, they are frequently considered in the differential diagnosis of spindle cell lesions with prominent vasculature in the skin and subcutaneous tissue. The goal of this project is to study the frequency of SFT in skin.

**Design:** We searched our database for cases diagnosed as SFT or HPC. We then classified cases into superficial and deep based on the clinical information and the pathology report. The slides of all potential superficial cases were pulled and evaluated microscopically for the presence of skin in the specimen, the location of the tumor in relation to the skin and the histomorphology of the lesion. Any associated immunostains were also evaluated.

**Results:** Our search retrieved 134 specimens, belonging to 108 patients, examined in our hospital over the course of 36 years. The specimens included 2 autopsies, 5 cytology specimens and 127 surgicals (biopsies and resections). 68% of the cases were considered superficial and 32% deep based on the clinical information and the pathology report.

**Conclusions:** It is very rare to encounter SFT as a primary cutaneous neoplasm. There are several lesions in soft tissue with “HPC-like” architecture such as myofibroma, synovial sarcoma and fibromyxosarcoma, but they do not specifically fit this tumor. Therefore, unless dealing with a patient with a known history of SFT, other differential diagnoses should be considered before making a diagnosis of SFT in the skin.

#### 32 Novel ZC3H7B-BCOR and MEAF6-PHF1 Fusions in Ossifying Fibromyxoid Tumors – Molecular Characterization Shows Genetic Overlap with Endometrial Stromal Sarcoma

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**Background:** PHF1 gene rearrangements have been recently described in around 50% of ossifying fibromyxoid tumors (OMFT) including benign and malignant cases, with a small subset showing EP400-PHF1 fusions. In the remaining cases no alternative gene fusions have been identified. PHF1-negative OTs, especially if lacking S100 protein staining or peripheral ossification, are difficult to diagnose and distinguished from other soft tissue mimics.

**Design:** In seeking more comprehensive molecular characterization, we investigated a large cohort of 39 OMFT of various anatomic sites, immunoprofiles and grades of malignancy. Tumors were screened for PHF1 and EP400 rearrangements by FISH. RNA sequencing was performed in two index cases (OMFT1, OMFT3), negative for EP400-PHF1 fusions, followed by FusionSeq data analysis, a modular computational tool developed to discover gene fusions from paired-end RNA-seq data.

**Results:** Two novel fusions were identified ZC3H7B-BCOR in OMFT1 and MEAF6-PHF1 in OMFT3. After being validated by FISH and RT-PCR, these abnormalities were screened on the remaining cases. With these additional gene fusions, the majority (85%) of OMFTs with classic morphologic appearance demonstrated recurrent gene rearrangements, regardless of degree of malignancy, presence of ossification or immunoprofile, which can be used as molecular markers in challenging cases. The most common abnormality is PHF1 gene rearrangement (80%), being present in benign, atypical and malignant lesions, with fusion to EP400 in 44% of cases.

**Conclusions:** ZC3H7B-BCOR and MEAF6-PHF1 fusions occurred predominantly in S100 protein-negative and malignant OMFT. Similar gene fusions have been reported in endometrial stromal sarcoma (ESS), a tumor seemingly unrelated to...
OFMT. Furthermore, similar with ESS pathogenesis, it appears that translocation genes involved in acetylation (MEAF6) and methylation (PHF7) have a role in the neoplastic development of OFMT.

33 Diagnostic Pitfalls of Wilms Tumor (WT) Versus Desmoplastic Small Round Cell Tumor (DSRCT): Overlapping Morphologic and Immunohistochemical Features
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Background: Blastemal predominant Wilms Tumor (WT) and Desmoplastic Small Round Cell Tumor (DSRCT) have overlapping histologic features, yet accurate distinction is critical because of differing clinical presentation and therapeutic option significance. We recently encountered a case of blastemal predominant WT in a neck mass of a young adult who also had an abdominal mass. The neck mass was diagnosed as DSRCT based on a desmoplastic stroma, small round blue cell morphology, and reactive desmoplastic and clear cell accentuation. However, careful review of the original biopsy elements were identified on deeper sections and EWSR1 rearrangement studies were negative; supporting the ultimate diagnosis of WT. Based on this challenging case, we undertook a comparison study of desmin and cytokeratin reactivity in WT and DSRCT.

Results: Since the blastema of WT can mimic DSRCT, we compared the reactivity patterns of the blastemal components of WT to DSRCT. Twenty two WT resections (triphasic=14, blastemal=8) and 12 DSRCT (including 10 cases from patients with confirmatory molecular studies) were retrospectively reviewed. H&E sections were compared to desmin, and CAM5.2 and/or AE1/AE3 immunohistochemical stains and scored by 3 pathologists.

Results: Desmin reactivity was seen in 11/22 WT blastema and 11/12 DSRCT. While diffuse desmin reactivity was limited to DSRCT (10/11 WT vs. 5/11 DSRCT), dot-like or perinuclear accentuation was seen in nearly all desmin positive cases of both WT and DSRCT (10/11 WT, 10/11 DSRCT); larger discrete dots were more common in DSRCT. Cytokeratin staining was seen in nearly all cases (11/12 WT, 10/12 DSRCT). Cytokeratin staining of WT blastema was more often diffuse compared to DSRCT (11/21 WT vs 3/10 DSRCT).

Conclusions: Herein, we report a comparison study of desmin and cytokeratin reactivity patterns in WT and DSRCT, which shows marked overlap. Moreover, although dot-like desmin reactivity is traditionally associated with DSRCT, we demonstrate that nearly all desmin positive cases of WT blastema displayed dot-like or perinuclear desmin accentuation; serving as an important diagnostic pitfall. This distinction is most challenging in blastemal predominant WT, particularly in metastatic sites with associated desmoplasia. In these cases, detection of EWSR1 rearrangement (seen with DSRCT) and immunoreactivity with antibodies to the amino-terminus of WT (seen in WT) remain the most reliable diagnostic tools.

34 Deep Myxomas: Repraisal of Desmin Expression and Correlation with Novel Genetic Finding
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Background: Deep myxomas (juxta-articular J-A) and intramuscular (IM) have been described to variably express desmin. While the 2013 W.H.O. Atlas affirms this for IM myxoma, it provides no data regarding desmin expression in J-A myxoma. However, other soft tissue tumor series state that desmin expression is absent in IM myxoma.

We reviewed recent cases to determine desmin reactivity in deep myxomas evaluating whether desmin reactive tumors could be distinguished clinically, histologically, or genetically from non-desmin-reactive myxomas.

Design: Twenty six deep myxomas were identified in Pathology with slides and blocks available. Patients were adults and comprised 13 males and 13 females with an age range of 40-70 years (mean 60). Tumors were located in extremity deep tissues. Cases were reviewed for clinicopathologic and ancillary studies and follow-up was available for 24 cases. Immunohistochemistry was performed on representative whole tumor sections using antibodies to desmin and a Dako desmin monoclonal antibody (clone D33 diluted 1:100) after antigen retrieval using Dako Hi pH Target Retrieval Solution in a pressure cooker decloaker for 20 minutes. Slides were incubated 30 minutes at room temperature. Review of clinical history, imaging studies, i.e. karyotypes (n=16) and all slides were performed. Desmin expression was assessed as percent reactivity and intensity.

Results: Deep Myxomas: Desmin Reactivity and Genetic Features.

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35 Head and Neck Meningeal Hemangiopericytomas Are a Histological Variant of Solitary Fibrous Tumors
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Background: Soft Tissue Hemangiopericytoma (HPC) and Solitary Fibrous Tumor (SFT) were considered by pathologists as two variants of a single tumor entity until they were reclassified only as SFTs due to the detection of novel markers like GRIA2 and STAB1 overexpression and principally the molecular fusion occurring between NAB2 and STAB1 genes. Our hypothesis is that HPCs and SFTs could be considered the same entity regardless of the anatomic localization and to elucidate this we tested these markers on a series of Head&Neck, Meningeal and Soft Tissue HPC/SFT tumours.

Design: Samples from 44 HPC/SFTs (11 meningeval, 5 Head&Neck and 28 S.T. tumours) were obtained from Pathology Departments. Representative areas were carefully selected from all sections of each tumour and 1-10 mm diameter tissue cores were obtained. Immunohistochemistry was carried out on sequential TMA sections using CD34, SMA, Bcl2, EMA, Ki67 to confirm the previous histological diagnoses; GRIA2 and STAB1 as novel markers. In order to detect the possible rearrangements of the NAB2-STAB1 fusion gene we undertook a correlation of this alteration with the nuclear reallocation of STAB1, specific RT-PCR primers for the two more common rearrangements were tested on the 53 samples after RNA isolation.

Results: We observed positive staining for CD34 and Ki-61 in the 86% of the cases, for SMA in the 27%, for Bcl2 in the 50% and for EMA in the 16% of the samples. Over expression of GRIA2 was observed in the 42.9% of the cases, being positive in 20% of HPCs and in 20.5% SFTs. Nuclear expression of STAB1 was positive in the 78.5% of the samples, 31.8% of HPCs and in 38.6% SFTs respectively. No staining was observed in negative control cases. We obtained positive RT-PCR amplification for the Exon4-Exon3 NAB2-STAB1 rearrangement in the 13% of the cases. For those cases, we undertook positive correlation with nuclear STAB1 expression in 5 out 6 of them. Unfortunately no samples showed the Exon6-Exon7/18 rearrangement, probably due to degradation of nucleic acid obtained from the FFPE tissues and the expected length of PCR amplification products.

Conclusions: Our results based on the GRIA2 and STAB1 expression suggest that HPCs and SFTs could be considered as one entity regardless of the anatomical localization. Specifically HPCs of the meningeval area behave like their soft tissue counterpart, indicating that they could belong to the SFT group. Due to the short amount of cases, HPCs of the Head and Neck tract require further studies to reach definitive conclusions.

36 Expression of p16 in Hibernomas – A Pitfall in Differentiating Adipocytic Tumors
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Background: Hibernoma is a rare adipocytic tumor composed of brown fat. It occurs predominantly in young adults but has a wide age distribution and may rarely involve elderly patients. While the tumor normally does not present a diagnostic dilemma in a large excision, it can be challenging on a small biopsy as some of the neoplastic cells have transparent cytoplasm with multicavulation, thus mimicking the lipoblasts commonly present in atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL). Distinguishing these entities is important for prognosis as excision is curative in hibernomas with no significant potential for recurrence. Recently, studies have shown that MDM2, CDK4 and p16 can be used as an adjunct to distinguish lipoma from WDL. Limited previous data have shown that about 50% of hibernomas immunoreacted with MDM2 and none expressed CDK4 and p16. In this study, we sought to further explore the specificity of CDK4 or p16 in distinguishing hibernoma from WDL. Moreover, given that these three molecules are closely related in p53 pathway and that the addition of MDM2+/p16+ profile is a frequent phenotype in WDL, the expression of p53 was also examined.

Design: The surgical pathology database of the authors’ institution was searched to identify hibernoma cases. Immunohistochemical stains for CD4 and p16 were performed. Unequivocal nuclear staining was regarded as positive and was further ranked 1+ (1-10%), 2+ (11-50%) or 3+ (>50%).

Results: Of 12 consecutive hibernoma cases retrieved, 7 (58%) demonstrated nuclear reactivity for p16, including 6 with 1+ and 1 with 2+ staining. One case showed 1+ staining for CDK4. All cases were negative for p53. Interestingly, this panel was also performed on a separate case of retroperitoneal WDL with prominent hibernomatous differentiation, which revealed the same p16+/CDK4+/p53- immunoprofile.

Conclusions: In contrast to a single previous study, p16 expression was seen in most hibernoma cases; therefore, it is not a promising marker in distinguishing hibernoma from WDL. In keeping with the prior study, CDK4 is a relatively sensitive marker, albeit in this setting although it is not entirely specific. Further, p53 overexpression was not seen in any of the hibernoma cases examined, thus it can be utilized as an adjunct to other markers in the differential diagnosis. Given that MDM2 expression is reportedly seen in 50% of hibernomas, in situ hybridization analysis of MDM2 in these cases is ongoing. Limited case studies to include other special types of benign adipocytic tumors are needed to investigate the utility of this “adipocytic tumor panel” in pathology practice.

37 Metastases to Bone: Analysis of 2,355 Cases over a 33-Year Period
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Background: The skeleton is a common site for tumor metastasis. Over 400,000 patients are diagnosed with bone metastasis (BM) annually in the US. It has long been accepted that osteopetrosis is an intrinsic property of certain malignancies, with carcinomas of the breast (BC), prostate (PC) and lung (LC) reportedly being the most prevalent primaries in general population. The highest incidences of BM have been seen in patients with these as well as thyroid and renal cell (RCC) carcinomas in postmortem examinations.
However, it has been unclear whether these trends have remained constant over time. The aim of the study was to examine the frequencies of primary tumors among all patients with bone metastases over the last 3+ decades.

**Results:**

- There were 2,355 cases identified by our inclusion criteria. LC was the most frequent primary tumor, followed by breast in men and breast and lung in women (50.4% vs. 43.6%, respectively).
- The majority of tumors were solitary, with a preponderance of lung cancer in men and breast cancer in women.
- The distribution of primary tumors varied significantly over the study period (1980-2005).
- The most common associated systemic diseases were metastatic prostate cancer in men and breast cancer in women.
- The majority of patients presented with relatively small tumors (1-4 cm in diameter) and were asymptomatic.
- The overall survival rate was low, with 5-year survival rates ranging from 13% to 23%.

**Conclusion:**

The study highlights the importance of surveillance and early detection of bone metastases. Further research is needed to improve outcome and quality of life for patients with bone metastases.
Conclusions: Our 3 cases do not fit the current diagnostic criteria for BNCT or chordoma. To date, we have no evidence to support the need for aggressive surgery in this setting. Thus we propose an alternative diagnostic term, “atypical notochordal cell tumor”, for this tumor subset. Additional cases with longer follow-up will be necessary to fully understand the biology of these unusual tumors.

42 Chromogenic In Situ Hybridization for FGF23 mRNA in the Diagnosis of Phosphaturic Mesenchymal Tumors
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Background: Phosphaturic mesenchymal tumors (PMT) are extraordinarily rare mesenchymal tumors, which can cause tumor-induced osteomalacia (TIO) through production of phosphaturic hormones, most often fibroblast growth factor-23 (FGF23). Distinction of PMT from morphologic mimics is important, as complete resection may be curative of debilitating TIO. Detection of FGF23 expression is a valuable diagnostic adjunct, especially in patients with occult TIO. However, commercial FGF23 antibodies lack specificity, and RT-PCR for FGF23 mRNA is excessively sensitive, detecting low levels of endogenous FGF23 mRNA in normal bone. For these reasons, we developed a novel chromogenic in situ hybridization assay for FGF23 mRNA.

Design: Cases of PMT (14) and histologic mimics (20) including chondromyxoid fibroma, chondroblastoma, osteoblastoma, and various soft tissue tumors were retrieved from our archives. In situ hybridization for FGF23 mRNA was performed in archival tissues using the RNAscope® 2.0 FFPE Assay (ACD Inc. Hayward, CA) with appropriate control probes. Using a HRP-based signal amplification system, punctate intracellular staining was scored as “positive” using a semi-quantitative scoring method (3+: >10 signals/cell; 2+: 4-10 signals/cell; 1+: 1-3 signals/cell).

Results: PMT occurred in 11 males and 3 females (median age 53 y, range 35-73 y), all with clinically apparent TIO, as masses (mean 3.9 cm, range 1.4-12 cm) in bone (N=7); femur (4), ilium, tibia, fibula or soft tissues (N=3); thigh (3); buttck, ankle, arm, shoulder). All tumors showed typical features of PMT, as previously described. FGF23 mRNA was detected in 80% (12/14) of PMT (3+: 6 cases, 2 cases, 1+: 1 case). One malignant PMT with metastasis had 3+ staining in both locations. No non-PMT had detectable FGF23 mRNA. Non-neoplastic osteocytes, which express low levels of FGF23 protein, did not show detectable staining. One patient with a FGF23 mRNA-negative PMT had normal serum FGF23 levels, consistent with production of an alternative phosphatonin.

Conclusions: Our novel semi-quantitative in situ hybridization assay for FGF23 mRNA is a highly sensitive and specific adjunctive test for the diagnosis of PMT, applicable to formalin-fixed, paraffin-embedded tissues. In our experience, this method has increased specificity in comparison immunohistochemistry. Compared to RT-PCR, this method preserves tissue morphology, and reduces “false positives” related to detection of FGF23 mRNA expression in normal tissues.

43 Desmoid-Type Fibromatosis-Associated Gardner Fibromas: Prevalence and Impact on Local Recurrence
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Background: Evaluation of surgical resection margins (SRM) fails to predict local recurrence of desmoid-type fibromatosis (DTF). Although Gardner fibroma (GF) is considered a precursor lesion of DTF, the prevalence of GF associated with DTF has not been systematically studied. We postulated that residual GF not excised during surgical resection of DTF may account for the limited prognostic value of SRM.

Design: Clinical and demographic data was abstracted from the medical records of 134 patients with DTF. Only 4 subjects had documented Gardner syndrome. Clinical and pathologic characteristics of GF-associated DTF and DTF without associated GF were compared using standard statistical methods. Log-rank tests of Kaplan-Meier recurrence-free survival (RFS) curves were also performed. Of 122 subjects followed after primary surgical resection, median follow-up was 2.3 years (range, 1 day-26.7 years) during which there were 44 local recurrences (36%), with a median time to recurrence of 1.5 years (range, 4 months-16.2 years).

Results: Of 109 evaluable primary DTF recurrences, 34 (31%) had an associated GF. In 8 additional cases, GF was present in either the incisional biopsy or local recurrence (39% of all patients). In 23 of 30 (77%) evaluable cases, GF was present at the surgical resection margin. GF was not associated with sex, age, adjuvant therapy or surgical resection margin status. DTF with GF were slightly larger than those without GF (mean, 7.4 vs. 5.8 cm, P=0.06). DTF arising in the abdomen, abdominal wall or superficial trunk were associated significantly less often with GF than tumors of the extremities, head/neck region or deep trunk (22% vs. 54%, P<0.001). Median RFS for patients with DTF-associated GF was 4.8 years compared to 16.2 years in patients without associated GF. Primary resection at an outside facility (P=0.004), deep, extra-abdominal location (P=0.008), and younger age at diagnosis (P=0.004), were also associated with shorter RFS. RFS was not affected by surgical resection margin status or adjuvant therapy.

Conclusions: Gardner fibromas are associated with 39% of DTF. The presence of under-recognized residual DTF precursor lesions after surgical resection might account for the unpredictability of local recurrence in DTF.

44 Detailed Analysis of Surgical Resection Margins in Desmoid-Type Fibromatosis
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Background: The prognostic value of surgical resection margins (SRM) in predicting recurrence of desmoid-type fibromatosis (DTF) is controversial. We analyzed whether the distance and tissue composition of negative margins, linear extent of positive margins, or adequacy of assessment affects the prognostic impact of SRM.

Design: The distance (clearance) and type of tissue composing the SRM was recorded for cases with negative SRM. The number of positive margins and linear extent of marginal involvement was recorded for cases with positive SRM. The number of tissue sections submitted for evaluation of SRM was also noted. Factors predictive of positive SRM were evaluated by logistic regression. Cox regression analysis of recurrence-free survival (RFS) was also performed.

Results: Of 128 surgical resection specimens, 71 (56%) had positive SRM. For the 57 cases with negative SRM, the mean clearance was 0.22 cm. Tissues composing the SRM were most often fibrous (n=15), skeletal muscle (n=15), or fibroadipose (n=10). In cases with positive SRM, the mean linear extent of SRM involvement was 0.8 cm. The number of tissue sections evaluating SRM was greater in cases with positive SRM (10.2 vs. 6.4, P<0.001). By logistic regression, only the number of tissue sections evaluating SRM was predictive of a positive SRM (odds ratio 1.15, 95% CI 1.05-1.26). SRM status was not associated with age, sex, anatomic site, radiation therapy, size, or specimen type (primary resection vs. local recurrence). Patients with positive SRM received chemotherapy more often than patients with negative SRM. Of 122 subjects who underwent primary resection, only SRM clearance was predictive of local recurrence.

Cox regression analysis of recurrence-free survival.

Limiting Cox regression models to samples meeting increasingly stringent thresholds for predicted probability of positive SRM or by number of sections evaluating SRM had no effect on the hazard ratios for SRM status.

Conclusions: Resection margins fail to predict RFS for DTF. The number of positive SRM, linear extent of margin involvement and tissue composition also fail to predict RFS. However, decreasing clearance appears to be predictive of recurrence in cases with negative SRM. Although the optimum number of tissue sections for evaluation of SRM is unclear, most cases appear to be adequately sampled.

45 STAT6 Is a Sensitive and Specific Marker of Solitary Fibrous Tumor
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Background: Recurrent NAB2-STAT6 gene fusions have recently been identified in solitary fibrous tumors (SFT) by integrative sequencing. Nuclear expression of STAT6 by immunohistochemistry (IHC) discriminates meningeal SFT from its mimics in the central nervous system. Our aim was to examine the sensitivity and specificity of STAT6 IHC for SFT versus other morphologically similar soft tissue tumors.

Design: STAT6 expression was evaluated by IHC in 53 SFT of various sites and 99 soft tissue tumors in the histologic differential diagnosis. We used two antibodies (Epitomics and Santa Cruz) using FFPE whole sections and tissue microarray slides. Only nuclear staining of STAT6 was considered positive. Staining was scored as: 0 (no staining), 1+ (1-25%), 2+ (26-50%), 3+ (>50%). Intensity was scored as weak, moderate or strong.
Results: Our preliminary workup of the STAT6 Santa Cruz antibody showed excessive noise to signal ratio, which precluded accurate scoring. Thus, we elected to focus on the STAT6 Epitomics rabbit monoclonal antibody (1:100), which has not previously been examined by others, in our expanded study. Nuclear STAT6 staining was present in 46/48 cases (95.8%, sensitivity 100%). The majority of cases showed 3+ and strong intensity staining. All tested cases of cellular angiofibroma (9/9), myofibroblastoma (10/10), spindle cell lipoma (10/11), benign fibrous histiocytoma (10/13), dermatofibrosarcoma protubersans (9/9), low-grade fibromyxoid sarcoma (7/7), schwannoma (8/8), desmoid fibromatosis (8/8), monophasic synovial sarcoma (11/11), malignant peripheral nerve sheath tumor (8/8), and mesenchymal chondrosarcoma (7/8) were positive for STAT6 (specificity 100%).

Conclusions: Our study provides further support that STAT6 is an extremely sensitive and specific marker for SFT and is a useful diagnostic adjunct in discriminating SFT from other soft tissue tumor mimics.

46 Expression of Growth-Associated Protein 43 (GAP43) in Malignant Peripheral Nerve Sheath Tumors Arising in the Neurofibromatosis-1 and Sporadic Settings

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Background: The malignant peripheral nerve sheath tumor (MPNST) is a relatively uncommon type of soft tissue sarcoma arising from a peripheral nerve or extraneural soft tissues and showing nerve sheath differentiation. The diagnosis of MPNST can be one of the more challenging tasks due to its uncommon type, morphologic resemblance to other spindle cell neoplasms and lack of sensitive and specific immunohistochemical markers. Therefore, we have sought to better characterize this tumor by determining the immunohistological and genetical setting of neurofibromatosis-1 (NF-1), but problems are mainly centered on the sporadic (non-NF-1) MPNSTs. We recently reported the utility of a novel marker, Growth-Associated protein 43 (GAP43), a membrane-associated phosphoprotein expressed in neuronal growth cones and Schwann cell precursors during neural development and axonal regeneration, in differentiating a set of benign and malignant nerve sheath tumors from other non-nerve sheath spindle cell neoplasms. We also showed that, in the setting of NF-1, GAP-43 has a sensitivity (86%) superior to S100 protein (62%). Here, we expanded our study to include a series of 19 sporadic (non-NF-1) MPNSTs.

Design: A series of 19 sporadic MPNSTs were selected from our surgical pathology archives, including 3 biopsies and 16 resection specimens. All cases showed at least positivity for one of the following three markers, namely S100 protein, collagen IV and Leu7. Immunohistochemical staining using anti-GAP43 and anti-S100 protein antibodies was performed on consecutive sections for each case.

Results: In this study, we showed that GAP43 is positively stained in 8/19 cases (42%), a result comparable to S100 protein (n= 10/19; 52%). (Table 1.)

Table 1. S100 protein and GAP43 expression in sporadic MPNSTs

| S100  | Pos | 50% | 75% | 100% |
|-------|-----|-----|-----|-----|
| 100   | 8/19| 10  | 5  | 0   |
| GAP-43| 8/19| 4  | 3  | 0   |

Conclusions: Even though GAP43 is a highly sensitive marker and superior to S100 protein for the diagnosis of MPNST in the NF-1 setting, the utility of this marker in the sporadic MPNSTs is more limited, and awareness of this caveat is important. Both comparative genomic hybridization studies and studies analyzing germline and somatic NF1 mutations suggest that the NF-1 and sporadic MPNSTs harbor different genetic changes, which may be reflected in part in the expression of GAP43. Our data provide further evidence that the MPNSTs arising from these two settings may reflect two different pathogenetic mechanisms.

47 CCNB3 Immunohistochemistry Is Highly Specific for BCOR-CCNB3 Fusion Sarcomas

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The Rizzoli Institute, Bologna, Italy; Department of Oncology, General Hospital of Trevizo, Trevixo, Italy.

Background: In contrast with the classification of soft tissue spindle/pleomorphic sarcomas, the classification of the much rarer spindle/pleomorphic sarcomas of bone is still limited to few entities as fibrosarcoma, undifferentiated pleomorphic sarcoma (formerly MHH), and leiomyosarcoma.

Design: 430 cases diagnosed as primary spindle/pleomorphic sarcomas of bone for the period 1937-2012 were retrieved from our archives. Thirty cases were excluded for the lack of material. Clinical records, pathology and radiology reports were reviewed. Secondary spindle/pleomorphic sarcomas of bone, cases without adequate slides, and spindle/pleomorphic sarcomas secondarily involving bone were excluded. Immunohistochemistry for cyclin B3 (BCOR-CCNB3), GAP-43, S100 protein (n= 10/19; 52%). (Table 1.)

| Diagnosis | n | CCNB3 positive | EWSR1 rearrangement |
|-----------|---|----------------|---------------------|
| SFT       | 1 (2%) | 1/1 | 1/1 |
| Desmoids  | 4/63 (7%) | 3/4 | 3/4 |
| Undiff. pleom. | 3/154 (2%) | 3/3 | 3/3 |

Conclusions: These results support that CCNB3 positivity by immunohistochemistry is infrequent, even among SFT cases that lack EWSR1 rearrangement. Importantly, CCNB3 staining is highly specific since no EWSR1 rearranged SFT case demonstrated staining. Given the rarity of these tumors, it remains to be seen whether this antibody would be of value for routine clinical use. The oncogenetic mechanisms of the BCOR-CCNB3 fusion protein may provide insight into the pathogenesis of this rare family of sarcomas.

48 Reappraisal of Primary Spindle/Pleomorphic Sarcomas of Bone

4P De Toi, A Right, M Gambardotti, D Vanel, C Ferrari, S Benini, S Ferrari, P Picci
The Rizzoli Institute, Bologna, Italy; Department of Oncology, General Hospital of Treviso, Trevixo, Italy.

Background: In contrast with the classification of soft tissue spindle/pleomorphic sarcomas, the classification of the much rarer spindle/pleomorphic sarcomas of bone is still limited to few entities as fibrosarcoma, undifferentiated pleomorphic sarcoma (formerly MHH), and leiomyosarcoma.

Design: 430 cases diagnosed as primary spindle/pleomorphic sarcomas of bone for the period 1937-2012 were retrieved from our archives. Thirty cases were excluded for the lack of material. Clinical records, pathology and radiology reports were reviewed. Secondary spindle/pleomorphic sarcomas of bone, cases without adequate slides, and spindle/pleomorphic sarcomas secondarily involving bone were excluded. Immunohistochemistry for cyclin B3 (BCOR-CCNB3), GAP-43, S100 protein (n= 10/19; 52%). (Table 1.)

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Conclusions: These results support that CCNB3 positivity by immunohistochemistry is infrequent, even among SFT cases that lack EWSR1 rearrangement. Importantly, CCNB3 staining is highly specific since no EWSR1 rearranged SFT case demonstrated staining. Given the rarity of these tumors, it remains to be seen whether this antibody would be of value for routine clinical use. The oncogenetic mechanisms of the BCOR-CCNB3 fusion protein may provide insight into the pathogenesis of this rare family of sarcomas.

49 STAT6 Immunohistochemistry Is Useful in the Diagnosis of Solitary Fibrous Tumors

EG Demicco, PW Harms, RM Patel, SC Smith, SL Careskador, S Camelo-Piragua, JB McGough, J Siddiqui, N Palamisany, DR Lucas, AJ Lazer, W-L Wang, Mount Sinai Medical Center, New York, NY; University of Michigan Medical Center, Ann Arbor, MI; The University of Texas MD Anderson Cancer Center, Houston, TX.

Background: Solitary fibrous tumors (SFT) are rare mesenchymal tumors that can be challenging to diagnose, particularly in small biopsies, resected bone and those tumors with anaplasia. Recently, SFTs have been discovered to harbor a recurrent gene fusion involving NAB2 and STAT6, resulting in overexpression of STAT6. We assessed the diagnostic utility of nuclear expression of STAT6 in identifying SFT, and inquired if STAT6 might also play a role in other mesenchymal neoplasms.

Design: Tissue microarrays and tissue sections of a variety of mesenchymal tumors (see Table 1) were stained for STAT6 (1:200; M-20, SC-981, Santa Cruz), using an automated immunohistochemical stainer (Ventana). Nuclear and cytoplasmic staining were scored as 0 (absent-minimal blush), 1 (weak), 2 (moderate), or 3 (strong). Only 2+ or 3+ nuclear stain was considered positive.

Results: Of the 1419 cases assessed (Table 1), nuclear STAT6 was 2+ in 240 cases (17%), including 202/250 SFT (81%), 6,55 (11%) unclassified sarcomas, 16,184 (9%) desmoids, 4,63 (7%) neurofibromata, and 3,154 (2%) undifferentiated pleomorphic sarcomas. When present, STAT6 nuclear stain was seen diffusely in a majority of tumors. Amongst non-mesenchymal tissues, scar was positive in 6/17 (35%). Nearly 1/3 of meningial and intrabdominal tumors were negative for STAT6, compared to less than 10% of pleural tumors.

Conclusions: STAT6 immunohistochemistry is a relatively sensitive and specific test for SFT. Although occasionally moderate nuclear staining may be seen in other proliferations including unclassified sarcomas, neurofibromas, desmoids and sarcomas, the role of STAT6 in these tumors is yet to be determined. Correlation with RT-PCR studies for NAB2-STAT6 fusion are ongoing.
| Tumor Type                        | STAT6 positive | Total % cases | Positive |
|----------------------------------|----------------|---------------|----------|
| Adipocyte sarcoma                | 7              | 10            | 70       |
| Angiosarcoma                     | 12             | 27            | 45       |
| Clear cell sarcoma               | 10             | 24            | 42       |
| Dermatofibrosarcoma protuberans + | 9              | 20            | 45       |
| Liposarcoma                      | 21             | 50            | 42       |
| RMS                              | 16             | 41            | 39       |
| Synovial sarcoma                 | 19             | 50            | 38       |
| Unspecified sarcoma              | 16             | 41            | 39       |
| Total                            | 87             | 219           | 40       |

Table 1: STAT6 Immunohistochemistry in Soft Tissue Tumors

50 Perineurial Tumors with Typical and Atypical Features: A Clinicopathological Study of 46 Cases
S. Dolic, JM Carter, AL Polpe. University Hospital Center, Zagreb, Croatia; Mayo Clinic, Rochester, MN.
Background: Perineuriomas are uncommon soft tissue tumors showing exclusively perineurial differentiation. Most perineurial tumors are histologically banal and behave in a benign fashion, but some atypical tumors show specific biological features and behave aggressively; some of these tumors have been reported as perineurial malignant peripheral nerve sheath tumors. We studied a large series of perineurial tumors to better understand the natural history of these rare lesions, and better define criteria for malignancy in perineurial tumors.

Design: Cases were retrospectively reviewed for morphology (growth pattern, cellularity, mitotic rate, nuclear pleomorphism, and necrosis), and immunophenotype (EMA, GLUT1, claudin-1, CD34, and collagen IV). By definition, S100 protein expression was absent. Follow-up information was obtained.

Results: The tumors occurred in 19M and 27 F (median age 42 yrs.; range 12-78 yrs.) and ranged from 0.9-14cm (median 3.5 cm) in size. Common sites of occurrence included the extremities and trunk; the head/neck and viscera were rarely involved. Growth patterns, when evaluable, were circumscribed (15) and infiltrative (20). Nuclear grade was low (16), intermediate (18) and high (12). Cellularinity was low (30), intermediate (11) and high (5). Necrosis was present in only 3 cases. Mitotic count was 0-100 mitotic figures/50 HPF (median 1/50 HPF). IHC results: EMA (66/66, only focal staining in 11/46), claudin-1 (30/43), GLUT1 (35/42), CD34 (14/18), collagen IV (9/9). Clinical follow-up of >10 mos. was available for 10 patients (median 41 mos., range 21-106 mos.); 8 were alive without disease, 1 alive with disease and 1 dead of disease. Local recurrences occurred in 2 cases and metastases in 1 case. Local recurrences and metastases occurred only in tumors showing atypical features (e.g., high nuclear grade or cellularity, necrosis, mitotic count >1/50HPF).

Conclusions: A combination of careful morphological study and ancillary IHC should allow for the correct diagnosis of perineurial tumors, including those with atypical or worrisome morphological features. Preliminary follow-up data suggests that perineurial tumors lacking atypical morphological features behave in a clinically benign fashion, with adverse events occurring only in morphologically atypical tumors.

51 Genomic Analysis of 423 Sarcomas: A Single Institution Experience
LA Doyle, DL Tao, A Marino-Enriquez. Brigham and Women’s Hospital and Harvard Medical School, Boston.
Background: STAT6 is a member of the STAT family of cytoklasmic transcription factors. Recent studies have detected a recurrent intrachromosomal rearrangement in some pleomorphic sarcoma that results in the formation of a STAT6 fusion. Nuclear expression of STAT6 by immunohistochemistry (IHC) is found in nearly all cases of SFT and serves as a useful diagnostic marker. STAT6 is located in 12q13, a chromosomal region containing well-characterized oncogenes that are commonly amplified in dedifferentiated liposarcoma (DDLPS), and expression of STAT6 has been reported to occur in a subset of DDLPS. The aim of this study was to determine the frequency of STAT6 expression and the underlying genetic mechanism in DDLPS.

Design: STAT6 protein expression was evaluated in whole tissue sections from a well-characterized series of 35 DDLPS, all with nuclear MDM2 and CDK4 expression by IHC and/or cyogenetic features of DDLPS. IHC was performed following pressure cooker antigen retrieval (0.01 M citrate buffer, pH 6.0) using a rabbit polyclonal STAT6 antibody (1:1000; sc-621, Santa Cruz Biotechnology, Santa Cruz, CA). Dual color FISH was performed with a commercial probe targeting the 12q13 region, which includes a SpectrumOrange probe spanning the STAT6 locus and a telomeric SpectrumGreen probe (Abbott Molecular Inc, Des Plaines, IL), on 4-µm-thick formalin-fixed paraffin-embedded sections on all cases with STAT6 expression, and a subset of control cases without. 100 cells were scored per case. The presence of 5 or more orange signals was considered indicative of STAT6 amplification. Non-neoplastic diploid cells were used as internal controls in each case.

Results: 4/35 cases (11%) showed nuclear expression of STAT6 by IHC <3 with multifocal moderate to strong staining and 1 with weak focal staining- in either well-differentiated sclerosing or dedifferentiated components. FISH demonstrated amplification of STAT6 in 4 positive cases; in contrast, FISH demonstrated no STAT6 amplification on 4 tumors negative for STAT6 expression by IHC. Of the 4 STAT6 amplified cases, 3 patients were male and 1 female, ranging in age from 51 to 76 years. Tumors were located in the mediastinum (n=2), paratesticular soft tissue (1) and periurethral soft tissue (1). 3 patients received chemotherapy +/- radiation therapy prior to resection.

Conclusions: STAT6 is amplified in a subset of DDLPS, which leads to nuclear expression of STAT6 that can be detected by IHC. These findings suggest a role for STAT6-mediated transcriptional activity in some cases of DDLPS, and highlight the genomic complexity and heterogeneity of DDLPS.

52 STAT6 Is Amplified in a Subset of Dedifferentiated Liposarcoma
LA Doyle, DL Tao, A Marino-Enriquez. Brigham and Women’s Hospital and Harvard Medical School, Boston.
Background: STAT6 is a member of the STAT family of cytoklasmic transcription factors. Recent studies have detected a recurrent intrachromosomal rearrangement in some pleomorphic sarcoma that results in the formation of a STAT6 fusion. Nuclear expression of STAT6 by immunohistochemistry (IHC) is found in nearly all cases of SFT and serves as a useful diagnostic marker. STAT6 is located in 12q13, a chromosomal region containing well-characterized oncogenes that are commonly amplified in dedifferentiated liposarcoma (DDLPS), and expression of STAT6 has been reported to occur in a subset of DDLPS. The aim of this study was to determine the frequency of STAT6 expression and the underlying genetic mechanism in DDLPS.

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Results: 4/35 cases (11%) showed nuclear expression of STAT6 by IHC <3 with multifocal moderate to strong staining and 1 with weak focal staining- in either well-differentiated sclerosing or dedifferentiated components. FISH demonstrated amplification of STAT6 in 4 positive cases; in contrast, FISH demonstrated no STAT6 amplification on 4 tumors negative for STAT6 expression by IHC. Of the 4 STAT6 amplified cases, 3 patients were male and 1 female, ranging in age from 51 to 76 years. Tumors were located in the mediastinum (n=2), paratesticular soft tissue (1) and periurethral soft tissue (1). 3 patients received chemotherapy +/- radiation therapy prior to resection.

Conclusions: STAT6 is amplified in a subset of DDLPS, which leads to nuclear expression of STAT6 that can be detected by IHC. These findings suggest a role for STAT6-mediated transcriptional activity in some cases of DDLPS, and highlight the genomic complexity and heterogeneity of DDLPS.

53 Nodular Fasciitis and Aneurysmal Bone Cyst Share the Novel SRSF3-USP6 Fusion Transcript: Further Evidence for Their Common Pathogenesis
MR Erickson-Johnson, B Evers, C Roth, A Seyes, M Lonzo, Y Asmann, X Wang, MM Chou, AM Oliveira. Mayo Clinic, Rochester, MN; Children’s Hospital of Philadelphia University of Pennsylvania, Philadelphia, PA.
Background: Nodular fasciitis (NF) and aneurysmal bone cyst (ABC) are mesenchymal tumors that predominantly occur in younger patients and exhibit overlapping histologic features. While ABC is primarily a bone neoplasm, nodular fasciitis is exclusively extracellular. Recent studies have shown that both tumors harbor USP6 fusion genes but with distinct 5’-end partner genes. In this study we describe a novel fusion of the pre-mRNA splicing factor gene SRSF3 (serine/arginine-rich splicing factor 3) to the ubiquitin protease USP6 in both NF and ABC.

Design: One example of each of ABC and NF were identified with the same t(6;17) (p21;13) by conventional cytogenetic analysis. Additional cases of NF (n=7) and ABC (n=6) that were previously shown to harbor USP6 rearrangement but without a known partner gene were also studied. Histologic diagnosis was confirmed in all cases according to the 2013 WHO classification. DNA was extracted from archival FFPE from both ABC and NF with t(6;17). cDNA libraries were prepared using RNA was prepared for transcriptome analysis by paired-end sequencing using the SureSelect Human Exome enrichment for Illumina Paired-End Multiplexed Sequencing kit (Agilent Technologies, Englewood CO). Transcriptome sequencing analysis was performed using a HISeq 2000 sequencer (Illumina Inc, San Diego, CA). SnovShoes-FTD algorithm for paired end mRNA-Seq data was used to identify any potential fusion gene (Asnmann Y et al., 2011). Break- apart FISH using custom-designed probes for SRSF3 and USP6 and RT-PCR were used to confirm the rearrangement of these loci and presence of the novel fusion transcript, respectively.

Results: Transcriptome sequencing analysis identified the fusion of SRSF3 exon 1 to USP6 exon 2 in an ABC with t(6;17). RT-PCR confirmed this findings in both index ABC and NF, and also identified a second splicing variant in which SRSF3 exon 1 was fused to the USP6 exon 1. Among 6 ABC and 7 NF with previously unknown USP6 partner genes, FISH and RT-PCR identified 3 additional tumors (2 NF and 1 ABC) with the same SRSF3-USP6 fusion. One additional ABC was identified with the typical NF fusion MTHR-USP6.
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**Primary Myxoma of Bone**  
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**Background:** Myxomas of bone are rare, benign, but locally destructive, recurrent neoplasms. Infrequently, these lesions present in the craniocervical bones and mimic other soft tissue tumors, radiologically, clinically, and histopathologically. We present three pediatric cases of primary myxomas of bone emphasizing the clinicopathologic presentation and diagnostic evaluation of this rare entity.  

**Design:** A retrospective search for cases of primary myxoma of bone within the surgical pathology files at two tertiary care centers was performed. Clinical, morphologic, and immunohistochemical data was analyzed.  

**Results:** Three cases of primary myxoma of bone were identified. Each was located within the craniofacial bones of pediatric patients (age range 4-16). While the maxillary lesion was asymptomatic and discovered incidentally, the remaining cases found within the mandible were identified due to gross visualization, which was positive for infection in 67% and negative in 33% of NOREV cases, and positive in 4% and negative in 96% of REV cases, with a PPV of 80% and a NPV of 92%. The PPV of NOREV cases compared to that for gross visualization indicates that it is a better test for “ruling out” infection. Average pair-wise Cohen’s Kappa (CK) was 0.421 for all test categories, with notable CK values for operative decision versus gross visualization:FS/culture of 0.355, producing both PPV and NPV are similar to that of previous studies. There was a good correlation between FS and REV (CK=0.667), with PS showing a small increase in sensitivity.  

**Conclusion:** Gross visualization showed the highest correlation with decision regarding arthroplasty and culture results. FS is utilized more often in cases where the end decision is weighted towards REV rather than NOREV. The benefit of FS over gross inspection is not clearly documented by this study.

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**Clinicalopathological and Immunohistochemical (IHC) Analysis of 46 Cases of Myxoinflammatory Fibroblastic Sarcoma (MIFS)**  
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**Background:** MIFS is a rare low-grade tumor of modified fibroblasts with a predilection for the distal extremities. Due to the diagnostic challenges posed by its varied morphology and nonspecific IHC features, further characterization may be helpful in distinguishing this entity from inflammatory processes and malignant lesions of higher metastatic potential.  

**Design:** 46 cases of MIFS were retrieved. The clinical and histologic features were characterized, and immunohistotyping was performed using tissue microarray.  

**Results:** Patient ages ranged from 20 to 89 (median 47), with no gender predilection. The anatomic distribution was as follows: foot 26%, hand 24%, forearm 17%, calf/knee 15%, axial trunk 9%, proximal arm 5%, gluteus 2%, and proximal leg 2%. Histologic features showed varying amounts of myxoid and fibrotic stroma populated by a mixed inflammatory cell infiltrate. All 46 cases contained scattered large, bizarre-appearing tumor cells with vesicular chromatin, prominent inclusion-like nuclei, and abundant eosinophilic and variably vacuolated cytoplasm. Seven of 46 cases (15%) contained focal areas with a solid, syncytial proliferation of neoplastic cells that outnumbered inflammatory cells and spindle cells; however, areas of conventional MIFS were also present. By IHC, neoplastic cells exhibited strong nuclear positivity for cyclin D1 (86%), cytoplasmic positivity with distinct perinuclear dot-like accentuation for CD10 (79%), cytoplasmic positivity for PGP 9.5 (67%), and membranous positivity for D2-40 (40%) with occasional perinuclear dot-like expression (67%); tumor cells showed patchy positivity for CD68, CD34, and CD15 in 40%, 35%, and 29% of cases, respectively. Factor XIIIa and bcl-2 positivity were observed in 7% of cases. All cases were negative for AE1/AE3, S100, CD21, CD30, CD68, CD117, p63, ALK1, FLI-1, GLUT1, HBME-1, TLE1, WT1, MDM2, PAX5, SOX10, MITF, and beta-catenin.  

**Conclusions:** The presence of focal syncytial neoplastic cell growth is reported. We also propose novel markers, which may be of diagnostic utility, including frequent expression of cyclin D1, CD10, PGP 9.5 and D2-40. Due to its high sensitivity and striking perinuclear dot-like pattern, CD10 and D2-40 may be of particular interest.
58 Expression of ROS1 Predicts ROS1 Gene Rearrangement in Inflammatory Myofibroblastic Tumors

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Background: Inflammatory myofibroblastic tumor (IMT) is a distinctive, rarely metastasizing mesenchymal neoplasm composed of spindle or epithelioid cells with a prominent inflammatory infiltrate. Roughly 50% of IMTs harbor ALK receptor tyrosine kinase gene rearrangements. Such tumors are usually positive for ALK by immunohistochemistry; the pattern of ALK staining correlates with the gene fusion partner. The molecular pathogenesis of ALK-negative IMTs is largely unknown. A recent study identified rearrangements of ROS1 (which encodes a related receptor tyrosine kinase) in a subset of ALK-negative IMTs [J Clin Oncol. 31 (suppl), 2013 (abstr 10513)]. Immunohistochemistry for ROS1 has recently been shown to correlate with ROS1 rearrangement in pulmonary adenocarcinoma. The purpose of this study was to determine whether immunohistochemistry for ROS1 could predict ROS1 rearrangement in IMT.

Design: In total, 30 IMTs were evaluated, including 21 ALK-positive tumors (10 confirmed to harbor ALK rearrangements, with TPM3, CLTC, RANBP2, and FN1 fusion partners) and 9 ALK-negative tumors (including 2 known to harbor ROS1 rearrangements, with YWHAE and TFG fusion partners). Immunohistochemistry was performed on whole tissue sections following pressure cooker antigen retrieval using a rabbit anti-ROS1 monoclonal antibody (clone D4B6; Cell Signaling Technology, 1:100 dilution). The results were scored as “positive” or “negative”, and the pattern of staining was recorded.

Results: Three ALK-negative IMTs (including both tumors with known ROS1 rearrangements) showed immunoreactivity for ROS1, whereas all of the ALK-positive IMTs were completely negative for ROS1. One ROS1-positive IMT (with ROS1-YWHAE fusion) showed strong, diffuse cytoplasmic and nuclear staining; one case (with ROS1-TFG fusion) showed weak, granular cytoplasmic staining; and one case (genotype unknown) showed strong, diffuse cytoplasmic and dot-like staining. Next-generation sequencing to determine the ROS1 fusion partner in the latter case is in progress.

Conclusions: The expression of ROS1 was not seen in non-neoplastic skeletal muscle in human. The cytoplasmic staining of Dlk1 was found in rhabdomyosarcoma cells in various degree. The percentage of Dlk1-positive rhabdomyosarcoma was 100% in embryonal type, 100% in alveolar type, 83% in spindle type, and 88% in pleomorphic type. Dlk-1 was almost negative in control diseases except 1 case of Ewing sarcoma and undifferentiated sarcoma. The distribution of Dlk-1-positive cells were not similar to myogenin or desmin.

Conclusions: The expression of Dlk-1 was frequently seen in all subtype of rhabdomyosarcoma and Dlk-1 was almost negative in sarcomas similar in morphology. Dlk-1 seems to be useful marker for the histological diagnosis of rhabdomyosarcoma and also decision of tumor area.

59 Delta-Like 1 Homolog (Dlk1) Is a Useful Marker for Diagnosis of Rhabdomyosarcoma

H Beda, H Kimura, S Kitamura, A Ooi. Kanazawa University Hospital, Kanazawa, Ishikawa, Japan.

Background: Delta-like homolog (Dlk1), a member of the epidermal growth factor family, is expressed in several organs during development, and has been detected in various carcinomas. Recently, the relationship between Dlk1 and skeletal muscle regeneration has been reported in rodent experiments and implicated to associate with myogenic tumor. Occasionally, it is difficult to discriminate between alveolar rhabdomyosarcoma and other small round cell tumor, also spindle or pleomorphic rhabdomyosarcoma and high grade sarcomas. We examined the expression of Dlk1 in rhabdomyosarcoma and various sarcomas, similar in morphology.

Design: We collected 40 cases of rhabdomyosarcoma (7 cases were embryonal type, 10 cases were alveolar type, 6 cases were spindle type, 17 cases were pleomorphic type). The cases of Ewing sarcoma, desmoplastic small round cell sarcoma were used for control disease of alveolar rhabdomyosarcoma, and the cases of leiomyosarcoma, liposarcoma, undifferentiated sarcoma were used for control disease of spindle/pleomorphic rhabdomyosarcoma. We examined Dlk1 expression using immunohistochemistry.
Unexpectedly, trabecular bone was increased by microCT and histomorphometric analyses. Immunohistochemistry demonstrated an increase in the number of bone-lining OBs and a decrease in multinucleated OCs.

**Conclusions:** These findings suggest that loss of PPARγ in the bone marrow compartment has a significant role beyond adipogenic effects. Specifically, we found improved trabecular bone microarchitecture, increased osteoblastic and decreased osteoclastic effects. PPARγ silencing may have had a direct effect on OB and OC cell types, or altered the adipogenic milieu to favor intramedullary bone formation.

61 Epithelioid Malignant Peripheral Nerve Sheath Tumor: Clinicopathologic Features of 48 Cases
YJ Jo, CDM Fletcher. Brigham and Women’s Hospital and Harvard Medical School, Boston, MA.

**Background:** Epithelioid malignant peripheral nerve sheath tumor (EMPNST) is rare and may be confused with melanoma. It differs from conventional MPNST by showing diffuse S-100 staining, infrequent association with NF1, and occasional origin in a schwannoma. Loss of INI1 expression is seen in a subset of tumors. We describe the clinicopathologic features of this distinct variant in a large series.

**Design:** 48 cases were identified in consult files (2000-2013). H&E and immunohistochemcal stains were examined. Follow-up data was obtained from referring pathologists.

**Results:** Patients were 23 men and 25 women, median age 42.5 years (range 6-80). Anatomic sites were: lower extremity (20), upper extremity (3), neck (2), trunk (16), lip (2), and visceral (5). In some sites, 4 were dermal, 24 cutaneous, and 7 subfascial. Grossly tumors were well-circumscribed and cystic, firm, or lobular; 4 were associated with a nerve. Size range was 0.4-16 cm (median 2.95). Most tumors showed characteristics of multilobulated growth of relatively uniform, but atypical epithelioid cells; 4 were circumscribed nodules and 2 had solid sheet-like growth. Tumor cells had round nuclei and abundant amphophilic cytoplasm; some had spindled or myxoid foci. 7 tumors showed mild atypia with vesicular round nuclei and small nucleoli. The remainder showed moderate-to-severe atypia with irregular vesicular nuclei and prominent nucleoli. Mitoses ranged from 0-46/10 HPF; atypical forms were seen in 7 cases. 6 tumors had necrosis, all with at least moderate atypia and frequent mitoses.

**Conclusions:** EMPNST is a distinct variant that affects adults most frequently on the lower extremity, though a wide age range and site distribution are seen. Most are diffusely S-100 positive and two thirds of tumors show INI1 loss. Based on preliminary data, there is a risk of recurrence and metastases; better prognosis may be associated with completely excised small superficial tumors.

62 Relevance of FNCLCC Grade and MDM2 Amplification Levels in Dedifferentiated Liposarcoma
G Jour, A Guillet, M Lin, BL Hoch. University of Washington Medical Center, Seattle, WA; University of Washington, Seattle, WA.

**Background:** Dedifferentiated liposarcoma (DDLS) is a form of liposarcoma occurring mostly in the retroperitoneum. A limited number of studies have shown no reliable prognostic factors other than anatomical site. Molecular markers of tumor behavior, including amplification levels of MDM2 and CDK4 genes, have been explored in only a very small number of cases. Furthermore, the prognostic value of grading is uncertain in DDLS. Herein, we investigate whether FNCLCC grade and MDM2 gene amplification levels have prognostic value in DDLS in terms of local recurrence (LR) and disease free survival (DFS).

**Design:** 50 cases were retrieved. Cases were reviewed and FNCLCC grade was scored for the dedifferentiated component. Testing for MDM2 gene amplification was performed by fluorescence in situ hybridization (FISH). 40 nuclei were counted for each case. Amplification was categorized as high-level when one nucleus had 20 or more MDM2 copies, and as low-level when it had less than <20 copies. Follow up data was obtained through chart review and phone calls to clinicians. Log rank test and Cox proportional hazards models were used to determine the effect of grade and level of amplification on LR and DFS outcomes.

**Results:** Our series includes 50 patients [male n=28, female n=22] with an average age of 63 years old (range 28-88) and a median follow up of 28 months (range 2-120). Tumors were graded as grade 1 (6%), grade 2 (58%), and grade 3 (36%). Tumor sites included retroperitoneum (68%) and other sites (32%). When adjusted for age, sex, site, tumor size, and margin status, grade 3 patients had a higher recurrence rate than grade 1 and 2 (HR=2.07, 95% CI: 1.24, 7.62; p=0.015). Patients with high level of MDM2 amplification (>20) had higher recurrence rate on univariate (p=0.028) but not on multivariate analysis (HR = 1.69, 95% CI: 0.73, 3.94; p=0.221). No significant association was seen between FNCLCC grade or level of amplification and DFS. Furthermore, no significant association was noted between amplification and grade (χ2 = 1.49, p = 0.221).

**Conclusions:** FNCLCC grade 3 dedifferentiation confers a worse prognosis in DDLS in terms of local recurrence. MDM2 amplification level remains a useful diagnostic tool in DDLS, but has no prognostic value in terms of local recurrence. Additional studies investigating potential biomarkers such as CDK4 gene are warranted. This may yield an integrative grading system for DDLS combining both molecular and morphological parameters.

63 Loss of p16 (CDKN2A) Expression is Rare in Dedifferentiated Liposarcoma and Does Not Promote Tumor Progression
Y Kang, AE Horvai. UCSF, San Francisco, CA.

**Background:** Well-differentiated liposarcoma (WDL) and dedifferentiated liposarcoma (DDL) constitute the most common subgroup of liposarcomas and may represent a time-dependent form of tumor progression from lipogenic to non-lipogenic phenotype. WDL and DDL share amplification of chromosome subregion 12q13-q15 with resultant overexpression of the CDK4 gene. Loss of p16 may compensate for CDK4 amplification, but the role of p16 in progression is unknown. In this study, we investigate the correlation between p16 expression and progression to a non-lipogenic phenotype, and the relationships between p16 expression and copy number changes of CDKN2A.

**Design:** Twenty-one cases of DDL with chromosome 12q13-15 amplification previously confirmed by array comparative genomic hybridization (aCGH) and known MDM2 and CDK4 expression status were identified from the departmental archives. Matched lipogenic and non-lipogenic components of the DDLs were immunostained for p16 using standard methods. Staining was scored on a scale of 0-3+, based on the fraction of cells and intensity of staining. The p16 results were compared to aCGH and IHC data for copy number changes and CDK4 expression, respectively.

**Results:** All DDL were positive for p16 with complete concordance between staining scores for matched lipogenic and non-lipogenic components. Specifically, 20 tumors (95%) demonstrated strong, diffuse (3+), p16 staining in both components. One tumor (5%) showed weak, focal (2+) p16 staining in both components and a corresponding decreased copy number of 9p21.3, in the region of CDKN2A. This tumor also lacked CDK4 gene amplification and CDK4 protein expression in both components.

**Conclusions:** The concordance between p16 staining in matched components of DDL suggests that p16 loss likely does not mediate progression to a non-lipogenic phenotype, despite a small subset of DDLs with loss of p16 expression and CDKN2A deletion. This study provides evidence for DDLs with p16 deletion and CDKN2A inactivation, and has implications for the development of novel therapeutic strategies.

64 Diagnostic Utility of p16 Immunohistochemistry in Distinguishing Dedifferentiated Liposarcomas from Other Retropertioneal Sarcomas
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**Background:** The well-differentiated and dedifferentiated liposarcomas (WDL and DDL, respectively) are among to most common soft tissue sarcomas in adults. Both WDL and DDL demonstrate amplification of chromosome subregion 12q13-q15 with resultant overexpression of the MDM2 and CDK4 genes. Consequently, immunohistochemistry (IHC) for the MDM2 and CDK4 proteins is often used to
confirm the diagnosis of WDL and DDL. Recent studies have suggested that IHC for p16 (the product of the CDKN2A gene) may be a useful adjunct to MDM2 and CDK4 to differentiate WDL from benign adipocytic tumors. However, the utility of p16 IHC to distinguish DDL from morphologic mimics is unknown. In this study, we examine the utility of p16 IHC in differentiating DDL from other retroperitoneal spindle cell malignancies.

Design: This study compared 44 high-grade DDL to 32 other high-grade retroperitoneal sarcomas for the presence of p16 immunohistochemistry. All DDL showed 12q13-15 amplification and/or positive IHC for MDM2 and CDK4, whereas the control sarcomas lacked MDM2, CDK4 and a WD component. Based on clinicopathologic features, the control sarcomas consisted of leiomyosarcoma (LMS, n=10), undifferentiated pleomorphic sarcoma (UPS, n=13), sarcomatoid carcinoma (SCA, n=7), endometrial stromal sarcoma (ESS, n=1) and malignant gastrointestinal stromal tumor (GIST, n=1). IHC for p16 was performed on paraffin-embedded whole tissue sections using standard methods and the slides were scored 0 to 3+ based on intensity and fraction of cells staining.

Results: IHC stain results for p16 are summarized in Table 1. Although p16 staining was more common in DDL than the control sarcomas, the difference was greater when controlling for UPS and SCA. By contrast, LMS could not be distinguished from DDL by p16 status. The sensitivity of p16 for DDL was 98% with negative predictive value of 91%, but specificity (31%) and positive predictive value (67%) were low when comparing to other retroperitoneal sarcomas.

Table 1. p16 immunohistochemical expression in retroperitoneal sarcomas.

| Diagnosis                  | n  | p16 positivity | 0 | 1+ | 2+ | 3+ |
|----------------------------|----|----------------|---|----|----|----|
| DDL                        | 19 | 15 (79%)       | 4 | 0  | 0  | 0  |
| Other sarcomas             | 32 | 22 (69%)       | 10| 1  | 1  | 0  |
| LMS                        | 10 | 10 (100%)      | 0 | 0  | 0  | 0  |
| SCA                        | 7  | 7 (100%)       | 0 | 0  | 0  | 0  |
| GIST                       | 1  | 1 (100%)       | 0 | 0  | 0  | 0  |
| Malignant GIST             | 1  | 1 (100%)       | 0 | 0  | 0  | 0  |

Conclusions: These results demonstrate the utility of p16 in the diagnosis of retroperitoneal sarcomas. This may be used as a negative p16 result may exclude the diagnosis of DDL. However, a positive result lacks specificity to exclude other sarcomas, especially LMS.

65 Impact of Fluorescence in Situ Hybridization Analysis on the Final Diagnosis of Dermatofibrosarcoma Protuberans: About 448 Cases

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Background: Dermatofibrosarcoma protuberans (DFSP) is a rare superficial dermal tumor that tends to recur locally, which is why a high number of DFSP cases are studied in pathology archives. Histochemical and immunohistochemical markers have been used, with varying results, to distinguish between DFSP and other mimics. Due to the absence of specific markers, genetic analysis is of increasing importance in the diagnosis of DFSP. The aim of this study was to evaluate the role of the molecular analysis in the diagnosis of DFSP.

Design: 448 cases referred for second opinion or for confirmation of a diagnosis of DFSP since 2007 to 2013 were studied. For these cases a FISH had been performed to detect the COL1A1-PDGFB fusion gene. All cases were reviewed by two pathologists and classified in three categories according to the probability of the DFSP diagnosis before molecular analyses. The case was “certain” when DFSP was the only possible diagnosis; “probable” when DFSP remained the first diagnosis, but other differential diagnosis existed; “possible” when DFSP was considered as a differential diagnosis. Final diagnosis was supported by clinico-pathological findings and results of FISH analyses. Immunohistochemical analysis of CD34 was systematically performed and other markers when necessary. FISH assay was performed using the Histology FISH access kit (Dako) and home-made probes.

Results: For the 200 “certain” cases, 178 (89%) FISH analyses were positive, 7 (3.5%) negative and 15 (7.5%) non-interpretable (NI). For the 121 “probable” cases: 103 (85%) FISH analyses were positive, 8 (6%) were NI and 10 (9%) were negative. For these 10 cases, final diagnoses were: 1 low-grade myofibroblastic sarcoma, 3 undifferentiated sarcomas, 2 solitary fibrous tumors, 1 spindle cell lipoma, 1 periureterica, 2 undifferentiated spindle cell tumors without malignant evidence. For the 127 “possible” cases: 91 (71%) FISH analyses were negative, 14 (12%) were NI and 22 (17%) were positive. In these 22 cases, 7 undifferentiated sarcomas were finally considered as fibrosarcomas (FSP), 4 myofibroblastic sarcomas as myxoid FSP, 2 dermatofibromas, 2 reactive lesions, 1 solitary fibrous tumor, 1 periureterica, 1 myophthlotenia, 1 benign nerve sheath tumor, and 3 undifferentiated spindle cell tumor without malignant evidence as DFSP. FISH analysis has been helpful for confirming the diagnosis of DFSP in 23% of cases (103/448) and necessary for the diagnosis of DFSP in 5% of cases (22/448).

Conclusions: This study highlights the important role of the FISH analysis in the diagnosis of DFSP.

66 FOSL1 Protein Is Differentially Overexpressed in Desmoplastic Fibroblastoma and a Subset of Fibroma of Tendon Sheath

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Background: Desmoplastic fibroblastomas (DFBs) and fibromas of tendon sheath (FTSs) are benign fibroblastic tumors that comprise birefringent spindle cells. A recurrent chromosomal rearrangement involving 11q12 loci has been reported in DFBs and FTSs, suggesting a genetic link between the 2 entities. Recently, a microarray analysis of DFBs revealed mRNA elevation of FOSL1, which encodes a nuclear leucine zipper protein. As the FOSL1 gene is located close to 11q12, it has been proposed as a candidate involved in the 11q12 rearrangement. We here explored the diagnostic potential of FOSL1 immunohistochemistry by studying DFBs, FTSs and their histological mimics. In addition, we investigated FOSL1 rearrangement status in selected cases.

Design: FFPE samples of 9DFBs and 10FTSs were immunostained by using anti-FOSL1 monoclonal antibody. Ten desmoid-type fibromatoses (DMFs), 10 nodular fasciitis (NFs), 10 superficial fibromatoses (SFs), 6 spindle cell lipomas (SLs), and 3 neurofibromas (NFs) were also stained as histological mimics. Only nuclear reactivity was considered significant. The results were graded as 2+ (>50% of tumor cells stained with strong intensity), 1+ (10-50% of tumor cells stained with weak intensity), 0+) (<10% of cells stained with weak intensity), or O (<10% of cells stained with weak intensity). FOSL1 gene status was examined on FFPE samples of 6DFBs, 2FTSs, 1ND, and 1DMF, by using dual-color chromogenic in situ hybridization (CISH) with custom-made break-apart probes spanning FOSL1.

Results: All DFBS (9/9) showed 2+ FOSL1 immunopositivity, whereas 50% (5/10) of FTSs showed 2+ reactivity. The remaining FTSs showed 1+ (30%, 3/10) or 0 (20%, 2/10) staining. Histological appearance of FTSs did not predict FOSL1 expression status. Other spindle cell tumors showed 1+ (25%, 10, 40%) or 0 (75%, 30%) reactivity. None of the cases examined by CISH showed FOSL1 break-apart signals.

Conclusions: Strong diffuse immunoactivity of FOSL1 distinguishes DFBs from histological mimics such as DMFs. In contrast, similar overexpression was seen only in a subset of FTSs, suggesting that FTSs may not be a uniform tumor entity; FOSL1-overexpressing subset may be related to DFBS and might harbor 11q12 rearrangement. Our CISH analysis indicated that the FOSL1 is not rearranged in DFBS or FTSs, and suggested that FOSL1 expression may be induced by other mechanisms.
Design: We performed WES on 20 RMS (9 ARMS, 11 ERMS). We also genotyped additional ERMS samples using mass spectrometry-based genotyping (Sequenom). We collected clinicopathologic data and performed survival analyses and functional studies.

Results: By WES, 2 ERMS showed the same c.365T>G somatic point mutation in MYOD1, leading to a L122R substitution. The L122R mutation occurs in the conserved basic region of the DNA-binding domain of MYOD1, at a highly specific residue that is a leucine (L) in all myogenic BHLF TFs (MYOD1, MYF5, myogenin, MRF4) but is an arginine (R) in MYC. We genotyped an additional 93 ERMS for the L122R mutation using Sequenom genotyping. The mutation was found in 8 additional cases, resulting in a cumulative prevalence of 10% (10/104). The 10 ERMS with the MYOD1/L122R mutation were highly cellular with frequent spindle cell morphology and uniform strong immunoreactivity for MYOD1, suggesting, in some cases, an overlap with the recently described adult spindle cell variant of ERMS. Notably, 9 of the 10 ERMS with MYOD1 mutations were diagnosed in adolescence or adulthood (mean age = 25, median age = 23) and were more likely to arise in the head/neck (8/10 vs 16/80; p=0.003). Furthermore, the overall survival with MYOD1-mutant ERMS was significantly poorer than for ERMS lacking MYOD1 mutation (0% vs 48% at 10 yrs; p=0.02). We also observed a relationship between MYOD1 L122R and PIK3CA mutations in 66 cases with available sequencing data for both: PIK3CA mutations were seen in 3/10 MYOD1/L122R cases vs 0/56 MYOD1 wild type cases (p=0.003), suggesting possible cooperation between these mutations. Functional studies in C2C12 cells confirmed that MYOD1 L122R blocks myogenic differentiation and enhances proliferation.

Conclusions: ERMS with MYOD1 L122R represents a novel molecular subset of RMS with distinctive clinicopathologic features that should be considered for high risk protocols and targeted therapeutic development.

69 An Institutional Review of Non-epithelial Neoplasms of the Sinonasal Cavity of the Period of 10 Years at a Tertiary Care Center

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Background: The sinonasal cavities give rise to a heterogeneous group of neoplasms of mesenchymal, neural, epithelial, melanocytic and hematopoietic origin. These account for less than 1% of all cancers, but their overall frequency is unclear. Recurrence and treatment options are variable depending of the histopathological profile of the cancer.

Methods: We retrospectively reviewed all non-epithelial malignancies of the sinonasal cavities at a tertiary care center.

Results: Of 720 sinonasal neoplasms from 2003-2013, 37 cases (5%) were non-epithelial neoplasms. These were comprised of sarcomas (n=11), mucosal melanomas (n=8), benign neoplasms (n=7), lymphomas (n=2), and germ cell tumors (n=1). Of the 37 study cases, 35 were resected in an oncologic fashion at a single institution, to determine if historic LR/DM rates persist and to identify histologic predictors of clinical outcome. We are expanding our series through identification of additional cases with longer follow up to further investigate the effect of non-myxoid stroma and French grade on clinical prognosis.

72 MYC Expression in Sporadic and Radiation-Associated Sarcomas

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Background: The MTC proto-oncogene(8q21) regulates genes involved in cell division, cell cycle and apoptosis. The role of MYC in radiation-associated sarcomas has been described in radiation associated mammary angiosarcoma. The role and prevalence of MYC expression in sporadic and other radiation-associated sarcomas has not been extensively investigated.

Design: 53 radiation-associated sarcomas (49 undifferentiated pleomorphic sarcomas (UPS), 3 alveolar rhabdomyosarcomas, and 1 synovial sarcoma) were evaluated from 1992 to 2001. 17 of which had moderate to strong labeling. These were seen in UPS (12), 18 synovial sarcomas, 4 leiomyosarcomas, 71 UPSs, 14 unclassified sarcomas, and 27 radiation associated angiosarcomas (for comparison) were analyzed using formalin-fixed paraffin-embedded tissue microarrays. Immunohistochemical studies were performed using the rabbit monoclonal anti-Myc antibody to the N terminus of human Myc (Y69, Ventana Medical Systems, Tucson, AZ, USA). Immunoreactivity was graded for intensity (weak, moderate, and strong). Any labeling was considered positive.

Results: In sporadic sarcomas, MYC reactivity was observed in 87 of 119 cases (73%); 17 of which had moderate to strong labeling. These were seen in UPS (12), synovial sarcomas (2), alveolar rhabdomyosarcoma (1) and 1 synovial sarcoma (0.3%). In radiation-associated sarcomas (non-angiosarcoma), 22 of 53 cases (47%) had MYC expression, 17 cases with weak and 7 cases, all UPS, with moderate to strong labeling. In contrast, MYC was expressed in 26 of 27 (96%) radiation-associated angiosarcomas, with predominantly diffuse and strong labeling (20/26).

Conclusions: Variable MYC expression, including occasionally moderate to strong labeling, can be seen in sarcomas other than angiosarcomas including other radiation-associated sarcomas though less than radiation associated angiosarcoma. These findings suggest that MYC may play a role in tumorigenesis in sarcomas and may serve as a potential therapeutic target. The mechanism of overexpression in these tumors has yet to be elucidated.

73 MYC Expression in Mammary Vascular Tumors

SM Lee, I. Hwu, AJ Lazar, W-L Wang. University of Texas MD Anderson Cancer Center, Houston, TX.

Background: Post radiation angiosarcomas have high level JMC amplification resulting in the overexpression. Previous studies have shown that immunohistochemical studies are useful in distinguishing post radiation mammary angiosarcoma from other malig

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atypical vascular proliferation. However, the prevalence of MYC expression and its diagnostic utility in evaluating primary mammary vascular tumors have not been extensively studied.

**Design:** Formalin-fixed paraffin-embedded tissue microarrays and whole tissue sections of 20 mammary hemangiomas, 12 primary mammary angiosarcomas and 24 post radiation mammary angiosarcomas were analyzed by immunohistochemistry using monoclonal anti-Myc antibody to the N terminus (Y69; Ventana Medical Systems, Tucson, AZ, USA). Any amount of staining in the tumor cells was considered positive. The staining intensity was categorized as weak, moderate and strong.

**Results:** The staining results were summarized in Table 1. Most of the post radiation angiosarcomas had moderate to strong Myc staining (18/24, 75%). In contrast, only 33% (4/12) of primary mammary angiosarcomas had moderate to strong staining. Although none of the hemangiomas had strong staining, 2 had moderate staining. Weak staining was observed in tumors of all 3 types.

**Conclusions:** In breast, the sensitivity of Myc immunohistochemical staining is lower in primary angiosarcomas compared with post radiation angiosarcomas. Strong Myc staining can be potentially used to distinguish angiosarcomas from hemangiomas. While weak staining is not diagnostically helpful, moderate Myc staining in mammary vascular tumors need to be interpreted with caution because it can be seen in a small proportion of hemangiomas.

### Table 1. Summary of immunohistochemical patterns for MYC in mammary vascular tumor

| Group                        | Primary Hemangioma | Primary Angiosarcoma | Post Radiation Angiosarcoma |
|------------------------------|--------------------|----------------------|-----------------------------|
| All cases positive staining | 11/12              | 3/12                 | 20/24 (83%)                 |
| All cases weak staining      | 1/12               | 1/12                 | 3/24 (12.5%)                |
| Good outcome                  | 10/10              | 10/10                | 19/20 (95%)                 |
| Poor outcome                  | 1/10               | 3/10                 | 1/24 (4.2%)                 |

### 76 Desmoid-Type Fibromatosis: Radiologic-Pathologic Correlation and Clinical Predictors of Recurrence in an 18-Year Retrospective Cohort

**Background:** Desmoid-type fibromatosis is a relatively rare, locally aggressive, fibrous neoplasm with an extensive differential diagnosis. These tumors are estimated to have a 20-45% risk of recurrence. Higher risk of recurrence has been associated with age, tumor size, and mutation of the CTNNB1 gene. We aimed to establish specific criteria to predict the risk of recurrence and help guide individualized surveillance and treatment.

**Design:** We conducted a retrospective cohort study of 51 patients diagnosed with desmoid-type fibromatosis between 1995 and 2008. The subset of patients and clinical information was extracted from our clinical information system using Clinical Looking Glass, University of California, Los Angeles, USA. We compared the two groups with p-value <0.05 being considered statistically significant.

**Results:** Of 51 patients, 18 developed post-operative recurrences during follow-up (34.6%). Mean time to recurrence was 18.3 months. Females were more frequently affected (68.6%), and also showed a higher recurrence rate (42.9%) compared to their male counterparts (18.8%). The median age at diagnosis was 37.5 years, with 72% of patients below age 50. Blacks were more commonly affected (59.2%), followed by Asians (23.5%) and Caucasians (17.6%). There was no significant difference in the rate of recurrence. The abdominal wall was most frequently affected (30.8%), followed by the mesentery (13.5%) and upper extremities (13.5%). Tumors located in the upper extremities showed a markedly increased rate of recurrence, as well as those with positive and unknown surgical margin status (35% and 45%, respectively). Four patients developed different primary neoplasms during follow-up and two patients had separate metachronous fibromatoses. One patient had a prior diagnosis of adenomatous polyps of the colon. 32 patients underwent imaging studies prior to surgery. The majority received a CT scan as the initial imaging modality (68.5%), followed by MRI (21.6%). The latter showed the common radiologic diagnosis was suspicious for recurrence, followed by sarcoma (28.1%), hematoma (21.8%) and desmoid-type fibromatosis (21.8%).

**Conclusions:** In our cohort, desmoids were observed most commonly in women and patients below age 50. 40% of lesions occurring in the women, or the extremities or with positive surgical margins showed a higher rate of recurrence. Radiologic diagnosis was often nonspecific. A larger study is necessary to better determine relative risk for recurrence.
A Subset of Solitary Fibrous Tumors Express Nuclear PXAX8 and PXAX2: A Potential Diagnostic Pitfall
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Concentric growth of actin-positive myoid cells.

A McDaniel, N Palanisamy, S Smith, D Robinson, Y-M Wu, A Chinnaiyan, JK Greenson.

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Background: Solitary fibrous tumor (SFT) is an uncommon mesenchymal neoplasm of probable fibroblastic origin with widespread anatomic distribution which can be difficult to diagnose in limited samples. We recently encountered a diagnostically challenging needle aspiration of a pancreatic mass, which was initially incorrectly diagnosed as metastatic renal cell carcinoma based on strong PXAX8 expression by immunohistochemistry (IHC). After Whipple resection, morphologic features along with additional IHC (CD34 positive) identified this lesion as a SFT. PXAX8 and PXAX2 are transcription factors commonly used as markers of primary and metastatic renal and Mullerian malignancies. To date, no series has investigated the prevalence of PXAX8 or PXAX2 expression in SFT.

Design: IHC for PXAX8 (Cell Marque) and PXAX2 (Invitrogen) was performed on formalin-fixed paraffin-embedded tissue blocks from 37 biopsy and resection specimens of SFT from the pleura and thorax (n=12), head and neck (n=20), pelvis (n=3), extremities (n=1), and retroperitoneum (n=1). The mean patient age was 55.1 years (15 - 86). Confirmatory CD34 staining was present in 21 of 23 cases (93%). Tumors ranged in size from 1.2 to 27 cm. Six tumors were considered histologically malignant and six tumors were recurrences of previously incomplete resections. Staining intensity for both PXAX8 and PXAX2 (> no staining; 1+=equivocal; 2+=weak; 3+=moderate; 4+=strong) and extent (<50% of nuclei stained= focal; >50% of nuclei stained= diffuse) was recorded in each case, with only cases that had 2+ or 3+ staining scored as positive.

Results: In our cohort, nuclear PXAX8 staining was observed at least focally in 29.7% (11 of 37) SFT cases; additionally, nuclear PXAX2 staining was positive in 16.7% (6 of 36) cases. All cases positive for PXAX8 were also positive for PXAX2; while five cases of PXAX8 positive SFTs showed no nuclear staining for PXAX2. For both PXAX8 and PXAX2 positive cases, half (50%) of the cases showed diffuse expression across the tumor, while the other half showed focal expression. We found no correlation between PXAX8 and PXAX2 positivity and patient age, tumor size, site, cellularity, malignant categorization, or recurrence status.

Conclusions: A substantial minority of SFTs demonstrate nuclear expression of PXAX8 and PXAX2 by IHC, frequently with strong, diffuse expression. These findings present a diagnostic pitfall when evaluating possible metastases from the kidney or gynecologic tract, particularly when the primary tumor shows spindled or scirrhous cell morphologies.

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Osteosarcoma of the Foot: A Review of 15 Cases
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Background: Osteosarcoma (OS) is the commonest primary tumour of the bone, next only to multiple myeloma. The foot is an uncommon site comprising only 0.17-2.08% of all OS. This is a review of 15 OS of the foot accrued in the Pathology Department of a tertiary cancer hospital over ten years.

Results: Of the 15 cases of OS of the foot between 2003 and 2013, 10 were primarily treated at this hospital, and five were pathology consults. All clinical, radiological and treatment details were abstracted from the charts. All histology material (slides and paraffin blocks) were re-examined.

Results: The 15 cases comprised nine males and six females. The youngest patient was a 36 months (mean age 32 years). Five patients developed metastasis, of which one had metastasis to inguinal lymph nodes: 2 cases. Radiological data was available in 12 cases, of which 11 were positive for OS. Histologically all cases were conventional high grade OS, of which 50% were localized in the bone. In the single exception, the differential was between a chronic fungal infection or an inflammatory mass, which was initially incorrectly diagnosed as metastatic renal cell carcinoma based on strong PXAX8 expression by immunohistochemistry (IHC). After Whipple resection, morphologic features along with additional IHC (CD34 positive) identified this lesion as a SFT. PXAX8 and PXAX2 are transcription factors commonly used as markers of primary and metastatic renal and Mullerian malignancies. To date, no series has investigated the prevalence of PXAX8 or PXAX2 expression in SFT.

Design: IHC for PXAX8 (Cell Marque) and PXAX2 (Invitrogen) was performed on formalin-fixed paraffin-embedded tissue blocks from 37 biopsy and resection specimens of SFT from the pleura and thorax (n=12), head and neck (n=20), pelvis (n=3), extremities (n=1), and retroperitoneum (n=1). The mean patient age was 55.1 years (15 - 86). Confirmatory CD34 staining was present in 21 of 23 cases (93%). Tumors ranged in size from 1.2 to 27 cm. Six tumors were considered histologically malignant and six tumors were recurrences of previously incomplete resections. Staining intensity for both PXAX8 and PXAX2 (> no staining; 1+=equivocal; 2+=weak; 3+=moderate; 4+=strong) and extent (<50% of nuclei stained= focal; >50% of nuclei stained= diffuse) was recorded in each case, with only cases that had 2+ or 3+ staining scored as positive.

Results: In our cohort, nuclear PXAX8 staining was observed at least focally in 29.7% (11 of 37) SFT cases; additionally, nuclear PXAX2 staining was positive in 16.7% (6 of 36) cases. All cases positive for PXAX8 were also positive for PXAX2; while five cases of PXAX8 positive SFTs showed no nuclear staining for PXAX2. For both PXAX8 and PXAX2 positive cases, half (50%) of the cases showed diffuse expression across the tumor, while the other half showed focal expression. We found no correlation between PXAX8 and PXAX2 positivity and patient age, tumor size, site, cellularity, malignant categorization, or recurrence status.

Conclusions: A substantial minority of SFTs demonstrate nuclear expression of PXAX8 and PXAX2 by IHC, frequently with strong, diffuse expression. These findings present a diagnostic pitfall when evaluating possible metastases from the kidney or gynecologic tract, particularly when the primary tumor shows spindled or scirrhous cell morphologies.
substitutions, small indels, rearrangements, copy number alterations) were determined and then reported for these patient samples. Actionable GA were defined as those targeted by anti-cancer drugs on the market or in registered clinical trials (CT).

**Results:** There were 17 female and 25 male patients with a median age 32 years (range 9-73 years). There were 4 intermediate grade and 38 high grade tumors. Twenty-six (23 from bone, 3 from soft tissue,) were primary tumors and 16 were metastases biopsies. A total of 130 GA were identified in 36/42 (86%) with an average of 3.1 GA per tumor. The most common non-actionable GA were mutations in TP53 (38%), RB1 (21%), and DNM1L (7%) and amplifications in MYC (21%). Twenty-eight (67%) OS harbored at least 1 actionable GA with an average of 1.62 actionable GA per patient including: mutation/homologous deletion in CDKN2A/B (24%), PTEN (10%) and PIK3CA (7%), amp in PDGFR (14%), MCL1 (14%), KIT (12%), KDR (12%), CCNE1 (12%) CDK4 (5%), and MET (5%). A long tail of actionable alterations in a single case included: BRC2, CCND1, CCND2, FGFR1, GNAS, FBXW7, MAP2K2, MDM2, PTCH1, RAD50, RICTOR and TSC1.

**Conclusions:** Two-thirds of OS harbored actionable GA which has the potential to influence and personalize therapy selection. The diverse list of altered genes involved in oncogenic pathways indicate that a broad diagnostic assay is needed to maximize targeted therapeutic options for each OS patient. Thus, given the limited current treatment options for patients with metastatic OS, comprehensive NGS-based genomic profiling has the potential to identify new treatment paradigms and meet an unmet clinical need for this disease.

**83 Epidemiological Comparison of 9,200 Primary Bone Tumors Treated at Ji Shui Tan Hospital in Beijing, China with 11,839 Patients at Mayo Clinic, Rochester, MN, US**

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**Background:** Although primary bone tumors are extremely rare, current literature shows that there are worldwide variations in the epidemiological characteristics of this diverse disease. Mayo Clinic data, published in the Dahlin’s Bone Tumors 6th edition, is the largest and frequently cited regarding to the epidemiological characteristics of primary bone tumors from US. However, there was no parallel published data in China which precludes a direct comparison.

**Design:** This study utilized a newly created innovative online Bone and Soft Tissue Tumor Database (JST Database: http://www.sarcoma-jst.org), which encompasses the epidemiological data of 49 years (1973-2012). A comparison study of between 9,200 patients treated at Beijing Ji Shui Tan Hospital (JST) and 11,839 patients treated at Mayo Clinic (MC), Rochester MN, US was conducted to identify any potential epidemiological differences. The patients’ age and sex, the tumors’ site and histologic diagnosis were analyzed. Statistical analysis was performed with the SPSS software (version 20.0; IBM).

**Results:** Giant cell tumor and osteosarcoma had significantly higher incidences in the JST than the Mayo Clinic patients (P<0.001). However, JST patients had a significantly lower incidence of Ewing sarcoma, chordoma, fibrosarcoma, myeloma, and malignant lymphoma (P<0.001). For most benign and malignant bone tumors, the Chinese cohort showed a more distinct male predominance than the US cohort. In the JST patients, malignant bone tumors demonstrated a mono-modal age distribution with the peak incidence in the second decade of life (36.6%), while a bimodal age distribution in the MC cohort with an initial peak in the second decade of life (21.0%) and second peak between the fifth and seventh decades of life. Prediction to femur and tibia was also found in the JST patients (P<0.001).

**Conclusions:** This is the first study demonstrating the epidemiological differences of primary bone tumors between the largest Chinese and US cohorts. The result may guide future studies to better understand the contributing genetic and environmental factors of these tumors.

**84 Microarray-Based DNA Methylation Study of Ewing’s Sarcoma of Bone**

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**Background:** Alterations in DNA methylation patterns are a hallmark of malignancy. However, most epigenetic studies of Ewing’s sarcoma have focused on the analysis of only a few candidate genes and comprehensive studies were thus lacking and necessary. The aim of this study was to identify novel methylation markers in Ewing’s sarcoma using microarray analysis.

**Design:** We report herein the microarray-based DNA methylation study of 1,505 CpG sites of cancer-related 807 genes from 69 Ewing’s sarcoma samples. We used Illumina’s GoldenGate Methylation Cancer Panel 1 microarray. Using appropriate controls (n=14), we identified a total of 92 hypermethylated genes in the Ewing’s sarcoma samples.

**Results:** Most of the hypermethylated genes were related to cell adhesion, cell regulation, development and signal transduction. We compared overall methylation means between patients who survived and those who did not. The overall methylation mean was significantly higher in patients who did not survive (0.25 ± 0.03) than in those who did (0.22 ± 0.03) (p=0.0322). However, the overall methylation mean did not significantly correlate with age, sex and tumor location. GDF10, OSM, APC and HOX11 were the most significant differentially methylated genes but their methylation levels did not significantly correlate with the survival rate.

**Conclusions:** We characterized the DNA methylation profile of Ewing’s sarcomas and detected 92 genes that were significantly hypermethylated. A trend toward more aggressive behavior was identified in the methylated group. The results of this study suggest that methylation may play an important role in the development of Ewing’s sarcomas.

**85 CXCL16 and CXCR6 in Ewing Sarcoma Family Tumor**

**B Noh, H-S Kim, W-W Jung, J-Y Sung, BK Kullil, WY Kim, YK Park. Graduate School of Medicine, Kyung Hee University, Seoul, Republic of Korea; College of Health Science, Korea University, Seoul, Republic of Korea; College of Health Science, Cheongju University, Chungbuk, Republic of Korea; Kyung Hee University Hospital, Kyung Hee University Hospital, Seoul, Republic of Korea; Sarah Network of Rehabilitation Hospitals, Brasilia, Brazil.**

**Background:** Chemokines are a family of peptide mediators that play an essential role in cellular migration and intracellular communication in tumor cells as well as immune cells. We hypothesized that the CXCL16-CXCR6 ligand-receptor system plays an important role in Ewing sarcoma family tumor (ESFT) progression.

**Design:** Using real time quantitative reverse transcription-polimerase chain reaction, we investigated the mRNA expression of CXCL16, CXCR6 and ADAM10 in various cell lines. We also investigated the expression of CXCL16, CXCR6, ADAM10 and ADAM17 in tissue samples from 61 ESFT patients using immunohistochemistry.

**Results:** The mRNA expression levels of CXCL16 and CXCR6 in the ES cell line were higher than those in the other cell lines.
In addition, CXCL16 and CXCR6 expression was associated with shorter overall survival irrespective of other prognostic factors.

**Conclusions:** Our results suggest that CXCL16 and CXCR6 axis appears to be important in the progression of ESFT, resulting in more aggressive clinical behavior. Furthermore, our data support the growing hypothesis that synovial lipomatosis, including “primary” cases where the lipomatosis is the predominant pathologic finding in the joint, is a reactive non-neoplastic process.

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**87 Molecular Characterization of Epithelioid Hemangioendothelioma Identifies Novel Variants of WWTR1/CAMTA1 Fusion Transcripts**

NR Patel, A Alam, H Sayeed, SF Sarabia, M Warren, J Jackally, M Tanas, BP Rubin, AJ Lazar, D Lopez-Terrada, W-L Wang. Texas Children’s Hospital/Baylor College of Medicine, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Cleveland Clinic, Cleveland, OH.

**Background:** Epithelioid hemangioendothelioma (EHE) is a lower-grade malignant vascular neoplasm that may be difficult to diagnose due to morphologic features reminiscent of both epithelial and mesenchymal tumors. Recently, two subsets have been identified by translocations recruiting the WWTR1/CAMTA1 and YAP1/TFE3 fusion genes. We sought to develop molecular and immunohistochemical (IHC) assays to aid in the diagnosis and molecular characterization of these tumors.

**Design:** 62 formalin-fixed, paraffin-embedded (FFPE) cases of EHE diagnosed between 2001 and 2013 were retrieved from the pathology files of our institutions. Ages at presentation ranged from 12 to 78 (median: 46) years, with a male: female ratio of 33:29. Locations included: liver, lung, pericardium, skull, and long bones. Multiple primer sets were designed to optimize a RT-PCR assay for the detection of WWTR1/CAMTA1 fusion transcripts in FFPE tissue. In order to screen for the YAP1/TFE3 fusion gene, TFE3 protein overexpression was examined by IHC.

**Results:** RNA was extracted from 32 cases, with more recent cases providing a greater yield of high quality RNA. 8 of 10 (80%) informative cases were positive for WWTR1/CAMTA1 fusion transcripts by RT-PCR, one of which showed malignant features. Previously undescribed in-frame fusion transcripts were identified in 3 cases by Sanger sequencing. In one case, new fusion sites within exon 3 of WWTR1 and exon 9 of CAMTA1 were identified. Two cases demonstrated fusion of WWTR1 exon 2 and portions of intron 2 to new sites within exon 9 of CAMTA1. IHC revealed variable nuclear staining for TFE3 in 9 of 24 cases; three with patchy staining were found to have the WWTR1/CAMTA1 fusion transcript.

**Conclusions:** RT-PCR for WWTR1/CAMTA1 fusion transcript detection can be applied to clinical FFPE specimens to support the diagnosis of EHE; and fusion transcripts can be identified in cases with malignant features. We demonstrate additional structural complexity in WWTR1/CAMTA1 fusion transcripts. Initial results suggest that IHC for TFE3 is not entirely specific and further molecular testing is recommended. Molecular testing of additional cases, including identification of YAP1/TFE3 fusion, is currently on-going.

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**88 CIC-Rearranged Pediatric Sarcomas Associated with Novel Translocations and Unusual Clinical Presentations**

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**Background:** The accurate classification of pediatric primitive sarcomas has remained challenging. Some of these cases have recently been shown to harbor recurrent translocations involving the CIC gene, such as t(4;19) and t(10;19). In this study, we sought to identify additional pediatric cases to characterize their genetic alterations, as well as their histopathology and clinical characteristics.

**Design:** We searched the pathology files of our institution for primitive sarcomas confirmed to be negative for sarcoma-associated translocations. 26 cases diagnosed from 2001 to 2012 were identified and 8 unique patient samples with a small blue round cell morphology were retrieved. FISH analysis was performed using a dual-color interphase break-apart probe for the 5′ and 3′ regions of the CIC gene. Complete karyotypes were available in 6 cases.

**Results:** 5 of 7 cases showed CIC-rearrangements by FISH; one case could not be interpreted due to poor preservation. Patients with CIC-rearranged tumors showed a male: female ratio of 4:1 and mean age of 14.8 years at diagnosis. Primary lesions involved the liver, right hemithorax, pelvic soft tissue, and thigh, measuring from 3.5 to 28.9 cm. 3 cases showed multifocal disease at presentation. Histologically, they consisted of sheets of primitive round cells with occasional prominent nucleoli, focal spindle cells, geographic necrosis, and brisk mitotic activity. Immunohistochemical staining for CD99 was variably positive in a cytoplasmic or membranous pattern. One patient presented with a large liver mass encasing the colon and a diaphragmatic implant, and had a complex tumor karyotype with t(X;19), +8, +12, +20; this patient is free of disease 3 years post-resection, chemotherapy and radiation. A second patient presenting with multifocal involvement of the scrotum and inguinal soft tissue—and a tumor carrying a t(4;19) +8 with a subclone harboring a t(15;20)—developed recurrence post-chemotherapy and resection with subsequent death. A third patient presenting with a 28.9 cm thigh mass and metastases to the lung and lymph nodes also showed chemoresistance and died despite therapy.

**Conclusions:** CIC-rearranged Primitive Sarcomas are clinically aggressive and, thus, critical to recognize. We identified additional pediatric cases showing a wide clinical spectrum and novel cytogenetic findings associated with the CIC rearrangement, in addition to trisomy 8. Molecular studies are currently being performed to further characterize the variant translocations and fusion transcripts.
89 The BCOR/CCNB3 Fusion Gene Is Present in a Subset of Undifferentiated Pediatric Sarcomas

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Background: The BCOR/CCNB3 fusion gene, resulting from a chromosome X paracentric inversion, was recently described in 4% of bone sarcomas with “Ewing’s-like” features. Here, we investigated the prevalence of this fusion gene in undifferentiated/classified childhood sarcomas, a group of tumors lacking defining morphological features or markers.

Design: An institutional database was searched over a 10-year period to retrieve archived cases of undifferentiated sarcoma, small round cell tumor, peripheral primitive neuroectodermal tumor and/or Ewing sarcoma-like tumor, excluding cases with characteristic fusion genes or translocations detected by RT-PCR, FISH and/or cytogenetics. Three Ewing sarcomas with documented EWSR1 rearrangement served as negative controls. A RT-PCR assay was designed to amplify the BCOR/CCNB3 fusion from formalin-fixed paraffin-embedded and fresh-frozen tissue, with primers on BCOR exon 15 and CCNB3 exon 5. Long-range PCR and primer walking were used to map genomic breakpoints. CCNB3 expression was evaluated using an automated antibody.

Results: Twelve samples (3 bone, 9 soft tissue) from twelve unique patients (ages 1-17 years; M:F=2:1) were tested. RT-PCR on RNA from FFPE tissue revealed 3 cases with robust amplification of a 171-bp product with sequencing revealing an in-frame fusion of BCOR exon 15 and CCNB3 exon 5 (3/12+25%) that resulted from cryptic splice site activation in BCOR and skipping of the stop codon. The genomic breakpoint in each case mapped to unique sites within CCNB3 intron 4. All three cases were soft tissue tumors in male patients demonstrating both large pleomorphic round cells and areas of spindled cells with brisk mitotic activity, expressing vimentin and variable CD99. Tumor cells had prominent nuclear expression of CCNB3. The fusion was detected in multiple recurrent and metastatic lesions in 2 positive patients who succumbed to disease.

Conclusions: This study expands the clinical and morphological spectrum of BCOR/CCNB3-positive sarcomas. In our series of undifferentiated/classified sarcomas, fusion-positive lesions were soft tissue tumors with undifferentiated round and spindled cell morphology. Molecular techniques unambiguously identified fusion genes providing a useful aid for diagnosis. The BCOR/CCNB3 oncoprotein may drive tumorigenesis through aberrant cell cycle regulation. Further studies will shed light on the pathobiology of these tumors.

90 Human Cytomegalovirus Is Present in Alveolar Soft Part Sarcoma

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Background: Alveolar Soft Part Sarcoma (ASPS) is an exceedingly rare sarcoma of unknown histogenesis, with a predilection for adolescents and young adults, characterized by slow progressive clinical course and high frequency of metastases. These tumors are often chemoresistant, thus surgery remains the mainstay of therapy with very limited treatment options in the metastatic setting. Human cytomegalovirus (HCMV) is a DNA β-herpes virus and like all herpes viruses, it is characterized by the ability to persist lifelong and latent infection. There is growing evidence to indicate the presence of HCMV proteins and nucleic acids in glioblastoma multiforme (GBM), medulloblastoma and a variety of solid organ malignancies of the breast, prostate, lung and colon at very high prevalence. Immunotherapy based clinical trials targeting specific CMV proteins are currently in progress in the treatment of GBM. Herein, we evaluate the prevalence of HCMV in 92 cases of undifferentiated sarcomas with no or unknown transcripts.

Results: Immunohistochemistry showed nuclear positivity in all BCOR-CCNB3 cases, but also showed specific staining in cytoplasm and in necrotic areas of BCOR/CCNB3 negative sarcomas. On mRNA level all cases showed identical break-points. All cases showed discohesive small, plump to slightly spindled cell morphology with angulated nuclei lying within an edematous matrix. 7 of 8 patients were male. The age range was 13 to 18 years. 5 tumors were primarily located in bone and 3 in deep soft tissues. 3 occurred in the axial skeleton or soft tissues, 5 in the appendicular skeleton. 3 patients had metastatic disease at the time of diagnosis (lung x2, osseous x1). All patients were treated according to Ewing’s sarcoma protocols. 3 patients died of disease 27, 28 and 110 months after diagnosis, all of whom had tumors located in the axial skeleton, not amenable to curative resection. 3 patients are alive without evidence of disease at 69, 116 and 124 months. 2 patients are currently still receiving treatment.

Conclusions: BCOR-CCNB3 sarcomas are rare primitive small cell malignancies occurring in bone as well as in soft tissues. There is a male preponderance and the peak incidence is in the 2nd decade. Immunohistochemistry is a useful tool for screening, however RT-PCR and sequencing should be used for definitive identification. Correct identification of BCOR-CCNB3 sarcoma appears important for further characterization of this rare sarcoma.

92 Histopathological, Immunohistochemical and Molecular Cytogenetic Analysis of 22 Spindle Cell/Sclerosing Rhabdomyosarcomas

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Background: As per the current WHO classification of soft tissue sarcomas, spindle cell and sclerosing rhabdomyosarcoma (RMS), together, have been recognized as another variant of RMS.

Design: We evaluated clinicopathological, immunohistochemical (IHC) and molecular cytogenetic features of 22 spindle cell/sclerosing RMSs. Eleven tumors were tested for FISH analysis with RMS1, SPECT/CT and MRI, 110 months after diagnosis, all of whom had tumors located in the axial skeleton, not amenable to curative resection. 3 patients are alive without evidence of disease at 69, 116 and 124 months. 2 patients are currently still receiving treatment.
93 CD105: A Potential Diagnostic and Therapeutic Target for Angiosarcoma

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Background: Angiosarcoma may present a diagnostic challenge in poorly differentiated cases. Although several markers of endothelial differentiation are available, their sensitivities vary, and it is not uncommon to encounter an angiosarcoma which is negative for one or more of these. Additionally the therapeutic options for angiosarcoma are limited. Endoglin/CD105 is a homodimeric transmembrane glycoprotein expressed on the surface of endothelial cells, and there is evidence that anti-CD105 antibodies bind preferentially to activated endothelial cells. In this study, we investigated the value of anti-CD105 antibodies in the diagnosis of angiosarcoma. We also explored the expression of CD105 in non-neoplastic blood vessels in tumor and peri-tumoral tissue in angiosarcoma to evaluate CD105 as a potential therapeutic target.

Design: Immunohistochemistry for CD105 (Leica Biosystems) for was performed on 146 sarcomas and 12 benign vascular proliferations from the Mayo Clinic and University of Wisconsin tumor databases including 20 angiosarcomas, 19 chondrosarcomas, 7 Ewing sarcomas, 20 osteosarcomas, 40 leiomyosarcomas (LMS) (20 non-gynecologic, 20 non-gynecologic), 20 synovial sarcomas, 20 undifferentiated pleomorphic sarcomas and 12 hemangiomas. Following verification of diagnosis, either cytoplasmic or membranous expression was scored semi-quantitatively as 0 (<5% cells staining), 1+ (5-25%), 2+ (25-40%), and 3+ (>50%). Tumors with scores of 2+ and 3+ were considered positive. Intra-tumoral and peri-tumoral non-neoplastic blood vessels in cases of angiosarcomas were qualitatively evaluated as positive or negative.

Results: 80% of angiosarcomas (16/20) and 67% of benign vascular proliferations (8/12) were positive for CD105, while the vast majority of nonvascular sarcomas (113/126) were negative. No chondrosarcomas (0/19) or synovial sarcomas (0/20) expressed CD105. While one Ewing sarcoma (1/7), 2 osteosarcomas (2/20), 5 undifferentiated pleomorphic sarcomas (5/20), 2 non-gynecologic LMS (2/20), and 3 gynecologic LMS (3/20) were positive. In cases of angiosarcoma which had evaluable non-neoplastic vasculature, CD105 was positive in all intra-tumoral (17/17) and peri-tumoral (16/16) vessels.

Conclusions: CD105 is a sensitive (80%) and specific (99%) marker for angiosarcoma and may be helpful in poorly differentiated cases to confirm lineage. CD105 is a potential therapeutic target as it is expressed in both lesional cells and associated non-neoplastic vessels.

94 BRAF-Mutated GISTS: Immunohistochemistry Versus Molecular Analysis

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Background: Molecular testing of GISTs can sometimes be challenging, since specific subtypes and diagnostic markers are not always present. The BRAF-V600E mutation occurs very rarely in GISTs (5-20% of KIT/PDGFRA mutant GISTs). However, it has been considered a useful diagnostic marker for the clinical management of patients with GISTs. Our goal was to test the utility of BRAF-V600E immunohistochemistry in GISTs.

Design: A first set of 53 GISTs on freshly cut whole section with 5 BRAF-mutated and 20 BRAF WT cases (16 KIT and 4 PDGFRA-mutated) and a second set of 230 tumors showed more than one mutation: chondrosarcoma (1 case), dedifferentiated chondrosarcoma (1), and undifferentiated pleomorphic sarcoma (1) and other sarcomas (12). Mutations were detected using targeted sequencing (BRAF, KIT, PDGFRA, RTK-RAS, FGFR1, and RET) and Sanger sequencing.

Results: Of these 133 tumors, 20 (15%) had TP53 mutations, 3 (2%) had IDH1 mutations, 2 (1%) had ATM mutations, and 2 (1%) had APC mutations. Eight genes showed mutations in one case each (RB1, PTEN, NRAS, KRAS, GNAS, FGFR1, ERBB4 and C-kit). While 102 cases (76%) showed no somatic mutations by this targeted panel. Genetic analyses were then performed on more than 2500 tumors at our institution. Here we describe our initial experience with the application of a targeted clinical NGS panel on a variety of sarcoma cases.

Conclusions: Our molecular diagnostics lab database of clinical NGS was searched for soft tissue and bone sarcomas and 133 cases were recovered. During the time of this study (4/2012-9/2013) our clinical NGS panel (AmpliSeq, Life Technologies) consisted of the commonly mutated regions of 46 genes (focused on clinically actionable or common mutations in carcinoma, melanoma and brain tumors). The results were tabulated to determine mutation prevalence in sarcoma cases.

Results: Out of these 133 tumors, 20 (15%) had TP53 mutations, 3 (2%) had IDH1 mutations, 2 (1%) had ATM mutations, and 2 (1%) had APC mutations. Eight genes showed mutations in one case each (RB1, PTEN, NRAS, KRAS, GNAS, FGFR1, ERBB4 and C-kit). While 102 cases (76%) showed no somatic mutations by this targeted panel. Mutational prevalences varied amongst sarcoma types. For instance, TP53 mutations were very rare in Ewing sarcoma/PNET (2 of 29 cases), but relatively common in unsclerified sarcomas (9 of 34 cases). Of note, five tumors showed more than one mutation: chondrosarcoma (1 case), dedifferentiated chondrosarcoma (1), rhabdomyosarcoma (1) and undifferentiated sarcoma (2).

Conclusions: Our study shows that mutation rates are relatively low amongst sarcomas. However, this may be due to the use of a panel optimized for mutational events in non-mesenchymal tumors. As the genomic features of sarcomas are better defined, it is anticipated that NGS panels more appropriate to sarcomas can be developed.

95 Aggressive Angiomyloma (AAM) of Men and Women: Clinicopathological Review of 20 Cases

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Background: Aggressive angiomylomas are rare, locally aggressive, mesenchymal fibroblastic tumors involving the vulvovaginal, pelvic and perineal region occurring primarily in women. Aggressiveness in these tumors stems from their diffusely infiltrative nature and difficulty in surgical extirpation due to the intricacy of involved anatomic structures. Clinical misdiagnoses as Bartholin or vaginal cysts, lipomas and hernias and a lack of a clear cellular hallmark in core biopsy specimens frequently lead to delayed diagnosis.

Design: Twenty patients with AAM were referred to our center over the last 27 years (1986 – 2012). Clinical data and specimens, including biopsies and resections, were reviewed.

Results: Tumors occurred in 3 men and 17 women with a median age of 41 years (range, 20 to 86). The tumors ranged from 5.3 to 30 cm (median, 12.7 cm) in size, and were distributed as follows: vulva in 2/20 cases (5%), pelvis in 13/20 cases (65%), vagina in 12/20 cases (60%), perineum in 7/20 cases (35%), and retroperitoneum in 1/20 (5%). Histologically, the tumors were comprised of infiltrative, sparsely populated bland-appearing spindled and stellate cells in a fibromyxoid matrix with admixed small and large blood vessels. By immunohistochemistry, tumors were positive for ER and PR (11) and desmin (9). Clinical follow-up was available in 15 patients with median follow-up of 20 mo, range 2-307 mo. There were recurrences in 6/20 cases (30%); median interval to recurrence was 13 months (range 5-307 mos).

Conclusions: Aggressive angiomyloma is a potentially aggressive, non-metastasizing soft tissue tumor occurring in both men and women. Diagnostic definition in core biopsy specimens is particularly difficult when fatty infiltration is not present, small vessels are not numerous, or entrapped smooth muscle is seen. Large caliber vessels are often prominent in resection specimens as are less myxoid zones that may overlap or confused with angiomylolymphoblastoma. Cases occurring in males have a less prominent fatty component.
the entire tumor. Histiocytic tumor cells exhibited oval or polygonal vesicular nuclei, inconspicuous nucleoli, and pale eosinophilic cytoplasm with ill-defined borders. Typical multinodular growth was observed with whorls or loose trabeculae of tumor cells in hypocellular areas with prominent myxoid matrix and occasional transition to more solid nodules. Mucinous glands and scattered rhabdoid and giant cells were occasionally present in a subset of cases. Mitoses were scant and no necrosis was present. Mild to moderate atypia was observed in 4 cases; 1 tumor showed rhabdoid features. Tumor cells expressed EMA (11/20), desmin (13/20), CD99 (2/3), and CD68 (2/6). FISH was performed in 7 tumors and revealed EWSR1 rearrangement in 4 cases. Five tumors were excised with a suspected diagnosis of DFSP, 1 patient received preoperative radiotherapy. Following up data, available for 9 cases (median, 40 months), revealed that 3 patients developed local recurrence after 2, 7, and 48 months, respectively. All patients were alive without evidence of disease and none have developed metastases.

Conclusions: AMFH may rarely present with a prominent myxoid matrix, making diagnosis more difficult and causing possible confusion with other myxoid tumors such as extraskelatal myxoid chondrosarcoma, myxepithelial tumors, and low-grade fibromyxoid sarcoma.

98 Validation of Break Apart FISH Probes for the Detection of COL1A1-PDGF Rearrangements in Dermatofibrosarcoma Proteubrans H E Schildhaus, E Binot, R Buttner, I Tancheva-Poor, E Wiedelmann.

Clinically progressive DFSP with these genetic alterations respond to treatment with FISH probes do not recognize all types of rearrangements and that nearly 10% of cases will go unidentified by break apart probes for both genes which resulted in 100% sensitivity.

Results: Two out of eighteen evaluable DFSP (11%) were false negative with the dual color dual fusion probes (19 DFSP as well as 21 dermatofibromas) were investigated by using specific COL1A1-PDGF retrotransposon probes and all FISH break apart probes detected COL1A1-PDGF fusion in each case. Atypia was prominent in one case with rhabdoid features (B), and 1 tumor showed rhabdoid features with a suspected diagnosis of DFSP. Treatment based on the percentages of randomly “aberrant” signals determined in the dermatofibrosarcoma cohort.

Conclusions: We could demonstrate that the widely used dual color dual fusion probes do not recognize all types of rearrangements and that nearly 10% of cases will be missed by that approach. Dual color single fusion probes, on the other hand, are often false positive and may result in a misdiagnosis of DFSP, especially in cases of cellular/deep penetrating dermatofibromas. PDGFB/COL1A1 break apart probes are reliable techniques for the detection of therapeutically relevant COL1A1-PDGF fusions in DFSP.

99 Primary Pulmonary Myxoid Sarcoma Versus Pulmonary Angiomatoid Fibrous Histiocytoma: Cases with Overlapping Features? L Schmidt, SC Smith, N Palanisamy, B Betz, SA Tomlins, R Mehra, DR Lucas, JL Myers.

Background: Primary pulmonary myxoid sarcoma (PPMS) is a recently described, malignant mesenchymal tumor of the skin. The underlying molecular mechanisms are various chromosomal fusions in DFSP. Clinically progressive DFSP with these genetic alterations respond to treatment with FISH probes do not recognize all types of rearrangements and that nearly 10% of cases will go unidentified by break apart probes for both genes which resulted in 100% sensitivity.

Results: Two out of eighteen evaluable DFSP (11%) were false negative with the dual color dual fusion probes (19 DFSP as well as 21 dermatofibromas) were investigated by using specific COL1A1-PDGF retrotransposon probes and all FISH break apart probes detected COL1A1-PDGF fusion in each case. Atypia was prominent in one case with rhabdoid features (B), and 1 tumor showed rhabdoid features with a suspected diagnosis of DFSP. Treatment based on the percentages of randomly “aberrant” signals determined in the dermatofibrosarcoma cohort.

Conclusions: We could demonstrate that the widely used dual color dual fusion probes do not recognize all types of rearrangements and that nearly 10% of cases will be missed by that approach. Dual color single fusion probes, on the other hand, are often false positive and may result in a misdiagnosis of DFSP, especially in cases of cellular/deep penetrating dermatofibromas. PDGFB/COL1A1 break apart probes are reliable techniques for the detection of therapeutically relevant COL1A1-PDGF fusions in DFSP.
of this marker seems to be decreasing. The low frequency of ERG expression in enchondromas compared with conventional chondrosarcomas is interesting and may be related to the state of chondrocyte differentiation in these tumors. Further study is necessary to determine whether ERG may be useful in differentiating enchondromas from low grade conventional chondrosarcomas.

102 Kaposiform Hemangioendothelioma (KHE) Presenting as a Primary Tumor of Bone: A Clinicopathologic and Radiographic Study of 5 Cases
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Background: Kaposiform hemangioendothelioma (KHE) is a rare vascular tumor of intermediate (borderline) malignancy, typically involving the skin and soft tissues of the extremities, head & neck or retroperitoneum. While KHE of the deep soft tissues can occasionally erode into underlying bone, there are few reports of KHE presenting as a primary bone tumor. We reviewed 5 cases of primary bone KHE to evaluate its clinicopathologic and radiographic features.

Design: 5 cases diagnosed as KHE were retrieved from our institutional and consultation archives. HA & slides, radiographs (4 cases) or radiologic records (1 case), and clinical information were reviewed. For inclusion in this study, tumors had to be arising from bone and demonstrate the typical histologic features of KHE. Glut-1 immunohistochemistry was performed in 1 case.

Results: All 5 cases met inclusion criteria and included 3 females and 2 males (10 mos to 24 yrs, mean age 8 yrs). The tumors occurred in the metacarpal, humerus, ulna, distal femur and sacrum. To the best of our knowledge, none of the patients had Kasabach-Merritt syndrome. Radiographically, the tumors appeared benign. Histologically, all tumors showed typical features of KHE characterized by infiltrating nodules of small, compressed vessels associated with dense stroma. The neoplastic cells were relatively monomorphic and siliating glomeruloid structures were present. A Glut-1 stain was negative in the single tested case. Follow up was available in 2 patients. One patient received interferon therapy immediately following diagnosis and was alive with stable residual tumor at 3 years. One patient, treated with curettage and resection, developed recurrence at 6 years and was treated with pre-operative chemotherapy and surgical resection. One year later he developed multiple bone and soft tissue tumors. At latest follow-up, he was alive with residual disease.

Conclusions: KHE very rarely presents as a primary bone tumor. Similar to its extra-osseous counterpart, KHE of bone most commonly occurs in children. The tumors have a benign radiographic appearance. None of our ossseous KHE tumors were associated with Kasabach-Merritt syndrome, a common association with soft tissue KHE. Improved recognition of this primary bone tumor involving bone will elucidate its behavior and avoid misdiagnosis with histologic mimics such as juvenile hemangioma.

103 Overexpression of ETS-Family Transcription Factors in CIC-DUX4 Sarcomas: A Useful Diagnostic Adjunct?
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Background: Among small round cell sarcomas, recent reports identify a novel, highly malignant class harboring a recurrent genomic rearrangements t(4;19), CIC-DUX4. Studies in vitro suggest that the CIC-DUX4 fusion transgene may induce expression of multiple transcription factors of the ETS family, recapitulating the oncogenic properties of ETS fusions characteristic of Ewings family tumors (ETS) and prostatic adenocarcinoma. Available antibodies for these proto-oncogenes are unsuitable for use as diagnostic adjuncts.

Design: We employed a recently validated, cromogenic RNA in situ hybridization (RISH) strategy for detection of ETV1, ETV4, and ETV5, evaluating a tissue microarray and archival whole sections of 6 confirmed CIC-DUX4 sarcomas and up to 45 (t4;19)-negative lesions, predominantly ETS (N=43). The stain was scored as 1+ if present in >25% of cells, 2+ if present in 25-50%, 3+ if diffuse >50%.

Results: The table below summarizes the results by case and stain score. Considering 1+ stain as positive, sensitivity for CIC-DUX4 sarcomas for ETV1, ETV4, and ETV5 was 100%, and specificity ranged from 94-97%. One EFT showed focal expression of all three ETS family members. Two poorly differentiated synovial sarcomas were uniformly negative.

Conclusions: We identified expression of ETV1, ETV4, and ETV5 in six of six CIC-DUX4 sarcomas in a robust assay using routine paraffin sections. The sensitivity and specificity observed imply potential utility as a diagnostic adjunct, especially as rare focal positivity among ETSs would be excluded definitionally by detection of EWSR1 rearrangement.

104 Frequent Inactivating Mutations of the Cohesin Complex Gene STAG2 in Ewing's Sarcoma Associated with TP53 Mutations and Poor Outcome
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Background: Ewing’s sarcoma family of tumors (ESFT) are a group of malignant small round blue cell tumors most commonly arising in bone or soft tissue of children and young adults which are genetically defined by a translocation between the EWSR1 gene on chromosome 22 with various partners, most commonly the FLI1 gene on chromosome 11. Identifying the additional driving genetic events, determining molecular subgroups associated with distinct clinical outcomes, and discovering effective targeted therapies are major focuses of current research.

Design: While whole exome sequencing of 68 ESFT primary tumors was performed, with subsequent Sanger sequencing and HIC analysis of the STAG2 gene and protein. Molecular analysis of STAG2 and TP53 in 37 ESFT cell lines was performed. Clinical data from 210 patients with ESFT was correlated with tumor STAG2 status.

Results: Inactivating mutations of the cohesin complex gene STAG2 were identified in 12/68 ESFT primary tumors (18%) and 15/37 ESFT cell lines (41%), causing loss of STAG2 protein by IHC or Western blot using a monoclonal antibody directed at the C-terminus. Somatic mutations of STAG2 were recently reported in glioblastoma and urothelial carcinoma which were found to cause chromosomal instability and aneuploidy (Solomon et al, Science 2011 Aug 19; Solomon et al, Nature Genet 2013 Nov). We find that STAG2 mutations in ESFT are significantly correlated with the presence of chromosomal copy number aberrations and concurrent TP53 mutation. In a cohort of 210 patients with ESFT, STAG2 loss was found in 30 tumors (14%) and correlated with reduced overall survival (p<0.03). Cancer cell lines harboring STAG2 mutations were found to have increased sensitivity to small molecule inhibitors of the DNA repair enzyme PARP.

Conclusions: These findings identify a molecular subgroup of ESFT defined by STAG2 mutations which harbor frequent TP53 inactivation and have poor prognosis, and suggest PARP inhibitors as a potential new effective therapy for this subgroup of ESFT.

105 A Comparative Immunohistochemical and Molecular Study of CIC-DUX4-Fusion Positive Round Cell Sarcomas Versus EWSR1-Rearranged Ewing Sarcoma: Further Evidence toward Distinct Pathologic Entities
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Background: Round cell sarcomas harboring a t(4;19)(q35;q13) or a t(10;19)(q26;q13) with CIC-DUX4 fusion are aggressive tumors arising in soft tissue of young adults. Due to morphologic overlap with Ewing sarcoma (ES) and weak CD99 expression they have been classified under ES family of tumors and managed similarly. A systematic immunohistochemical or molecular comparison between these two groups of tumors has not been conducted. On the basis of an initial observation of WT-1, FLI1 and ERG immunoreactivity in CIC-DUX4 tumors, we performed a comparative IHC and molecular analysis including these markers, to further investigate the pathogenetic relationship between ES and CIC-DUX4 sarcomas.

Design: 19 CIC-DUX4 sarcomas and 20 EWSR1-rearranged ES were included in the study. Tumors were evaluated by IHC for CD99, FLI1, ERG and WT-1 expression. Additionally, gene profiling by microarray techniques was carried out in CIC-DUX4 cases (n=8) and gene signatures were compared with primary ES (n=8) or other sarcoma subtypes (n=30). QRT-PCR was validated microarray results.

Results: All 19/19 CIC-DUX4 cases expressed CD99 (focal and weak) and WT-1 expression. Additionally, gene profiling by microarray techniques was carried out in CIC-DUX4 cases (n=8) and gene signatures were compared with primary ES (n=8) or other sarcoma subtypes (n=30). QRT-PCR was validated microarray results.

Conclusions: 19/19 CIC-DUX4 cases expressed CD99 (focal and weak) and WT-1 expression. Additionally, gene profiling by microarray techniques was carried out in CIC-DUX4 cases (n=8) and gene signatures were compared with primary ES (n=8) or other sarcoma subtypes (n=30). QRT-PCR was validated microarray results.

106 Sclerosing Epithelioid Fibrosarcoma (SEF) of the Abdominal Cavity and Retroperitoneum: An Aggressive Form of SEF Simulating Carcinosarcoma
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Background: SEF is recognized as a low to intermediate grade sarcoma that is frequently associated with dense fibrous connective tissue or peritoneum. Local
107 Gastrointestinal Neuroectodermal Tumor (GNET)/Clear Cell Sarcoma-Like Tumor of the Gastrointestinal Tract (CCSLGT): A Clinicopathologic and Molecular Study of 41 Cases

**Background:** GNET/CSSLGT is a rare gastrointestinal tumor frequently confused with its soft tissue counterpart, Clear Cell Sarcoma of Tendons and Aponeuroses (CCSTA), because of their similar clinicopathological features despite epithelioid, ultrastructural and behavioral differences. Previous studies of GNET/CSSLGT have had too few cases or too little follow-up to provide a comprehensive pathologic and clinical picture of the tumor.

**Design:** GNET tumors with features of GNET/CSSLGT as had been previously described were identified and assessed based on previous studies; features to be included in the analyses included: clinical presentation, tumor characteristics, histology, immunohistochemistry, and molecular features.

**Results:** Results included in this study (N=41) occurred in 22F/19M (median 46 yrs) in various gastrointestinal (GI) locations (median size 4 cm, range 2-15 cm). Tumors involved the stomach (N=6), small intestine (N=24), colon (N=4), rectum (N=1), omentum and mesentery (N=5). The most frequent histologic findings were sheets of highly cellular, polygonal cells with slight nuclear pleomorphism and variable mitotic activity (median, 4 range, 1-30). Scattered, osteoclast-type giant cells and clear cell morphology was present in less than half the cases. Abortive rosette-like structures were seen in 18 cases. EWSR1 gene rearrangement was present in 32/35 (91%) cases, EWSR1-ATF1 in 10/25 cases and EWSR1-CREB1 in 8/25 cases. Ten patients died of their tumor after 3 to 115 months (median 31 months). Eighteen patients (44%) were alive at last follow-up of 2-125 months (median 23 months) and 12 of these patients had recurrent disease and 15 had metastases (mostly in liver) after periods of up to 107 months. Histologic differences, mitotic activity, and tumor size were not related to tumor behavior or patient survival.

**Conclusions:** GNET has a range of morphologic, immunophenotypic, ultrastructural and behavioral differences that separates it from CCSTA.

108 Granular Cell Tumors (GCT) of Soft Tissue: A Clinicopathologic Study of 35 Cases

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**Background:** GCTs are benign neoplasms of neurogenic origin commonly arising from skin, subcutaneous tissues and occasionally from deep structures. Their histogenesis remains uncertain, and a variety of terms have been used to describe similar lesions. The World Health Organization (WHO) currently recognizes the tumor as a benign, encapsulated proliferation of granulated cells with varying degrees of differentiation along neural lineage.

**Design:** GCTs involving deep soft tissues (i.e. +/- deep dermis and below) with no superficial dermal/mucosal involvement were selected. Clinical and follow-up data was obtained. H&E sections and immunostains including S-100, EMA, CD34, SMA and MOC31 were analyzed in all cases. Results: 35 cases (21 female, 14 male; ages: 5-69 years) were identified: arm (7), chest (7), hand (3), axilla (3), leg (3), foot (2), abdomen (2), scalp (2), cheek (1), vulva (1), back (1), finger (1) (size: 1-3.5 cm; median: 2.25 cm). Histologically, 22 tumors had a nodular well-circumscribed appearance, 9 tumors had infiltrative borders and 4 tumors were multinodular. Tumors were composed of sheets and nests of oval to polygonal cells with abundant, clear cytoplasm; cytologic features were similar to those seen in granular cell tumors of skin. The borders were invasive and 4 cases had lymphovascular invasion. Only 2 cases showed rare mitotic figures (1 per 10HPF) with no atypical mitoses. No necrosis or hemorrhage was identified in any case. All tumors were strongly positive for S100 protein and negative for all other markers. Follow up from 2 months-4 years revealed only one patient with multiple, multifocal recurrences (35 year-old male; 3 x 2 cm, arm). No atypical histological features, or perineural or vascular invasion were seen on initial presentation or upon recurrence.

**Conclusions:** None of the cases behaved as aggressive malignant neoplasms in spite of their deeper anatomical locations. The presence of occasional atypical features, such as cellular pleomorphism (25.7%), perineural invasion (25%), mitotic activity (5.7%) and lymphovascular invasion (2.8%), did not influence prognosis in these deep-seated tumors.

109 Osteomyelitis: Development of a Scoring System Based on Histologic Criteria to Improve Diagnosis in the Foot and Ankle

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**Background:** Histopathologic exam of bone specimens is the gold-standard of diagnosis for osteomyelitis (OM); however, strict criteria are not widely recognized. Accurate diagnosis of acute OM (AOM) and chronic OM (COM) is important for optimal treatment of patients. We developed a scoring system based on histologic criteria for AOM and COM, and correlated it with clinical follow up of OM in foot and ankle for the 2003-2013 period.

**Design:** 750 cases over 3 years were identified. Clinical, radiologic, laboratory and histopathologic findings were collected. From these findings and literature, we developed and weighted 13 histologic criteria to test the feasibility of improving diagnosis of OM. Acute inflammation, abscesses, bacteria, involution, and sequestrum are the most supported findings in OM and were assigned a score of 3. Fibromatosis necrosis and marrow fibroplasia, were assigned a score of 2. Nonspecific findings, including erosion, remodeling and chronic inflammation, were assigned a score of 1. A slide review was then performed with strict adherence to the criteria. Also included in the score were radiologic results (2 for AOM, 1 for suspicious for OM (SOM), and bone cortex was scored positive).

**Results:** A review of previously issued reports indicated 61% utilized descriptive criteria, none of which included complete criteria. 18% of autopsies had no margins submitted. Bone cultures were performed in only 14% of cases. The average score for AOM/SOM/COM was 14.89 with 87% of cases scoring above 11. The average score for COM was 8.95 with 81% scoring between 6 and 11. The average score for no acute OM (NAOM) was 1.94 with 100% scoring 4 or less. No diagnosis of AOM/COM scored less than 9, and no diagnosis of COM scored less than 6. COM was diagnosed in 25% of cases, compared to 6% without the scoring system. Clinical follow up results indicated that in all cases, immediate diagnosis, imaging and non-healing post-op wounds might have been avoided using our criteria. The criteria were particularly helpful in evaluating margins and fragmented biopsies.

**Conclusions:** Review of reports indicates that current histopathologic criteria for diagnosis of OM is ill defined and inconsistently utilized. Our scoring system shows scores greater than 6 are likely OM, scores greater than 11 are likely AOM, and scores less than 4 are NAOM. Bone cultures are infrequently utilized, but seem to correlate more highly with a diagnosis of AOM.

110 Quantitative miRNA Expression Profiling as an Objective Tool to Differentiate Malignant Peripheral Nerve Sheath Tumors and Desmoplastic Melanomas

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**Background:** Differentiating malignant peripheral nerve sheath tumor (MPNST) from desmoplastic melanoma (DM) can be a diagnostic challenge due to overlapping morphology and immunophenotype. We have recently demonstrated through microarray analysis that miR-138 is differentially expressed and can be used to differentiate these two entities. The aim of this current study is to expand our sample size and confirm our findings using quantitative polymerase chain reaction (qPCR). Initial global miRNA expression profiling was performed on archival formalin-fixed embedded tissue. Then a limited panel of candidate miRNAs was converted to a qPCR format for practicality and economy.

**Design:** A screening group of 7 MPNST and 8 DM cases with sufficient tissue was selected. Each case was independently confirmed by a soft tissue pathologist and a dermatopathologist. Universal miRNA expression was analyzed with the GeneChip miRNA 3.0 Array (Affymetrix Inc). Data was imported into R software and normalized using the robust multichip algorithm. Differential expression was assessed using the Wilcoxon signed-rank test. Significant human probe sets by miarray were identified based on a significant p-value (<0.05) and a difference of at least ± 1.5 fold-change. Candidate miRNAs demonstrating the most significant difference were selected (miR-138, mir-141, and mir-200a). A candidate miRNA demonstrating the least variance was selected as a calibrator (mir-892b). Total RNA was used for selective miRNA qPCR (Quenan Inc). Data was analyzed for relative expression fold change using the 2^-ΔΔCt method.

**Results:** miRNA-138 demonstrated the most significant relative fold change both on microarray (p=0.02) and qPCR (p=0.006). miR-141 and mir-200a showed a significant relative difference on the microarray; however, the trend could not be confirmed with qPCR (see table).
111 GRIA2 is a Novel Diagnostic Marker for Solitary Fibrous Tumor Identified through Gene Expression Profiling

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Background: Solitary fibrous tumors (SFT) is a fibroblastic neoplasm characterized by a haphazard growth pattern, bland, spindled cytotype, variable amounts of collagenous stroma, and dilated, branching vessels. Individual tumor histology, however, can vary greatly and overlap with other soft tissue tumors, making diagnosis challenging at times. Several existing markers, among which CD34 has been studied most extensively, are used for diagnosis of SFT, but none are specific, and all have been shown to stain histologic mimics of SFT. Recent gene expression profiling studies have revealed marked overexpression of the GRIA2 gene (GlutR2), which encodes a MAPK-selective ionotropic glutamate receptor subunit, in SFT. To evaluate the potential diagnostic utility of GRIA2, we examined protein expression in SFT and other soft tissue tumors, including histologic mimics.

Design: Paraffin-embedded whole tissue sections of 375 soft tissue tumors were examined, including 105 solitary fibrous tumors, 20 cases of dermatofibrosarcoma protuberosans (DFSP), 9 synovial sarcomas, 20 sarcomatoid mesotheliomas, 20 malignant peripheral nerve sheath tumors, 25 dedifferentiated liposarcomas, 20 monophasic synovial sarcomas, 22 low grade fibromyxoid sarcomas, 12 spindle cell/sclerosing rhabdomyosarcomas, 10 nodular Kaposi sarcomas, 10 cases of desmoid fibromatosis, 20 gastrointestinal stromal tumors, 10 cellular schwannomas, 11 deep fibrous histiocytomas, 21 spindle cell lipomas, 10 neurofibromas, and 20 soft tissue perineuriomas.

Results: Immunohistochemistry was performed using a rabbit anti-GRIA2 monoclonal antibody (Abcam; EP292Y; 1:100 dilution) following pressure cooker antigen retrieval. Results: In total, 84 of 105 (80%) SFT, including 18 of 21 (86%) malignant SFT and 4 of 4 (100%) dedifferentiated SFT, demonstrated positivity for GRIA2, which was usually moderate or strong in intensity and present in at least 25% of tumor cells. Expression of GRIA2 was also seen in 15 of 20 (75%) DFSP, 4 of 9 (44%) myoepitheliomas, one monophasic synovial sarcoma (<1% of cells), and one cellular schwannoma. No other soft tissue tumors were positive for GRIA2.

Conclusions: GRIA2 is a useful diagnostic marker to distinguish SFT from other histologic mimics. Among other CD34-positive tumors, GRIA2 is also positive in most DFSP; however, clinical and histologic features aid in their distinction from SFT. GRIA2 shows a very limited distribution in other soft tissue tumors.

112 HMG2 Expression is Usefull in the Diagnosis of Sperrnic Cord Fatty Lesions

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Background: Well differentiated liposarcomas (WDL) of the spermatic cord are rare tumors often found incidentally. These may be difficult to recognize and may be misclassified as a ‘cord lipoma.’ The advent of immunohistochemical (IHC) antibodies against novel antigens has provided a diagnostic tool. IHC antibodies against HMG2 label a large proportion (up to 86%) of lipomas and WDLs. We postulate that the large majority of ‘cord’ lipomas are not truly lipomas at all, but rather extensions of non-neoplastic preperitoneal adipose tissue into the inguinal canal; as such, they would not be expected to express HMG2, furthering the diagnostic utility of this antibody.

Results: From our files we collected 14 cases diagnosed as ‘cord lipoma’ and 4 cases diagnosed as lipomas from other locations. We reviewed the morphologic features for all 18 samples. Specifically, we assessed cellular size variability, nuclear pleomorphism and nuclear hyperchromasia of the lesional adipocytes and vascular prominence. HMG2 IHC patterns were performed on all 18 cases.

Results: All 14 ‘cord lipoma’ cases were entirely negative for HMG2 and contained large muscular vessels within the lesions. All 4 lipomas from other locations had diffuse and strong HMG2 labeling. Only one of the lipoma cases contained any large vessels within the tissue. In addition, 8 cases lacked nuclear hyperchromasia and pleomorphism. 3 out of 14 ‘cord lipomas’ and 2 out of 4 lipomas displayed cellular size variation.

Conclusions: Our findings support previous anatomic studies that discriminate the long-standing practice of designating fatty deposits within the spermatic cord as ‘lipomas.’ We found that the presence of muscular vessels within the lesion to be a distinguishing feature of spermatic cord fatty deposits, a feature not typically seen in lipomas. None of the cord lipoma cases exhibited HMG2 labeling, indicating a different pathogenesis than found in neoplastic adipocytic tumors. In addition to informing the nosology, these findings support the role of HMG2 as a diagnostic tool when evaluating spermatic cord fatty lesions.

113 Genetics of Melanotic Schwannomas – A Pilot Study by SNP-Array Analysis

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Background: Melanotic schwannomas are rare tumors of adulthood with a peak incidence in the 4th decade of life. Derived from neuroectoderm, several theories have been proposed regarding their etiology including melanomatous transformation of Schwann cells, phagocytosis of melanin by Schwann cells and simultaneous presence of two neoplastic populations of proliferating Schwann cells and melanocytes. The tumors occur in the spinal canal, paraspinal regions and rarely in organ systems such as the GI tract. While majority of the melanotic schwannomas behave of an indolent manner, up to 24% can metastasize and there are no morphological criteria which help distinguish the indolent from aggressive tumors. The genetics of this lesion are largely unknown. The objective of this project is to retrospectively study available melanotic schwannomas at MSKCC and analyze their genetic characteristics by array-based DNA copy number analysis.

Design: Nine cases were identified and in 5 cases FFPE tissue was available for genomic analysis. Pathology review was performed by two pathologists and 3 female. Median age was 53 years. Tumors were located in chest wall (2), vertebra (2), paraspinal region (2), sacrum (1), ilium (1) and metacarpal bone (1). Tumor size ranged from 2.5 cm to more than 7 cm. Genomic DNA was extracted from FFPE tumor material and Affymetrix Oncoscan SNP-array was used for copy number and allelic imbalance analysis.

Results: In total, 84 of 105 (80%) SFT, including 18 of 21 (86%) malignant SFT and 4 of 4 (100%) dedifferentiated SFT, demonstrated positivity for GRIA2, which was usually moderate or strong in intensity and present in at least 25% of tumor cells. Expression of GRIA2 was also seen in 15 of 20 (75%) DFSP, 4 of 9 (44%) myoepitheliomas, one monophasic synovial sarcoma (<1% of cells), and one cellular schwannoma. No other soft tissue tumors were positive for GRIA2.

Conclusions: GRIA2 is a useful diagnostic marker to distinguish SFT from other histologic mimics. Among other CD34-positive tumors, GRIA2 is also positive in most DFSP; however, clinical and histologic features aid in their distinction from SFT. GRIA2 shows a very limited distribution in other soft tissue tumors.

114 Multiple Sporadic Desmoid Fibromatosis: Clinical and Mutational Analysis

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Background: Desmoid fibromatosis is a benign myofibroblastic proliferation often characterized by mutations of the APC gene in sporadic cases. Those associated with germ-line APC mutations (with familial adenomatous polyposis, FAP) are often multifocal. However, non-FAP-related tumors can also rarely be multi-focal either regionally or at distant body sites. We examined a series of such cases and their clinical course.

Design: Twenty patients with sporadic multifocal desmoid fibromatosis (without FAP) were identified from prospective databases at two institutions. Demographics, number of tumors, sites involved, CTNNB1 mutational analysis, and clinical follow-up were tabulated.

Results: The median age was 39 (range:15-84) years with slight female predominance (M:F 8:12). Sites of involvement included: trunk (10), extremities (6), chest (4), intra-abdominal (3), head and neck (2) and abdominal wall (1), with 7 patients having multiple tumors at different sites. Number of tumors (n=12) ranged from 2 to 3. Median size (n=14) was 5 cm (range:0.4-24). 12/19 cases developed local recurrence. Follow-up varied, but was available in 19 patients: 14 alive with disease, 4 alive and well, and one dead likely from disease. CTNNB1 mutational analysis was available on multiple nodules in four cases: in 2 cases (one extremity and one intra-abdominal) both tumor foci revealed T41A; while two multi-focal intra-abdominal cases show 2 different results for CTNNB1 genotyping (S45P and WT or T41).

Conclusions: Patients can rarely have sporadic multifocal desmoid fibromatosis and interestingly, these tumors can harbor different mutations, arguing that they are separate clonal events. This finding raises the possibility that some patients may be prone to develop CTNNB1 mutations.

115 Immunohistochemical Study of BRAF V600E Mutant Protein Expression in High-Grade Sarcomas

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Background: Vraf murine sarcoma viral oncogene homolog B1 (BRAF), a serine–threonine protein kinase, is a member of the RAS-REF-MEK-ERK signaling pathway. The BRAF V600E has been considered as a cancer-driving mutation in a variety of neoplasms including melanomas, thyroid carcinomas, gastrointestinal stromal tumors, colorectal carcinomas, ovarian carcinomas and lung cancers. Zalboraf, a FDA approved BRAF V600E kinase inhibitor, has been applied in treatment of melanoma harboring BRAF V600E with considerable response. Although a few studies have been done in sarcomas including low-grade and high-grade sarcomas, the status of BRAF V600E in high-grade sarcomas remains unclear. In addition, current immunohistochemistry (IHC) with VE1 antibody for BRAF V600E protein is reported highly specific and sensitive to predict BRAF V600E DNA mutation, but its utility on high-grade sarcomas is unknown.

Design: Forty-eight cases of undifferentiated high grade sarcomas were constructed in duplicate or triplicate cores using tissue microarray technology. IHC with VE1 antibody against BRAF V600E protein (Spring Bioscience, 1:50) was performed as per manufacturer’s instructions. The microarrays were independently reviewed by two board-certified pathologists and one pathology resident. IHC staining intensity in cytoplasm was graded from 0 to 3+. 0 and 1+ were considered as negative while 2+ or greater as positive. Selected cases were tested for BRAF V600E gene mutation by real-time PCR for comparison.

Results: Forty-one out of 48 specimens remained intact in both cores after IHC processing, but, for 4 of the 48 cases 15% were scored as positive (2+ or 3+). These 6 cases were subsequently tested for the BRAF V600E mutation by PCR, and they were all negative. Additionally, weak nuclear staining, which was considered nonspecific, was seen in 14% (12/88) of cores examined.
Conclusions: Although VE1 antibody was previously reported as highly sensitive and specific for BRAF V600E in other neoplasms, it shows significant non-specific expression in high grade sarcomas, and caution should be exercised in interpreting the results. Nonetheless, BRAF V600E mutation seems rare in high-grade sarcomas.

116 PTEN Expression in Rhabdomyosarcoma: An Immunohistochemistry Study
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Background: PTEN (phosphatase and tensin homolog) acts as a tumor suppressor protein through inhibition of the PI3K-AKT-mTOR pathway. It regulates multiple cellular processes including cell survival and proliferation. Loss of PTEN leads to absence of this inhibitory signal and a variety of malignancies. Small molecule inhibitors that target members of the PI3K-AKT-mTOR pathway are available and may be of therapeutic benefit in tumors, which have lost PTEN inhibitory function. To date, we are aware of only rare studies evaluating loss of PTEN in rhabdomyosarcoma (RMS), including only one that directly evaluated tissues from a limited number (n=12) of human subjects. Our objective was to test for the loss of PTEN in human RMS cases by using immunohistochemistry.

Design: We retrospectively identified 222 archival cases of RMS specimens submitted for surgical pathology diagnosis. These cases were previously diagnosed as ARMS (n = 72), ERMS (n = 123), PRMS (n = 18), and URMS (n = 9) (alveolar, embryonal, pleomorphic, and undifferentiated subtypes, respectively). Representative sections were immunostained for PTEN and signal graded as absent or intact.

Results: PTEN staining was lost in the majority of RMS cases (186/222, 84%). When stratified by tumor type, there was no statistically significant difference in PTEN expression between subtype groups [table]. However, comparison of RMS to all other RMS subtypes combined revealed a tendency toward retention of PTEN in PRMS (N=5, p-value 0.08).

Conclusion: The majority of RMS cases demonstrated loss of PTEN staining by IHC, which identifies a significant subset of RMS patients that may therapeutically benefit from PI3K-AKT-mTOR pathway inhibitors. PTEN loss was not limited to the highly treated RMS cases, suggesting that PI3K-AKT-mTOR pathway may be less contributory in this subtype. A limitation of this study is the lack of molecular genetic data for FOXO1 in early archival cases. Fusion proteins resulting in increased retention of PTEN in PRMS, suggesting that PIK3-Akt-mTOR pathway inhibitors may be less effective in PRMS. More studies are needed to confirm the findings described here.

117 Primary Sclerosing Epithelioid Fibrosarcoma of Bone: Analysis of a Series
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Background: Sclerosing epithelioid fibrosarcoma (SEF) is a rare, aggressive malignant neoplasm characterized by small nests and linear arrays of epithelioid cells embedded in a dense collagenous stroma. Although IHC with VE1 antibody was previously reported as highly sensitive and specific for SEF, we examined our experience with a large series of SEF to determine the diagnostic accuracy of VE1, to determine prevalence of other markers, and to compare our findings with published data.

Patients and Methods: We examined 117 cases of SEF that were submitted to the The University of Texas MD Anderson Cancer Center from 1998 to 2013. Immunohistochemical stains included routine markers of mesenchymal neoplasms as well as stains for markers of epithelial differentiation (AE1/AE3, CAM 5.2, Calponin, EMA). PTEN was also evaluated. When appropriate, malignant lymphoma was considered and stains for BCL2, BCL6, and MUM1 were performed. Malignant bone tumors were excluded from this analysis.

Results: One hundred fifteen cases met criteria for SEF. Immunohistochemical stains were positive for markers of epithelial differentiation in all cases, with greatest expression in 91% (n = 106) of cases. Positive staining for AE1/AE3 was seen in 91% (n = 106), AE3 in 100% (n = 117), CAM 5.2 in 90% (n = 107), Calponin in 36% (n = 42), EMA in 53% (n = 61), and MUC in 1% (n = 1). PTEN was intact in 14% (n = 16) of cases. Differences were seen when cases were compared with published data. However, comparison of SEF to all other RMS subtypes combined revealed a tendency toward retention of PTEN in PRMS (N=5, p-value 0.08).

Conclusion: Sclerosing epithelioid fibrosarcoma is a rare and potentially aggressive bone tumor. The histological appearance of SEF of bone is highly variable, and may mimic a variety of benign and malignant tumors of bone. Careful attention to the history of denosumab therapy is crucial to avoid misdiagnosis. Features useful in the distinction between treated and untreated SEF are the absence of infiltration of pre-existing bone and mimetic activity.

118 Denosumab-Treated Giant Cell Tumor of Bone May Mimic Primary Benign and Malignant Tumors of Bone
JB Wojcik, IA Chebib, AE Rosenberg, GP Nielsen, V Dephande. Massachusetts General Hospital, Boston, MA; University of Miami Miller School of Medicine/Jackson Memorial Hospital, Miami, FL.

Background: Giant cell tumor (GCT) of bone is a locally aggressive benign neoplasm characterized by a preponderance of osteoclastic giant cells admixed with mononuclear cells. Giant cell proliferation is induced by the neoplastic mononuclear cells that express high levels of RANKL. Denosumab, a RANKL inhibitor with proven efficacy in the treatment of GCT, can lead to a marked histological alteration of the tumor leading to diagnostic difficulties. Herein we provide the first detailed histomorphological assessment of denosumab-treated GCT.

Design: Four cases of GCT of bone in patients who had received denosumab therapy were identified from the case files at our institution. Both pre- and post-therapy materials were reviewed.

Results: The patients included two males and two females, aged 16-32 years. All presented with lytic bone lesions with extension into adjacent soft tissues. One tumor was sacral, one tribal, one in the pelvis and one in the first metacarpal bone. The time from initiation of therapy to resection/repeat biopsy/curettage ranged from 7 months to 39 months. In all cases the initial biopsy had classical GCT morphology. The post-therapy histology was highly variable. Osteoclast-type giant cells varied from sparse (2 cases) to absent (2 cases). In two cases, the histologic appearance was dominated by osteoid which was deposited both in delicate interlacing networks and in large seams. The osteoid was rimmed by a spindle cell population that showed mild to moderate atypia. Osteoblasts were conspicuously absent. The appearance was reminiscent of a low-grade osteosarcoma. One of the other lesions was characterized by a storiform fibrohistiocytic proliferation with moderate cytologic atypia and reactive bone formation. The overall appearance was suggestive of a non-ossifying fibroma. One tumor was composed of oval mononuclear cells and foam cells. The post therapy tumors lacked mite activity and did not infiltrate preexisting bone. In two cases the above showed evidence of remodeling adjacent to cartilage formation with an appearance reminiscent of osteopetrosis.

Conclusion: The histological appearance of GCT of bone following denosumab therapy is highly variable, and may mimic a variety of benign and malignant tumors of bone. Careful attention to the history of denosumab therapy is crucial to avoid misdiagnosis. Features useful in the distinction between treated GCT and osteosarcoma are the absence of infiltration of pre-existing bone and mimetic activity.

119 Primary Bone Lymphoma: Prognostic Significance of Soft Tissue Extension, International Prognostic Index and Multifocality
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Background: Primary bone lymphoma (PBL) is a rare disease. There has not been any study of prognostic factors using the new definition of primary non-Hodgkin lymphoma of bone described in the 2013 WHO Classification of Tumors of Soft Tissue and Bone.

Design: We examined PBL cases at Moffitt Cancer Center from 1998 to 2013 using the 2013 WHO criteria. Patient characteristics, survival, and prognostic factors were analyzed and compared with published data in the literature.

Results: Seventy PBLs diagnosed and treated at Moffitt Cancer Center from 1998 to 2013 were found, and 53 (75.7%) were histologically confirmed as primary bone diffuse large B-cell lymphoma (PB-DLBL). Adjacent soft tissue extension and multifocal bone lesions were both common findings in PBL. The data of PB-DLBL subgroup were further analyzed to assess survival. The patients with PB-DLBL had 3- and 5-year overall progression free survival (PFS) of 61.2% and 46.9% respectively, while 4- and 10-year overall survival (OS) were 81.1% and 74.7%. In univariate analysis, soft tissue extension, multifocal lesions, stage IV, elevated LDH, high International Prognostic Index (IPI) score, and single-modality therapy were significant poor prognostic factors for both PFS and OS. Age>60 and high Performance Score (PS>2) were also significant adverse prognostic factors for OS. Multivariate analysis revealed that soft tissue extension and IPI score were the most important unfavorable prognostic factors for both PFS and OS. Multifocality appeared to be highly associated with a worse PFS and OS, although it was not identified in multivariate analysis due to its incorporation into IPI.

Conclusion: This is the first study using the new 2013 WHO classification to identify prognostic indicators in PBL. PB-DLBL patients with soft tissue extension or high IPI score were found to have a significantly poor survival. The prognostic significance of soft tissue extension needs further confirmation in large well-characterized clinical cohorts. Moreover, further investigation is warranted to address whether PBL with multifocal bone lesions could be considered as a systemic disease rather than a conventional PBL.

120 Giant Cell Tumor of Bone with Chondroid Differentiation. A Series of 7 Cases
F Yamami, AE Rosenberg. University of Miami Miller School of Medicine/Jackson Memorial Hospital, Miami, FL.

Background: Giant cell tumor (GCT) of bone is a benign locally aggressive tumor that is composed of neoplastic mononuclear cells and benign multinucleated osteoclast type giant cells. The mononuclear cells usually grow in a syncytial pattern, the giant cells are diffusely distributed, and contain numerous usually centrally located nuclei. GCT may contain intratumoral tumor however areas of chondroid differentiation are extremely rare. In this study we describe the clinicopathologic features of GCT with chondroid areas.
Design: 7 cases of GCT of bone that contain chondroid areas; 6 cases were derived from the consult series of one of the authors and 1 case from University of Miami Hospital. 3 cases had immunohistochemistry (IHC) for S100, 2 had p63, and 1 had EMA available for review. Radiographic information was available for 4 cases, tumor size for 2, and pathology report for 3.

Results: The 7 cases represent a mean age of 24 years (range 8-42), 4 males and 3 females. 4 GCT were located in the distal femur, and the remaining 3 in metatarsal, patella, and scapula. Radiographically, a radiolucent, well circumscribed mass associated with thinning of cortex was present. Tumor size ranged between 4.7 and 6.1 cm. Histologically the tumors contained scattered foci of chondroid matrix. The matrix consists of cartilage which is hyaline and fibrocartilaginous in appearance and that in areas appears to be associated with bone. The matrix is surrounded by regions of tumor that have the appearance of GCT and areas where the mononuclear cells have a spindle cell morphology. Minimal necrosis and tumor cell necrosis was observed and no cystic atypia was observed. By IHC, 2 cases were positive for S100 in chondroid areas when initially diagnosed but were negative when recently repeated. 1 case was negative for S100 in the chondroid areas. In 1 case p63 was positive in the neoplastic mononuclear cells and the cells inhabiting the non-chondroid areas. EMA was positive in chondroid areas in 1 case. Followup at this time is limited; 1 patient is free of disease 5 years after curettage and 2 have been disease free for 4 months.

Conclusions: GCT of bone with chondroid differentiation are well circumscribed, radiolucent tumors that arise in the epiphyseal and metaphyseal regions and are extremely uncommon. The differential diagnosis of this tumor includes chondroblastoma, osteoblastoma, giant-cell rich osteosarcoma, and other cartilage containing tumors. Further investigation is required to determine the exact nature of the chondroid matrix.

121 STAT6 Immunohistochemistry Is Helpful in the Diagnosis of Solitary Fibrous Tumors
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Background: Solitary fibrous tumor (SFT) is an uncommon fibroblastic neoplasm. Although histological characteristics and frequent CD34 expression allow for an accurate diagnosis in the majority of SFT cases, a wide histological spectrum and an occasional resemblance to other tumors render immunohistochemistry a diagnostic challenge. Molecular analyses have discovered that almost all SFTs harbor a NAB2-STAT6 fusion gene, which is considered specific to this tumor type. Recent studies have suggested that STAT6 immunohistochemistry is a reliable surrogate for detection of the fusion gene. Our aim was to validate these findings by examining a large number of SFT cases and a broad array of non-SFT types of non-SFT tumors

Design: A total of 49 SFTs with a range of histological characteristics (including 33 conventional cases and 16 cases with unconventional histology) and 15 benign or uncommon. The differential diagnosis of this tumor includes chondroblastoma, osteoblastoma, giant-cell rich osteosarcoma, and other cartilage containing tumors. Further investigation is required to determine the exact nature of the chondroid matrix.

Results: All 49 SFTs (100%) showed STAT6 expression that was restricted in the nucleus, irrespective of the tumor sites and histological patterns. The staining was diffusely in all but 1 case. The intensity was strong in 45 cases, moderate in 3 cases, and weak in 1 case. The staining was uniform in most cases, but was heterogeneous in about 20% of cases where zonal staining attenuation was observed likely reflecting variability in fixation or tissue sections. In contrast, only 4 non-SFT tumors (2.5%) showed weak nuclear STAT6 expression, while the remaining 15 cases showed no staining (81 cases) or often weak reactivity in both the cytoplasm and the nucleus (74 cases).

Conclusions: Nuclear STAT6 immunoactivity, typically in a diffuse strong manner, is highly sensitive and specific for SFTs and is diagnostically helpful. This pattern of expression likely reflects the NAB2-STAT6 fusion protein, and should be distinguished from the usually weak cytoplasmic/nuclear expression associated with full-length STAT6 that can be seen in some non-SFT tumors. STAT6 reactivity may depend on preanalytical conditions, and the quality of specimens and preparations needs to be carefully monitored if this technique is to be applied to routine diagnosis of SFTs.

122 Differential SALL4 Immunexpression in Epithelioid Sarcomas and Malignant Rhabdoid Tumors
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Background: Epithelioid sarcoma (ES) and malignant rhabdoid tumors (MRT) are distinctive malignant neoplasms with characteristic clinicopathologic features. However, these tumors share some phenotypes such as epithelial/rhabdoid cytology, expression of epithelial markers, and immunohistochemical loss of INI1. This differential can be particularly problematic when tumors with MRT-like histology present in adults and ancillary diagnostic tools are needed to separate the 2 entities. CD34 expression is widely believed to favor the diagnosis of ES, but no formal comparative study has been available on 8 patients (22 months to 26 years, av. 10 yrs.) showed that they were all disease free after treatment. Three cases involving the pubic ramus showed the most aggressive features, and one of the cases underwent malignant transformation after multiple recurrences.

Conclusions: While it is rare, GCT occurs in children and adolescents with a female predominance, and a predilection for the ends of major tubular bones (53.5%). In comparison to adults it affects the small bones of the hands and feet more frequently (18.6%). Curettage is the mainstay of therapy and patients usually have a good outcome.