1990 MSCP Fall Seminar

CASE HISTORIES

Case 1

82-year-old male non-smoker who presented with a cough, clinically thought to be bronchitis, in September 1989. Chest x-rays showed a prominent right hilum and subsequent CT scans showed an 8 cm. left anterior mediastinal mass. At surgery, a mobile tumor was noted over the ascending aorta which did not appear to be related to the lung or pericardium and which separated easily from surrounding structures.

Case 2

Dr. V.A. Livolsi
University of Pennsylvania Medical Center
Philadelphia, PA

TISSUE: Liver

This 38-year-old woman underwent liver transplantation for end stage cirrhosis.

Case 3

36-year-old female who began experiencing night sweats and left upper abdominal cramps accompanied by a menstrual period that was two weeks late and unusually light. She was able to palpate a solid, mobile, painless mass in her upper left quadrant and was concerned about the possibility of an ectopic pregnancy. She sought medical attention and an abdominal CT was performed which showed a mass in the left lobe of the liver. It was described as having variable density, being hypervascular with good circumscription. The remainder of the liver appeared normal. There was no history of alcohol use and the patient had not been on birth control pills for the previous ten years. Hepatitis, serology and liver functions were normal. Serum alpha-fetoprotein was undetectable as well serum carcinoembryonic antigen. She underwent exploratory laparotomy at which time a 16 cm. mass was removed from the liver.
Case 4

Dr. Lawrence Lu
Winnipeg, Manitoba, Canada

TISSUE: Liver

The patient is a 78-year-old male admitted to hospital with a history of episodic hematemesis and increasing anorexia. He had noticed a 25 pound weight loss over the past two months. His abdomen was distended but no masses were palpable. Chest x-ray showed a left upper quadrant radiopaque mass as well as diffuse calcifications throughout the liver. Endoscopic examination revealed beating esophageal varices. Four days thereafter the patient expired. At autopsy the liver was found to weigh 1225 gm and demonstrated multiple yellow-white streaks as well as purple discolored areas on its capsular surface. The parenchyma was slightly firm with brown to gray patches containing dilated blood vessels. These zones were relatively circumscribed and measured 2.5 to 4 cm.

Case 5

Dr. V.A. LiVolisi
University of Pennsylvania Medical Center
Philadelphia, PA

TISSUE: Appendix

This 37-year-old man presented with a history of right lower quadrant pain for approximately three days. Although he had no fever, nausea or vomiting, his white count was slightly elevated to 12,000 without a left shift. He was explored with the preoperative diagnosis of "rule out appendicitis" and was found to have a thickened appendix. A periappendiceal "mass" considered to be a periappendiceal abscess.
Case 6

Dr. K.K. Unni
Mayo Clinic
Rochester, MN

TISSUE: Soft tissue, right orbit

The patient is a 3-year-old male who at age 2 had an accidental fall resulting in a "black eye". Nine months thereafter proptosis was noted as was some facial asymmetry not present on baby pictures. Visual examination showed an acuity of 20/80 on the right. Radiographs demonstrated the presence of a mass in the right superior orbit with associated deviation of the orbital roof. A biopsy was done and a diagnosis of "hemangioendothelioma" was made. Steroid injections were performed, but within nine months regrowth of the mass to its preoperative size was noted. On physical examination the eye resisted retropulsion and the upper lid appeared full. A left orbitotomy was performed. The 3x2.5x1.5 cm firm tumor was removed with blunt dissection leaving the periorbita entirely intact.

Case 7

Dr. Arthur Cohen
Charlotte, NC
Dr. B.W. Scheithauer
Mayo Clinic
Rochester, MN

TISSUE: Distal Wall

The patient is an obese 53-year-old female who presented with thoracoabdominal pain. Fifteen months prior she experienced severe left upper quadrant pain radiating to the mid back. Costovertebral angle tenderness was noted on percussion. Pain medications, antacids and dietary modifications brought some relief. Two weeks prior to the present evaluation she experienced "exploding" costovertebral angle pain. Gastrointestinal x-rays showed medial and downward displacement of the stomach. CT examination disclosed a subcardiac mass adherent to the diaphragm. A CT needle biopsy revealed a "spindle cell neoplasm". The 13 cm en bloc resection specimen consisted of a discrete rubbery, white tumor within the intercostal space, a portion of chest wall, diaphragm and pericardium. Margins of resection were free of tumor.
Case 8

Dr. K.K. Unni
Mayo Clinic
Rochester, MN

TISSUE: Femur

The patient, a 14-year-old girl, noted thigh pain for a week prior to painful spontaneous fracture of her right femur while walking at school. A mid femoral fracture was noted on routine x-rays as was diffuse infiltration of the femur by an osteoblastic lesion with associated endosteal destruction and periosteal new bone formation. An MRI scan also demonstrated significant soft tissue extension. After biopsy she underwent a right hip disarticulation. The femur showed a largely intermedullary tumor replacing the femur from the proximal metaphysis to the distal epiphysis. The 37x6x5 cm lesion was associated with a 10 cm long, 2 cm wide zone of soft tissue invasion. Margins of resection were free of tumor as was an inguinal lymph node.

Case 9

Dr. V.A. LiVolsi
University of Pennsylvania Medical Center
Philadelphia, PA

TISSUE: Peritoneum

This 18-year-old man presented with three days of intermittent right lower quadrant pain. He had no nausea, vomiting, fever or elevation of white count. With a preoperative diagnosis of possible appendicitis, he underwent exploratory laparotomy with removal of a right parietal peritoneal mass.
Case 10

Dr. L.A. LiVolsi
University of Pennsylvania Medical Center
Philadelphia, PA

TISSUE: Omentum

This 62-year-old woman had undergone hysterectomy and bilateral salpingo-oophorectomy in 1973 for a left ovarian adenocarcinoma of unknown histologic type, grade or stage. She had at that time received total abdominal radiation, dose unknown. She presented in 1989 with a right pleural effusion with was tapped and showed cells suspicious for malignant cells on cytology. While being evaluated, it was noted that she was having increasing abdominal girth and had difficulty with respiration. Because of the possibility of recurrent ovarian carcinoma and probable ascites, she underwent exploration with removal of residual omentum and multiple bowel adhesions.

Case 11

45-year-old female with a history of Cowden's disease and thyroid enlargement. The patient underwent two previous attempts at surgical excision of the thyroid several years ago.

Case 12

70-year-old female with a 2.2 x 2 x 1.2 cm. mass on the palate. Following excision, the lesion recurred in the same area seven years later.

Case 13

56-year-old female who underwent a hysterectomy for in situ squamous cell carcinoma of the cervix. A 1 cm. nodule was noted on the outer aspect of the uterus. This nodule was soft, uncut surface with a tan appearance.
Case 14

This patient presented in February 1986, at 52 years of age. He had a 10-15 year history of seizures which had been well controlled but which recently recurred. He also had some dizziness, difficulty ambulating and left-sided weakness. CT scan showed a calcified frontal lesion, crossing the midline. This was treated with radiation therapy and decreased markedly in size. In August of 1988 he began having difficulties walking again and a large left frontal mass was noted. He underwent decompression laser vaporization. In July 1989, he complained of a one-month history of low back pain which radiated into the right leg. A chiropractor performed an x-ray which showed a mass in the lumbar vertebrae. At surgery, there was a tumor which appeared to arise from the L3 nerve root, which is the specimen included for study.

Case 15

28-year-old male who presented with a syncopal episode in February 1989. He had a long history of headaches which had been gradually worsening until they were almost constant and woke him up at night. He also developed blurry vision. He was treated with anti-inflammatory medications which did not improve his symptoms. Further work-up of the headaches included a CT scan which showed a large predominantly left frontal tumor crossing the midline.

Case 16

27-year-old male with glycogen storage disease type 1A develops multiple hepatic tumors.

Case 17

Dr. G. Sharifi
Morris, MN

TISSUE: Lymph Node

The patient is a 49-year-old male with a 5 cm right neck mass of several weeks' duration. He complained of "feeling sick", weight loss and night sweats. Laboratory parameters were remarkable for a sedimentation rate of 132. Chest x-ray and abdominal computerized tomographic scan were normal. At surgery, difficulty was encountered in separating the lesion from the jugular vein. The specimen was firm and fibrous and associated with adherent fat and small lymph nodes.
Case 18

Dr. V.A. LiVolsi
University of Pennsylvania Medical Center
Philadelphia, PA

TISSUE: Spleen

This 21-year-old man with a history of inguinal adenopathy which, on biopsy, showed Kaposi's sarcoma, underwent splenectomy for splenomegaly and what, on CAT scan, was an intrasplenic mass.

Case 19

Dr. H.D. Tazalaar
Mayo Clinic
Rochester, MN

TISSUE:

The patient is a 44-year-old man who presented with a right axillary mass. The mass was visible on a preoperative chest x-ray. After biopsy, the patient had a systemic workup which was negative, as was a CBC and chemistry profile. No other lymphadenopathy was identified. He underwent four courses of Cytoxan, adriamycin and vincristine and had postoperative radiation therapy to a total dose of 5,000 rads to the right axilla.

Case 20

Dr. V.A. LiVolsi
University of Pennsylvania Medical Center
Philadelphia, PA

TISSUE: Kidney

This 65-year-old woman presented with an abdominal mass originally considered to be of liver origin. CAT scan and MRI demonstrated a left renal mass consistent with a carcinoma of the left kidney. She underwent left radical nephrectomy.
1990 MSCP Fall Anatomic Pathology Seminar

Case Diagnoses List

1. Thymic Carcinoma
2. Cirrhosis of Liver - Alpha-1-Antitrypsin Deficiency
3. Angiomyolipoma of the Liver
4. Angiosarcoma - Cholangiocarcinoma, Liver
5. Crohn's Disease of the Appendix
6. Juvenile Fibromatosis
7. Glomangiomyoma
8. Osteosarcoma with Pathologic Fracture, Femur
9. Synovial Sarcoma, Abdomen
10. Angiosarcoma, Postradiation
11. Cowden's Disease, Thyroid
12. Polymorphous Low-Grade Adenocarcinoma of Minor Salivary Glands
13. Uterine Leiomyoma with Lymphoid Infiltration
14. Glioma
15. Glioma with PNET
16. Adenoma, Liver, Glycogen Storage Disease
17. Inflammatory Pseudotumor of Lymph Node
18. T-Cell Malignant Lymphoma in Wiskott-Aldrich Syndrome
19. Dendritic Reticulum Cell Sarcoma
20. Metastasizing, Malignant Pheochromocytoma

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Fatty tumors of the liver are rare entities and have been classified into pseudolipomas, angiolipomas, angiomyolipomas, angiomyelolipomas, and myelolipomas.

Pseudolipomas represent adhesions of appendix epiplioicae to the liver capsule; because of their formation, they are located as would be expected at the surface of the liver. These lesions have been referred to as liver lipomas; true lipomas of the liver probably do not exist.

The group of angiolipomas, angiomyolipomas and the myelolipomas are quite rare. The angiomyolipomas can range from 1-20 cm., are usually solitary and can be incidental findings at surgery or autopsy. They are soft and demarcated and are composed of varying proportions of blood vessels, smooth muscle and fat. The myelolipomas contain also hematopoietic elements.

These tumors resemble the same lesions found in the kidney; although in the liver they have not been associated with hamartomatous syndromes such as tuberous sclerosis. They also have not been known to involve lymph nodes as can the renal lesions.

The histogenesis of angiolipomas of the liver is not known; they may represent hamartomas; an intriguing hypothesis is that they arise as expansions of the sinusoidal cells of Ito which contain fat in the normal liver and which undergo hyperplasia in Vitamin A intoxication.

The prognosis for all of these lesions no matter what the proportion of the various components is benign.

REFERENCES
CIRRHOSIS OF LIVER--ALPHA-1-ANTITRYSIN DEFICIENCY

Alpha-1-antitrypsin (AAT) the major proteinase inhibitor (Pi) in the serum, is an acute phase reactant secreted by hepatocytes. In normal phenotypes, the serum concentration of AAT rises in inflammatory conditions. Homozygotes for the Z allele (PiZZ) synthesize an abnormal form of AAT which is poorly transported into the circulation and accumulates in hepatocytes. Heterozygous persons (PiMZ) have a lower basal level of AAT, but can raise the level to normal range under stimulatory conditions.

Alpha-1-antitrypsin deficiency is an autosomal hereditary disorder associated with a major reduction in serum AAT levels. Clinically, AAT deficiency is associated with emphysema in adults and neonatal liver disease. A1AT is a 52 kDa 394 amino acid single chain glycoprotein normally present in the serum at 150-350 mg/dl. The AAT protein is a member of the class of protease inhibitor proteins known as serpins. Its major function is to inhibit neutrophil elastase. AAT is a highly pleomorphic protein and at least 75 variants determined at the gene or protein level are known. These variants can be grouped as: normal, deficient, dysfunctional or absent. Variants have been grouped as Z allele (in which aggregation of AAT in hepatocytes is seen and there is deficiency in the serum levels), the S variant (in which there is no accumulation of AAT in the cells and serum levels are usually in the range of low normal; lung disease is rare), the M variant (in which there are very low serum levels of AAT and no intracellular accumulation) and the null variant in which there is no AAT present but there is no accumulation in cells and hence no liver disease, but an extraordinary risk for emphysema.

AAT is PAS positive and appears as granular intracytoplasmic material. Immunostaining for AAT is also widely used. Callea et al. studied the staining distribution in three groups of individuals who had liver biopsies: phenotypically normal patients biopsied for malignancy, patients who were homozygous and biopsied for systemic disease or tumor, and homozygous patients biopsied for liver disease. This study disclosed three main cytoplasmic staining patterns: inclusions filling the whole cytoplasm (Type I), inclusions marginated towards the cell periphery in the form of crescents along the sinusoidal border (Type II), and inclusions located in focal areas of the cytoplasm (Type III).

These authors noted that the staining pattern varied among the various phenotypes. In PiMZ individuals with normal or higher than normal AAT serum levels, positive staining was found to extend over the whole lobule. PiMZ patients with lower than normal AAT showed a lower degree of intra-lobular extension of positivity—the staining was restricted to zone 1 hepatocytes. Zone 1 hepatocytes account for the major protein synthesis. Under basal conditions, they can be considered routine AAT synthesizing cells. Under stimulatory conditions (as indicated by AAT serum elevation), an increasing number of hepatocytes is recruited to synthesize AAT. Hence zones 2 and 3 hepatocytes become involved. Since there is defective export, however, the newly recruited cells retain the Z AAT which is seen by immunostaining.
Clausen et al. studied 600 liver biopsies from normals and AAT deficient cases. They found that AAT globules $>3$ $\mu$m were seen in patients with PiZ allele (94% specific), whereas AAT globules $>1$ $\mu$m were found in 77% of PiZ patients. However, only 47% of biopsies from PiZ patients contained large globules of AAT. Hence although large globules are highly specific as a morphologic marker of the PiZ allele, their rather infrequent occurrence in carriers of the PiZ allele indicates that all investigations concerning the correlation between AAT deficiency of the PiZ type and liver disease should be based on phenotyping of sera not biopsy results.

PAS positive globules vary in size from a few $\mu$m to more than 20 $\mu$m stain bright magenta and are mainly localized to the periportal hepatocytes in biopsies with preserved architecture and near connective tissue in biopsies with destroyed architecture. Immunostaining shows intense positive staining at the periphery of the globules giving them a ring like appearance; smallest globules showed granular immunostaining. PAS positive diastase resistant globules similar to AAT globules can be found in primary biliary cirrhosis, alcoholic liver disease and large duct obstruction. Hence immunostaining is needed to define them as AAT. Occasionally AAT positive granules are seen in livers of normal phenotype persons. This is usually in alcoholic liver disease; since alcohol is known to enhance synthesis of and diminish export of hepatic proteins it may be responsible for disturbances in the secretory process of the proteins and accumulation of AAT in the cytoplasm of the liver cells.

In livers with ischemic change (centrilobular sinusoidal dilatation and centrilobular necrosis), PAS positive diastase resistant globules of pale pink color and staining negative for AAT can be found. They are either IgG or albumin.

In most biopsies from phenotypically normal patients, AAT globules are not seen. But some can be and in these the staining is diffuse and homogeneous in the cytoplasm, often with varying intensity in different cells.

Pariente et al. reported that PAS staining and even positive immunostaining for AAT in these globules cannot be taken as proof of an abnormal phenotype. Klatt et al. showed that 15% of unselected adult autopsies in which there was hepatic congestion had staining for AAT in the liver. Theaker and Fleming studied 158 liver biopsies and found no correlation between staining pattern, phenotype and serum concentrations of AAT.

The liver disease associated with AAT deficiency is less well understood than the lung disease. In persons with homozygous inheritance of the Z gene, neonatal cholestasis develops in 11%. Most of these persons recover, but in about 20% of those affected, hepatitis and cirrhosis develop. Two hypotheses have been proposed to explain the origins of the liver abnormalities: the engorgement hypothesis and the protease imbalance hypothesis. The engorgement hypothesis is based on the morphologic observation in PiSZ and PiZZ persons that there is an accumulation of AAT in the cytoplasm of hepatocytes suggesting that accumulated AAT damages the liver cells by its bulk or by some toxic effect. The protease imbalance hypothesis suggests that
the liver abnormalities result from a lack of sufficient AAT in the systemic or portal circulations or both allowing for protease to act on the cellular matrix of the liver cell thus damaging it. The fact that in null-null persons liver disease does not develop despite the absolute lack of AAT suggests that the engorgement hypothesis is correct.

Several reports indicate that not only cirrhosis but possibly also hepatocellular carcinoma is a complication of true AAT deficiency. The only treatment for liver disease in AAT deficiency is liver transplantation.

REFERENCES


ANGIOSARCOMA--CHOLANGIOCARCINOMA, LIVER

Adenocarcinoma may arise anywhere along the biliary tree. Intrahepatic adenocarcinoma, called cholangiocarcinoma, is usually a well to moderately differentiated tumor which is often difficult to distinguish from metastatic disease to the liver. These lesions arising from the small intrahepatic ducts, have been associated epidemiologically with ulcerative colitis, hepatic cysts, hepatolithiasis, Clonorchis sinensis infestation, hemochromatosis and Thorotrast. All of these predisposing situations have in common bile stasis and cholangitis. About 10% occur in cirrhotic livers.

Grossly the lesions can occur as one massive tumor or contain multiple nodules. Histologically they are fairly ordinary adenocarcinomas usually making small glands or tubules; mucin production is common. Occasional tumors show transitions to recognizable hepatocellular carcinoma. The presence of CEA in cholangiocarcinoma may be useful in differentiating it from hepatocellular carcinoma, but will not help to tell it apart from metastatic cancer. Differential immunostains for low versus higher molecular weight keratins may also be helpful.

Angiosarcoma comprises less than 0.5% of primary hepatic malignancies. It usually occurs in males and presents with abdominal pain and a mass. Known etiologic factors include Thorotrast, vinyl chloride, arsenic, and anabolic steroids; about one-fourth of hepatic angiosarcomas will be associated with one of these agents. The latent period between exposure and the development of the angiosarcoma is long, often 20 or more years. Often hepatic fibrosis or cirrhosis is present.

The lesions can involve both lobes and be multiple. The tumors are spongy and hemorrhagic. The range of differentiation of hepatic angiosarcoma is similar to angiosarcomas of soft tissue and can appear rather bland hemangioma-like, through stages of endothelial cell atypia to spindle cell sarcomas. Invasion of vessels is common.

Like angiosarcomas arising elsewhere, Factor VIII immunostaining is helpful if positive, but may show variability from block to block.

The prognosis of angiosarcoma of the liver is dismal with most patients dead of liver replacement, hemoperitoneum and/or metastases within 1-2 years.
ANGIOSARCOMA OF LIVER

ETIOLOGIC FACTORS
THOROTRAST
VINYL CHLORIDE
ANABOLIC STEROIDS
???ORAL CONTRACEPTIVES

HEPATOCELLULAR CARCINOMA

IMMUNOSTAINING FOR KERATINS
(JOHNSON ET AL 1988)

If hepatic carcinoma: Positive for CAM 5.2; negative for AE1/3
If mixed hepato-cholangiocarcinoma: Positive for both
If cholangiocarcinoma: Positive for both
If metastatic cancer: Positive for both

REFERENCES

ADENOMA, LIVER, GLYCOGEN STORAGE DISEASE

Hepatic adenomas achieved fame and fortune in the 1970s when they were described as a complication of oral contraceptive use in young females. These lesions are far more common in women than in men (about 90% occur in females). Those that occur in men are often associated with the use of anabolic steroids.

Patients with hepatic adenomas may present with abdominal pain or life threatening hemoperitoneum when these lesions rupture; some are incidental findings.

Grossly, hepatic adenomas are usually solitary masses, often subcapsular and encapsulated; they usually arise in a non-cirrhotic liver. Fibrous septa are not present in most cases. In children, where they occur in the setting of metabolic disorders as in the seminar case, they may be multiple. They vary in size from 1 to over 30 cm., with most reported in the 5 to 15 cm. range. About 10% are pedunculated.

Microscopically, the neoplasm is composed of cords of normal sized hepatocytes one to two cells thick. The cords may appear as sheets although sinusoids are present. The cells of the tumors contain clear cytoplasm due to glycogen or fat. Bile ducts and portal tracts are absent and this finding is a major clue to the diagnosis of adenoma and against focal nodular hyperplasia. Rarely is nuclear atypia found. Mitoses are not seen. Special stains can show bile production, PAS+ material which can stain as alpha-1-antitrypsin, and Mallory's hyalin. Dilated sinusoids and even peliotic areas can be present. Hemorrhage may be seen in the lesion.

The major differential diagnosis is focal nodular hyperplasia (FNH) and of course well differentiated hepatocellular carcinoma. FNH is considered a hamartoma which can be affected by, but not induced by steroid intake. Most occur in women and most are incidental findings or present as a mass lesion. Rarely, malignant hepatic lesions have been described in oral contraceptive users.

FNH is a solitary subcapsular mass which is well circumscribed but not encapsulated. Typically it contains central fibrous septa. Hemorrhage and necrosis are rare. FNH may coexist with hemangiomas and this may reflect the hamartomatous nature of both these lesions.

Microscopically the nodule is composed of one-two cell thick hepatocyte plates with sinusoids and Kupffer cells separating them. The hepatocytes resemble normal liver cells or are slightly larger. Fat or glycogen can be found within these cells. Alpha-1-antitrypsin can be present. Bile is virtually always absent. Nuclear pleomorphism and mitoses are not seen. The lesions do contain proliferating bile ducts and larger vessels usually in the fibrous scars.

The well differentiated hepatocellular carcinoma differs from the hepatic adenoma by the trabecular growth pattern, focal nuclear enlargement, intranuclear inclusions and invasion. However, on the basis of biopsy
or FNA material it may be impossible to tell these apart. Fibrolamellar carcinoma is so distinctive in its cytology, that it should not present a diagnostic problem.

The prognosis of hepatic adenoma and FNH is benign unless they rupture. Regression of these lesions after withdrawal of oral contraceptives has been documented.

Type I glycogenosis is caused by a congenital deficiency of the enzyme glucose-6-phosphatase in the liver, kidney and small intestine. Two subtypes are known, la and lb. Glycogen storage disease, type la is the more severe since there is almost complete absence of the enzyme. The clinical features of both are similar and include: hepatomegaly, fasting hypoglycemia, lactic acidosis, hyperlipidemia, and renal enlargement. Because dietary therapy can prolong life in these individuals, late complications such as the development of liver adenomas are now seen.

Coiré et al. reviewed the subject of hepatic adenomas in glycogen storage disease and up to 1987, 35 documented cases were accepted by these authors. The male:female ratio was 2:1. A few of the patients developed the complication of hemorrhage from the adenoma. Multiple lesions may be seen in this setting; they may also regress with appropriate dietary therapy for the underlying disease.

HEPATIC CARCINOMA ADENOMA: ETIOLOGIC FACTORS

ORAL CONTRACEPTIVES
ANABOLIC STEROIDS
THOROTRAST
VINYL CHLORIDE

REFERENCES

CROHN'S DISEASE OF THE APPENDIX

In the original description of Crohn's disease, it was stated that the appendix is never involved and the inflammation is limited to the small bowel. This is now known not to be true. Indeed, the appendix is involved in about 25% of cases of Crohn's of the terminal ileum. Isolated Crohn's disease of the appendix is quite rare with fewer than 100 cases recorded.

Some authors claim that if Crohn's disease is initially diagnosed in the appendix, it is likely to involve other parts of the GI tract. However, this has been questioned by recent papers.

The diagnosis of appendiceal Crohn's is made using criteria similar to those used for other GI sites. Hence, a combination of transmural inflammation, lymphoid aggregates and thickening of the appendiceal wall are seen; mucosal fissures are common as are granulomas. Less commonly one sees actual crypt abscesses, neural hyperplasia and lymphangiectasia. Ariel et al. studied 22 cases which showed these pathologic features.

Clinically, these 22 patients comprised 10 males and 12 females ranging in age from 9 to 47 (mean 24). In the majority of cases, the symptoms were of short duration: 2-3 days with fever and abdominal pain and tenderness. These patients were felt to have acute appendicitis. In a few cases, the clinical presentation suggested a periappendicular abscess with ill-defined tender masses in the RLQ. Three patients had several recurrent episodes of abdominal pain. Other systemic signs of Crohn's (arthritis, uveitis, etc.) were not seen.

Surgical findings included an enlarged appendix with a markedly thickened wall. Mesenteric nodes were large in 4 cases. In those cases considered to have periappendicular abscesses, masses of inflamed intestinal loops and omentum without pus were seen. In all cases examination intraoperatively of terminal ileum and ascending colon was negative.

Follow-up ranging from 2-15 years (mean 6) showed no recurrences. Radiologic examination in all cases was negative. Serology for Yersinia pseudotuberculosis in 20% of cases (those in which it was measured) was negative. From the literature, Ariel et al. found that of patients with initial
appendiceal Crohn's disease, only 7-9% show further involvement of the GI tract on follow-up. Ruiz et al. recently reviewed the literature again and found a 16% recurrence rate. Hence the majority of patients who present with appendiceal Crohn's do not seem to progress and this lesion may represent either a form fruste of the disorder or a mimic of some as yet uncertain etiology but which is limited to the appendix and cured by simple appendectomy.

The differential diagnosis of appendiceal Crohn's disease includes:

**Sarcoidosis.** GI sarcoid is extremely rare and usually is a manifestation of systemic sarcoid—so these patients will have chest involvement.

**Infection.** Tuberculosis, parasites, fungus and Actinomycosis can involve the appendix; however, demonstration of organisms or cultures of the tissue are needed to diagnose these entities.

**Yersinia pseudotuberculosis.** This disease rarely involves the appendix. When it is affected, the lesions affect the mucosa and submucosa with the rest of the wall being spared; this differs from the panmural pathology of Crohn's. The granulomas in Y. pseudotuberculosis infection have central necrosis and suppuration, rather than the sarcoid like granulomas in Crohn's.

**Resolved or healed appendicitis.** Even individuals with resolved periappendicular abscesses show mainly serosal chronic inflammation with granulation tissue, not granulomas. In patients whose appendiceal pathology suggests Crohn's but in whom no granulomas are found (as in the case under discussion), the rest of the features of Crohn's are present.

REFERENCES


GROUP 2: Soft Tissue/ Bone

JUVENILE FIBROMATOSIS

This lesion is the equivalent of the adult desmoid tumor. It affects children under the age of 5 and arises as a solitary mass in the skeletal muscle, or fascia. Morphologically, it ranges from primitive cellular lesions to lesions the are similar to desmoids but with somewhat greater cellularity.

The tumors are firm, poorly circumscribed and deep. The common sites are head/neck, upper arm, shoulder and thigh. The lesions infiltrate skeletal and can surround vessels and nerves. In one case which I have seen, a 7 year old boy underwent amputation of his leg because after several recurrences, the tumor had so invested his neurovascular bundle that he was left with a useless limb.

Grossly, the lesions are firm and ill-defined white masses of variable size, even reaching considerable proportions. In very young children the lesions are extremely cellular and have been called fibrosarcoma. In the older child, as in our case, these is considerably more collagen although the cells are abundant. Infiltration of muscle, fat, etc., is the rule.

The differential diagnosis is not long in these lesions; if the biopsy is from an edge or from a myxoid area, the differential with lipoblastic tumors arises. If the tumor is paucicellular, it may not be recognized for the aggressive infiltrative actor it is.

The prognosis is good in terms of the lack of metastatic potential. However, recurrences are common since the location of the tumor and its tendency to infiltrate around vital structures, like vessels etc., makes it difficult to remove with an adequate surgical margin.

REFERENCES

GLOMANGIOMYOMA

The normal glomus is a specialized arteriovenous anastomosis that acts in temperature regulation. It is composed of an afferent arteriole containing smooth muscle cells and elastica in its wall. Among the smooth muscle are glomus cells. The other end of the anastomosis is composed of thin walled veins.

Glomus tumors make up about 1-2% of soft tissue tumors, occur in both sexes with a predominance of females when the lesion is found in the most common site, the subungual area. The lesion clinically appears as small blue-red nodules, and is relatively small (most <1 cm.); exquisite pain is a classic symptom in the usual subungual locations, most commonly the finger.

Three types of tumors related to the glomus are recognized: classic glomus tumor; glomangioma, and glomangiomyoma, as in the seminar case. The differences among these revolve around site, size and relative degree of glomus cells, vessels and smooth muscle. The glomangioma and glomangiomyoma tend to be larger tumors and can occur in areas of the extremity away from the digits, as well as on the trunk.

The classic glomus tumor consists of capillary vessels surrounded by collars of glomus cells in a myxoid or hyalinized stroma. The tumors can resemble hemangiopericytoma if excessively vascular or, if epithelial structures predominate, paraganglioma.

The glomus cell is round and has a round nucleus and abundant eosinophilic cytoplasm. Occasionally, presumably as a degenerative change, atypical nuclei can be found.

Glomangiomas are less well circumscribed and resemble cavernous hemangiomas. They are composed of gaping vessels with glomus cell clusters in their wall.

Glomangiomyomas about 10% of the total in the AFIP files, are identical to the above except they gradually change into smooth muscle cells of readily recognizable type. This is best seen in the area of large vessels where the edges of the vessel blend with the tumor.

The nature of the glomus cell has elicited debate. Originally considered related to the pericyte, EM studies suggest more resemblance to smooth muscle. Many immunostudies claim lack of desmin immunoreactivity; however, in our own laboratory, Dr. Jack Brooks has studied a few examples in which desmin was present.

The biologic behavior of all of these lesions is benign; rare recurrences of incompletely excised lesions are reported.
REFERENCES

OSTEOSARCOMA WITH PATHOLOGIC FRACTURE, FEMUR

Osteosarcoma is a malignant neoplasm the cells of which have the capacity to produce osteoid. Most osteosarcomas arise in the appendicular skeleton of young individuals; these have been classified as conventional osteosarcomas. Some less common types of osteosarcoma include those arising in the setting of Paget's disease, post-radiation, or following bone infarcts—all of which may occur in non-long bones and in older age groups.

Parosteal and periosteal osteosarcomas are associated with a more favorable outcome and should be differentiated clinically and radiologically.

Conventional osteosarcoma is generally a disease of adolescents and young adults, more commonly seen in males. The lesions usually arise in the metaphysis of a long bone with the femur being most affected. Often the presenting complaint is a painful swelling or trauma may lead to the discovery of the tumor.

X-rays show a mass lesion which may or may not show calcification depending on the degree of bone produced by the tumor. Bone destruction is obvious and often soft tissue extension will be found. Grossly the tumor is a bulky mass destroying the involved bone and extending into soft tissues.

Microscopically, the lesions are very variable but obviously malignant. Bone formation may be seen in many areas or just focally. The tumors range from having an almost epithelioid appearance to spindle cell sarcomas. Mitoses are easily found and giant cells both benign (osteoclastic) and malignant are seen. Three major subtypes of conventional osteosarcoma are recognized: osteoblastic in which the production of osteoid is abundant, often with calcification; chondroblastic; and fibroblastic.

Recent progress in the treatment protocols for osteosarcoma have raised the outlook for survival and have spared limbs in the process.
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SYNOVIAL SARCOMA, ABDOMEN

Synovial sarcoma occurs primarily in the paraarticular regions, usually associated with tendons, bursae or joint capsules; it is very rarely found in the joint space. Rare locations for this lesion including the parapharyngeal space and the abdominal wall as in the present case, are devoid of relationships to joints.

Controversy exists as to its name since by ultrastructural analysis the cells of this tumor bare no resemblance to cells of the normal synovium. It has been suggested that the term "carcinosarcoma" or "carcinoma of soft tissues" be substituted. However, since synovial sarcoma is so well engrained in the literature it seems we must stick with it no matter what the actual histogenetic make up of the tumor.

Synovial sarcoma is a rare lesion, comprising between 6 and 10% of sarcomas. Four types are recognized: classic biphasic, monophasic spindled, monophasic epithelial, and poorly differentiated.

This sarcoma is a tumor which affects young individuals, with the median age of 26 years. These tumors tend to arise in the extremities especially around the knee; about 8-9% occur in the head and neck and about 2-3% in the abdominal wall. Most patients complain of a mass and many are associated with pain; trauma may bring the mass to attention.

Grossly the lesions may be circumscribed and some are cystic. Most are attached to tendons or joint capsules. Calcification is common and is a
helpful hint on X-ray as to the diagnosis. In the abdominal wall as in our case, the tumors are deep seated and usually in the lower abdomen.

Classic biphasic synovial sarcoma is composed of epithelial cells in glands, cords, clefts or nests containing cells which are large round and have abundant cytoplasm; nuclei are vesicular. Some examples contain papillary foci or squamous cells giving the impression of carcinoma. The epithelial component is, however, surrounded by a spindle cell element with uniform cells resembling fibrosarcoma. The vascular pattern in the stroma often resembles hemangiopericytoma. Mitoses are usually readily found in both components. The stromal component varies from cellular to paucicellular with myxoid or pale areas. Calcification is found microscopically in 30% of synovial sarcomas.

In monophasic spindle cell type, the stroma is similar to the above, but the glandular or epithelial nests are not seen. Immunostaining for keratin will often show these latter, however. EM studies of some of these lesions show intercellular spaces with pseudopodia.

Monophasic epithelial type is difficult to diagnose and can be impossible to distinguish from carcinoma either metastatic or of adnexal origin; careful search of many sections may show foci of stroma which will aid in this diagnosis.

Poorly differentiated synovial sarcoma are rare (20% of AFIP series) and can be recognized only if associated with more easily recognized variants or if keratin is found in the tumor. The stroma resembling hemangiopericytoma is helpful.

Special staining helps also since the epithelial cells and the intraglandular secretions stain with mucicarmine or PAS stains. The mucin is diastase and hyaluronidase resistant. Stromal mucin is hyaluronidase sensitive and stains with colloidal iron and alcian blue. Reticulin stains are helpful to define the nests of epithelial components. Immunostaining has been a boon in the diagnosis of this sarcoma. Cytokeratin and EMA staining is seen in many examples and is virtually diagnostic in the monophasic spindle variant.

Ultrastructural studies of the classic type show both elements and transitions between them. Tonofilaments can be found in the epithelial cells. In the spindle monophasic type, the cells resemble the stromal component of the classic type with intercellular cleft-like spaces and microvilli, and desmosomes like junctions.

Differential diagnoses include: for classic variants: epithelioid sarcoma, clear cell sarcoma (melanoma of soft parts), and carcinoma and fibrosarcoma for the monophasic variants.

The outlook for synovial sarcoma is poor, but in modern times with adjuvant chemotherapy, prolongation of survival seems possible. Since late recurrence and metastases is not rare, cure rates are difficult to define. Better prognosis is seen with the heavily calcified tumors, in younger
patients, in tumors under 5 cm., and in tumors located more distally on the extremities; and worse prognosis if mitotic count is high.

Ghadially has furiously discussed the inappropriateness of the name synovial sarcoma since normal synovium does not stain for keratins or EMA and by EM contains neither microvilli, filapodia or desmosome like junctions. He prefers "carcinosarcoma of soft parts".

REFERENCES

ANGIOSARCOMA, POSTRADIATION

This is an unusual tumor is an unusual clinical setting. It represents an angiosarcoma which arose in the abdominal wall sixteen years following radiation to the abdomen for an ovarian epithelial tumor. The problems we had with the diagnosis revolved around the fact that we really never got to sample the primary extensively, since all we had of the abdominal wall was a skin scar, which contained a very small focus of the tumor. Indeed, the surgeon did, however, state that the lower abdominal wall was quite thickened, a finding he attributed to radiation.

The patient had chylous ascites and chylous pleural effusions and whether this lesion should be considered an angiosarcoma or a lymphangiosarcoma is still opened to debate. The follow-up in this case indicates that despite aggressive sarcoma chemotherapy, including Adriamycin, the patient died of uncontrollable disease in the chest and abdomen 9 months after the diagnosis was made.

Angiosarcoma are rare soft tissue tumors, probably less than 1% of soft tissue sarcomas. They usually arise in superficial soft tissues or skin, especially in the head/neck area, the breast, and the liver and spleen. In the latter location, epidemiologic studies have shown an inordinate number of such lesions are related to either Thorotrast or vinyl chloride exposure. The Stewart-Treves lesion (postmastectomy lymphangiosarcoma) belongs in the group of angiosarcomas which can be seen after radiation.

The etiologic factors related to angiosarcoma appear to be radiation, Thorotrast, vinyl chloride, and chronic lymphedema. Thus angiosarcomas arise in the postmastectomy site as a result of lymphedema with or without radiation; they can also occur in congenitally lymphedematous limbs.

The postradiation lesions have been reported to occur in the chest wall (post breast removal) or in the abdomen (following radiation for cancer of the cervix, endometrium, ovary and Hodgkin's disease). Usually there is a long latent period (average 12 years).

In the relatively common site of the head and neck, the lesions usually occur in elderly individuals who complain of a spreading bruise. The lesions may be multifocal or certainly there are skip areas and it is often difficult to determine the extent of the lesion. We have seen two cases in which the surgeons have biopsied at least 12-16 margins of the lesion which were grossly free of disease before performing the definitive resection; despite the fact that the biopsies in these cases failed to show tumor, the definitive resection specimens in both cases had tumor extending to resection margins.

Microscopically the tumors range from hemangioma-like lesions to spindle cell sarcomas. Variable areas can be seen in the same tumor and point up the need for extensive sampling. The vessels in the better differentiated tumors dissect through connective tissue, interanastomose with each other and are lined by plump and atypical endothelial cells. In some examples, and this is where the diagnosis is easy, there are tufts of tumor cells jutting into the neoplastic channels.
EM findings reflect the degree of differentiation of the tumor and can recapitulate the EM of normal endothelial cells, with Weibel-Palade bodies, tight intercellular junctions and pinocytic vesicles. However, not all angiosarcomas read the book and many show none of the diagnostic changes at the ultrastructural level.

Immunostaining results are also variable; Factor VIII will stain some of the tumors, or some parts of some tumors. Ulex lectins have a little better track record, but these are not specific and can stain carcinomas which, in the skin, can cause problems in differential diagnosis.

The recent finding of keratin immunostaining (aberrant expression) in angiosarcomas as well as in other benign and even reactive endothelial proliferations only adds to the confusion.

The prognosis for angiosarcoma is dismal; some studies of breast lesions have shown the well differentiated ones may have prolonged survival and that chemotherapy may help. Further studies are needed, however, in these tumors.

### ANGIOSARCOMA: ETIOLOGY

**LYMPHEDEMA**
- POSTMASTECTOMY
- CONGENITAL
- TRAUMATIC

**RADIATION**
- WITHIN FIELD
- LONG LATENCY
- NO CHRONIC EDEMA
- AFTER RT FOR CANCER OF CERVIX, ENDOMETRIUM, OVARY, BREAST
- LOCATION: CHEST WALL, LOWER ABDOMEN

**ENVIRONMENTAL**
- THOROTRAST
- VINYL CHLORIDE
- STEROIDS

### REFERENCES


GLIOSARCOMA

Mixed or combined tumors of the nervous system and elsewhere can be classified into three types:

a) Collision tumors—wherein independent primary tumors are apposed to one another and the only intermingling is at the junction;

b) Composite tumors in which there is concurrent participation of both parenchyma and stroma in the neoplastic process; and

c) Dependent tumors in which secondary neoplastic change occurs in the stroma and/or adjacent host tissue.

Some cases of glioblastoma are mixed with spindle cell areas having a sarcomatous appearance. These tumors have been designated as gliosarcomas. It has been hypothesized that the sarcomatous elements, which can be negative for GFAP and Factor VIII, arise from the proliferating endothelial cells or fibroblasts of the stroma. An alternative explanation is that they represent glioblastomas with focal sarcomatoid transformation. An even more striking development is the presence in some glioblastomas and gliosarcomas of keratin positive areas with gland like appearance which perhaps represent an extreme form of glial metaplasia. Gliosarcomas are associated with an increased incidence of extracranial metastases.

In another tumor designated as sarcoglioma, the sarcomatous element, which is centrally located, is supposed to be the primary event; the glial malignant component is postulated to arise on the basis of the reactive glial proliferation that is frequently seen around the sarcoma. As Dr. Rosai states in his book, "These proposals are highly imaginative and backed by considerable authority. Yet it seems that an alternative explanation (i.e., that the tumors represent gliomas with an undifferentiated sarcomatoid component) is just as likely". Naturally, these considerations do not apply to collision tumors in which two separate and distinct primary neoplasms such as meningioma and glioma are found close to each other or even sharing a common side.

Some neuropathologists consider that the sarcomatous components represent a reactive change in the meninges overlying an invasive highly malignant glial tumor. Of course this cannot explain those lesions in which the stromal sarcomatous areas do not abut the meninges.

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GLIOMA WITH PNET

The PNET (primitive neuroectodermal tumors) concept is that a germinal neuroepithelial cell, regardless of its location in the brain, spinal cord, or peripheral soft tissue, has the potential to differentiate along a number of specific neural and even mesenchymal lines. If one accepts this hypothesis, a variety of tumor types either in the central or peripheral tissues can seem to be related at least morphologically. Thus the central PNETs include classic medulloblastoma and all its variants, cerebral neuroblastoma, ependymoblastoma, pinealoblastoma, olfactory neuroblastoma, retinoblastoma; the peripheral system includes classic neuroblastoma and all its variants, Askin's tumor, melanotic progonoma, ectomesenchymoma, and peripheral neuroectodermal tumor. In addition, germ cell or teratoma derived tumors of similar histology can be grouped into PNETs.

What do these tumors share? By light and electron microscopy, these tumors are composed of monotonous small dark cells with or without rosette and pseudorosette formation; by EM, they contain neurosecretory granules, microtubules and complex interdigitating cytoplasmic processes. Immunostaining has given some equivocal results: NSE is found in these lesions; some contain neurofilament as well. More specific markers are needed to define the more subtle interrelationships among these tumors. Similarly studies of GFAP in the central PNETs have been difficult to interpret; most of the positive results are probably related to invasion of nearby structures and false positivity due to "pick-up" of antigen by the PNET cells. However, a number of reports imply that glial differentiation in central PNETs can and does occur.

All PNETs studied have contained synaptophysin, most contain desmoplakin, vimentin and in frozen tissue GFAP; most also contain various epitopes of neurofilaments. The consistent expression of synaptophysin and neuropeptides by CNS PNETs indicates that they share very significant neuroendocrine markers similar to peripheral neuroendocrine neoplasms (neuroblastoma, pheochromocytoma). However, their cytoskeletal protein construct is different from the peripheral tumors. The cytoskeletal profile of central PNETs differs from gliomas and meningiomas since none the latter express synaptophysin. The immunophenotyping studies on central PNETs have shown their diversity, but also their homology--they have neuroendocrine differentiation.
REFERENCES


POLYMORPHOUS LOW-GRADE ADENOCARCINOMA OF MINOR SALIVARY GLANDS

Some salivary gland neoplasms do not fit into the commonly accepted categories of pleomorphic adenoma, monomorphic adenoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, MMT, or acinic cell carcinoma. The term "adenocarcinoma, NOS" has been used as a wastebasket category for such lesions; this approach, however, produces little data on the epidemiology, morphology or prognosis of such lesions.

In 1984, Evans and Batsakis examined a large number of adenocarcinomas, NOS of salivary gland origin and identified an important variant—the polymorphous low-grade adenocarcinoma (PLGA). This lesion had been previously reported as "lobular carcinoma" by Freedman and Lumerman in the oral pathology literature and by Batsakis et al. as "terminal duct carcinoma."

Although not completely accepted by all, the most widely used term for this subset of lesions is PLGA. Several variants have been described—trabecular, tubular, solid, papillary and cribriform growth patterns can be seen as can admixtures, supporting the view that they can all be lumped under the PLGA umbrella, since they appear to share a common histogenesis and an indolent biological behavior.

About 100 cases of polymorphous low-grade adenocarcinoma involving minor salivary glands have been reported, with over 50% occurring in the palate (other areas of origin include in decreasing order of frequency—
buccal mucosa, retromolar area, lip and tongue). The female: male ratio is 1.5:1; age range is 23-79 (mean 60-70). Swelling is the most common symptom. Because of their location, the lesions tend to be relatively small when discovered.

Microscopically, the polymorphous low-grade adenocarcinoma is composed of nests often in lobulated pattern of cytologically small, bland cells with oval nuclei and inconspicuous nucleoli. The cytoplasm is scanty, eosinophilic or clear. Mitoses are rare. The malignant nature of this epithelial proliferation is noted by the presence of infiltrative edges, although the tumor may be grossly circumscribed. Invasion of salivary gland, muscle, fat, bone and even overlying squamous mucosa with ulceration may be seen. These tumors invade avidly perineural spaces.

The individual tumor units may be arranged in cords, tubules, streaming columns or cribriform nests. In areas, the stroma may be hyalinized or mucinous, but no cartilage is seen. Concentric growth is common especially around nerves. In some examples, cysts form with intracystic papillae seen.

Prognosis is good with recurrence in 10-15% (not all have had initial adequate margins of resection); metastases are rare and so far have been seen only to regional lymph nodes. It is suggested from the available data that the papillary subvariant may be somewhat more ominous. Very rare deaths have been reported due to tumor and these have involved locally uncontrollable (CNS) extension. However, the complete story may require longer follow-up of larger numbers of cases.

The differential diagnosis includes chiefly mixed tumors and adenoid cystic carcinoma. Although pleomorphic adenomas may contain lobulated surface growths, these are rounded and not invasive: also, cartilage in the stroma is not seen in polymorphous low-grade adenocarcinoma. Adenoid cystic carcinoma is much more difficult to differentiate especially in small biopsies; the adenoid cystic carcinoma tends to show more cribriform and solid patterns and more obvious perineural growth. Although some authors have postulated that the polymorphous low-grade adenocarcinoma is a low-grade adenoid cystic carcinoma, the PLGA does not contain the basaloid cells seen in adenoid cystic carcinoma; the latter also has a more prominent stroma and basement membrane "cylinders." On biopsy it may, however, be impossible to distinguish these lesions.

REFERENCES


THYMIC CARCINOMA

The term "malignant thymoma" is a poor one since it has been used to describe three different entities of thymic neoplasm. The problem of assessing malignancy in thymomas is quite a real one. However, the terms used are often not benign or malignant, but benign, and invasive (both microscopically and grossly); rarely, metastasizing thymomas are termed malignant.

Rare carcinomas of many types (most often squamous cell carcinoma) arise from the thymic epithelium; these should be termed thymic carcinomas. (Of course, there are malignant germ cell tumors and lymphomas which arise in the thymus, but these are self explanatory with regard to their biological potential.)

Thymic carcinoma is the diagnosis for the case under discussion today. Most neoplasms arising from thymic epithelium are well circumscribed, encapsulated and so not invade surrounding structures. Microscopically, they are composed of a combination in varying proportions of cytologically benign epithelial cells and nonneoplastic lymphocytes. When thymic epithelium in these lesions is cytologically malignant, the term "thymic carcinoma" appropriate.

Such tumors are very rare. In a recent series, Truong et al. accepted 62 previously reported cases and added 13 more. Most cases occurred in adults (age range: 4-81) and most (all but one) presented with signs of a mediastinal mass. Only three of the previously reported cases has had an associated paraneoplastic syndrome. At surgery, invasion of surrounding structures was common, but in some patients, the lesions appeared encapsulated and could be "shelled out."

Grossly, the tumors are often large 6 cm. or larger. Fibrotic areas and necrosis can be seen in these lobulated tan-white lesions.

The histologic subtypes of thymic carcinoma are listed in the table below. Characteristically, the features of usual thymoma are absent, especially lymphocytic admixture, perivascular lakes and medullary differentiation. In thymic carcinoma, mitoses are easily found, as is necrosis and cyto-
logic pleomorphism. In some reported cases, transition from usual lymphoepithelial thymoma to thymic carcinoma has been documented.

Individual cases of mucoepidermoid and adenosquamous carcinoma of the thymus have been recorded. The adenosquamous tumor shows a poorly differentiated squamous cancer with lymphoepithelial pattern and areas of poorly formed glands containing mucin.

The immunohistochemical profile is as expected with the presence of keratin easily demonstrable in these epithelial tumors.

The differential diagnosis is with metastases to the mediastinum from lung or other primary site (clear cell lesions deserve to have the benefit of ruling out a primary renal lesion, before being accepted as of thymic origin), neuroendocrine cancers from a variety of sites, lymphoma, and germ cell tumors. The last two are usually not too problematical; to bolster the diagnosis of thymic carcinoma in the first two instances, the important points are that (a) the lesion is truly thymus-based and not a mass of matted mediastinal nodes, and (b) transitions from thymic epithelium or usual thymoma to the cancers if documented are very strong evidence for thymus as the primary site.

The prognosis for thymic carcinoma is poor even with postoperative radiation therapy; often the lesion is incompletely resected and recurrence and spread is not rare. Those patients who have survived this type of lesions tend to have grossly encapsulated tumors, and usually of pure squamous histology.

**THYMIC CARCINOMA**

*(TRUONG ET AL. 1990–75 CASES TOTAL)*

<table>
<thead>
<tr>
<th>Type</th>
<th>Cases</th>
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<td>Squamous cell carcinoma</td>
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<tr>
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<td>14</td>
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<tr>
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<tr>
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<tr>
<td>Mucoepidermoid</td>
<td>1</td>
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<tr>
<td>Adenosquamous</td>
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</tbody>
</table>
COWDEN'S DISEASE, THYROID

Cowden's disease or multiple hamartoma syndrome is an autosomally inherited disorder consisting of ectodermal, mesodermal and endodermal hamartomatous lesions. Manifesting initially in young adult life (2nd-3rd decades).

The disorder is characterized by mucocutaneous lesions of trichilemmomas, acral keratosis and oral papilloma.

In the GI tract, polyposis can occur. The large bowel, mainly the distal part, is affected most. These polyps have been variously considered hyperplastic, hamartomatous or inflammatory. They are composed of slightly elongated crypts, fibrotic lamina propria and disorganized and hypertrophic smooth muscle. In the stomach, the polyps show foveolar hyperplasia and cystically dilated glands. In the esophagus, simple papillomatous lesions can occur. No malignant change is known to occur.

Benign and malignant breast tumors are common; bilateral breast cancers are reported (estimated to occur in 50% of affected women).

Goiter and thyroid adenomas occur in a large number of patients, especially women; some of these have been malignant tumors.

The pathogenesis of the initial events in the formation of nodules in the thyroid has elicited much interest; numerous studies utilizing a variety of techniques have been reported. Investigators working in non-endemic
goiter regions have postulated autoimmune mechanisms for the origin of nodules.

Certain follicular cells or groups thereof are intrinsically more rapidly growing than their neighbors. The initial proliferation is a polyclonal one involving one or more likely a group of follicles. These proliferate, while adjacent follicles remain quiescent. Interfollicular stroma and the vessels contained therein participate in the process and vascular compression leads to focal ischemia, necrosis and inflammatory and reparative changes. At later times, the same process may affect another group of follicles until large zones of the thyroid are affected. As the process continues the secondary phenomena so characteristic of longstanding nodular goiter take place: follicular destruction, hemorrhage, fibrosis, hemosiderosis, calcification, and even ossification. The associated follicular distortion by fibrous tissue may lead to diagnostic interpretative problems and be misinterpreted as invasion by follicular structures—hence a misdiagnosis of follicular carcinoma may be rendered.

While these changes occur, the hormonal stimuli to the gland continue. However, with distortion of vascular supply as well as the presence of dilated follicles filled with colloid (colloid lakes as it were), the distribution of iodide and thyrotropin becomes uneven. Hence some portion of the gland will "see" excess thyrotropin and focal hyperplasia may occur; other areas will have relative iodide and/or thyrotropin deficiency leading to zones of atrophy or inactivity. It seems that once the process begins, it is self-perpetuating. The question still of interest and still unanswered is why does it begin?

Adenomas are solitary; if there are multiple nodules in a lobe or a thyroid gland, it is probably more appropriate to diagnose multinodular goiter with adenomatous change (adenomatous hyperplasia) and call attention to the discrete nodules in that way. The features used to distinguish histologically between adenoma and adenomatous nodules include: solitary versus multiple nodules; encapsulation versus merely circumscription; uniformity of pattern within the adenoma and divergence from surrounding thyroid; and compression of the surrounding gland by the adenoma and its capsule.

Follicular carcinomas require the finding of invasion (vascular, capsular, both) to make the diagnosis.

REFERENCES

Group 4: Lymphoid lesions

UTERINE LEIOMYOMA WITH LYMPHOID INFILTRATION

Uterine leiomyomas are extremely common neoplasms. The myriad morphologic patterns these tumors can assume have been described extensively in the literature. However, only rare examples of uterine leiomyomas with extensive lymphoid infiltration are reported. I believe that the seminar case is an example of such a lesion.

Significant yet benign lymphoid infiltration involving the uterus is found most often in the cervix and less commonly in the endometrium; such extensive lesions have been diagnosed as lymphoma-like lesions. In the current case which is identical to the seven tumors reported by Ferry et al. as "uterine leiomyomas with lymphoid infiltration simulating lymphoma", the lymphoid infiltrate is confined to the leiomyoma.

Of the seven cases previously described the age range was 35-50 years (mean 41 years); the parity was known in 5 cases--two were gravida 3, and three had had 4 pregnancies each. In many of the patients, abnormal uterine bleeding led to hysterectomy; in one case, pain was the complaint; and one other woman was apparently asymptomatic.

Pathologically, the tumors ranged from 2 to 12 cm. in size and were described as looking like ordinary fibroids. In 3 of the 7 woman reported by Ferry et al., other leiomyomas were present in the uterus. Histologically, the lesions were composed of well circumscribed smooth muscle tumors extensively infiltrated by small lymphocytes. Occasionally, large lymphoid cells were seen; plasma cells were also present although not in large numbers. Poorly developed germinal centers with macrophages were seen in two examples; better developed germinal centers were seen in one case.

The abutting myometrium did not contain lymphoid infiltration; in fact, the lymphocytic infiltration ended abruptly at the junction of the leiomyoma with the surrounding myometrium.

Immunohistologically, desmin is found in the underlying smooth muscle tumor; in some prominent sclerosis has been noted. Lymphocyte markers showed a polyclonal population in every case studied (some lymphocytes stained as B cells ((L26)); others as T cells ((UCHL 1))).

Follow-up data on all patients reported has been benign; even one patient who only had removal of the tumor and went on to a successful pregnancy was well.

The obvious differential diagnosis of this lesion is with malignant lymphoma. Although malignant lymphoma presenting in the Gyn tract is rare, it can occur and can be localized to this site--i.e., an extranodal lym-
phoma. Most lymphomas involving the uterus, however, do not have the gross appearance of leiomyomas, but are bulky soft, fleshy masses with necrotic foci. Microscopically, most uterine lymphomas are of the large cell subtypes and would not contain germinal centers or admixed plasma cells. In addition, the demonstration of mixed T and B cells in the population of lymphocytes would argue against a neoplastic lymphoid process. Lastly, true malignant lymphoma would not be confined to the smooth muscle tumor as is the case with the benign process.

The cause of lymphoid infiltration of the leiomyomas is unknown. Whether it is a reflection of a viral infection, an autoimmune phenomenon or an unknown insult is not clear. The endometrium in those cases in which it has been sampled has failed to show evidence of chronic endometritis; no specific inflammatory disorder has been uniformly found in the cases studied so far.

REFERENCES


INFLAMMATORY PSEUDOTUMOR OF LYMPH NODE

The term "inflammatory pseudotumor" has been applied to lesions of similar morphology which can affect a variety of organs. These include lung, orbit, gastrointestinal tract, soft tissues, spleen and lymph node.

The lesions present as masses, and appear neoplastic on gross inspection. Clinically, they may be asymptomatic, or, if large, may present as a result of mass effects; in the lung, associated pneumonia may be the initial clinical event, if the lesion is within or enwraps a bronchus.

Histologically, these masses resemble granulation tissue with fibrosis, eosinophilia, and lymphoid hyperplasia. Focal necrosis, granulomatous foci and macrophages even with cholesterol clefts can be seen. In certain organs, plasma cells are particularly prominent—the pseudotumor of the lung.
is the best example of this. In lesions of the stomach, eosinophils are often numerous (Vaneck tumor).

The differential diagnosis of inflammatory pseudotumor depends on the organ involved and the predominant histologic pattern or cell type (eosinophils, fibrosis, granulomas, plasma cells, lymphocytes), but includes a number of lesions both benign and malignant: infections (fungi, parasites), malignant lymphoma, hamartoma (Castleman's disease of nodes, splenic hamartoma), Hodgkin's disease, and inflammatory malignant fibrous histiocytoma.

The absence of monomorphous cell infiltrate or mitoses and the vascularity and pleomorphic nature of the cellular composition of the lesion strongly suggests a nonneoplastic lesion on histologic examination.

The cause of inflammatory pseudotumor is unknown; it has been postulated that it represents an unusual host response to either an infectious agent (none has ever been found) or a vascular or traumatic event. In the stomach, the association of the inflammatory pseudotumor with overlying ulceration of the mucosa has suggested that the mass lesion is a reaction to the ulcer. However, in my view, it is just as likely that the ulcer is secondary to the expansile "growth" of the underlying mass.

In order to address the particular diagnostic and etiologic problems associated with inflammatory pseudotumor of lymph nodes, some rather recent studies may shed some light on the process. Five cases of lymph node inflammatory pseudotumor were evaluated by Facchetti et al.. The patients are usually young individuals with enlarged lymph node(s); some have been superficial nodes, others retroperitoneal. The clinical impression is usually that of malignant lymphoma.

Histologically, the changes are found predominantly in the hilum, and the capsule of the node rather than in the lymphoid parenchyma. In these areas, there is a highly cellular spindle cell proliferation which alternates with paucicellular fibrous zones. Admixed with the spindle cells are inflammatory cells including macrophages, plasma cells, lymphocytes and some neutrophils. Another prominent feature is the vascular proliferation composed of vessels with flat endothelium; microthrombi can be seen in some of these vessels. Larger vessels trapped in the proliferation can show destruction of their walls by the inflammatory pseudotumor. The lymphoid parenchyma shows nonspecific reactive changes.

Immunohistologically, the spindle cells contain vimentin and macrophage markers; a few also contain actin and rarely desmin. The plasma cells and lymphocytes stain as polyclonal families of cells. The vascular endothelium shows appropriate staining for Ulex and Factor VIII. These results are helpful in deciding that one is dealing with an inflammatory pseudotumor rather than a spindle cell sarcoma involving a node. Sarcomas of dendritic cells retain the staining characteristics of the presumed normal counterpart--S100, CD 35--the inflammatory pseudotumor cells are negative for these markers. Kaposi's sarcoma immunostaining remains controversial, although most authors conclude that the spindle cells in KS lesions do stain for endothe-
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Spindle cell markers—the spindle cells in the inflammatory pseudotumor do not; in fact, the cells in inflammatory pseudotumor that do stain as endothelial clearly are associated with vessels and are different from the spindle cells. Malignant fibrous histiocytoma immunostaining is also controversial, but most authors agree that these malignant tumors do not show staining for macrophage markers in the spindled neoplastic cells. The recently described intranodal hemorrhagic spindle cell tumor shows myoid differentiation by immunohistochemistry (and ultrastructure) which the inflammatory pseudotumor does not.

Although these studies do not shed light on the histogenesis of the inflammatory pseudotumor, Facchetti et al. speculate that the central problem affects the macrophages which become activated and release cytokines. These in turn can lead to the proliferation of the various elements which comprise the inflammatory pseudotumor. Hence, IL-1 and TNF-alpha can produce vascular proliferation; both these macrophage products can be mitogenic for fibroblasts perhaps leading to the spindle cell proliferation. Stimulation of macrophages, fibroblasts and endothelial cells by IL-1 can lead to release of IL-6 by these cells; the latter factor is stimulatory to B lymphocytes, thus explaining the presence of lymphocytes and plasma cells in the process. These are speculations only since immunohistochemical studies have not been able to demonstrate these cytokines in inflammatory pseudotumor; more involved techniques of extraction or search by in situ hybridization may be needed to detect these factors in these lesions.

REFERENCES

DENDRITIC RETICULUM CELL SARCOMA

Dendritic reticulum cells are found normally as a meshwork in lymphoid follicles in human lymph nodes. It was originally believed that these cells were prominent in the light zones of reactive follicles in reactive hyperplasias. Studies with antibodies directed against these cells have, however, shown that they do not have a homogeneous distribution in reactive nodes. The antigenic staining patterns of these cells has shown that they are Leu 6 positive and are related to Langerhan's cells in the skin. Indeed, they appear increased in nodes with dermatopathia.

In 1986, Monda et al. described 4 cases of lymph node based malignancies which were postulated to arise from the dendritic reticulum cells. These tumors occurred in adults who presented with cervical lymphadenopathy. No other adenopathy, organomegaly or laboratory abnormalities were found at initial presentation in these patients. Histologically, the node architecture was effaced partially or completely by a proliferation of oval to spindle cells arranged in whorls and occasionally storiforming. In some areas there was a resemblance to dermatofibrosarcoma protuberans.

Some of the nodes were completely replaced and in those which were only partially involved the rest of the node appeared normal or hyperplastic. Mature benign lymphocytes were always found admixed with the tumor cells.

The tumor cells contained oval or spindled nuclei with inconspicuous nucleoli. Mitoses were rare. The cells contained moderate amounts of cytoplasm, and indistinct cell borders. Polykaryons were seen. Necrosis was absent. The peripheral sinuses were obliterated and the tumor sometimes extended into perinodal fat.

Special stains showed that the tumor cells were mucicarmine and PAS negative, positive results were found for LCA, the defined dendritic reticulum cell antigen (R4/23) and C3b complement receptor.

By electron microscopy, the tumor cells showed plump, smooth nuclei, scant organelles and the presence of complex, long undulating cytoplasmic extensions. These interconnected the cells through cell junctions of the adherens type. There were neither secretory granules, tonofilaments, basal lamina nor Weibel-Palade bodies.

The differential diagnosis on the light microscopy is with metastatic carcinoma, melanoma, MFH, and malignant lymphoma. The EM and immunostudies basically rule these out.

The follow-up in the initial cases was one of progression to a more aggressive appearance in subsequent biopsies; it is believed that they represent rare node based malignancies.

Four types of reticulum cells have been described in normal lymph nodes; dendritic, interdigitating, histiocytic and fibroblastic.
The dendritic reticulum cell found in the light zone and mantles of follicles in nodes have long branching cell processes by EM, and form a meshwork on which B-cells rest. These membranes contain Fc and complement receptors which enable the dendritic reticulum cells to trap antigen-antibody complexes; they may then present antigen to B cells during development of the immune response.

The interdigitating reticulum cells reside in the T cell areas (paracortex) of nodes, resemble Langerhan's cells, are positive for S100; their function is unclear. Tumors of presumed interdigitating cell origin have been described.

Histiocytic reticulum cells are the tingible body macrophages in the center of germinal centers. They are phagocytes. The fibroblastic reticulum cells comprise much of the framework of the node.

The cases of van der Valk et al. have been considered by subsequent authors to represent malignant lymphomas. These cases did not show the characteristic spindle cell growth so common in the "reticulum cell sarcomas." The current case, based on the morphology and ultrastructure and absence of lymphocyte characteristics, is considered a dendritic reticulum cell sarcoma.

REFERENCES


T-CELL MALIGNANT LYMPHOMA IN WISKOTT-ALDRICH SYNDROME

The node pathology of patients with Wiskott-Aldrich syndrome, a congenital immunodeficiency has been described by Snover et al. The nodes show depletion of T cell (paracortical) areas and the presence of germinal centers, i.e. B-cell areas are relatively preserved. Recurrent infections stimulate B-cells which in the absence of suppressor T cells can proliferate. Abnormal and increased numbers of plasma cells can be seen. In some patients, abnormal lymphoid proliferations occur and some of these are indeed clonal malignant lymphomas. In the past, the lymphomas arising in the setting of Wiskott-Aldrich immunodeficiency have been of B cell lineage.

Our case is apparently unique in that the lymphoma in the mediastinum and spleen typed as a T cell lymphoma. In addition, the lymph node biopsy in this patient, which did not contain the lymphoma, showed evidence of Kaposi’s sarcoma.

T cell malignant lymphomas are unusual lesions and come in a great variety of patterns; they certainly do not morphologically easily fit into any easily learnable scheme as do the B cell lesions (although, as time goes by, I sincerely believe these become more and more difficult to recognize too!).

T cell neoplasms can be marrow based--T cell CLL, acute lymphoblastic leukemia-lymphoma; or skin based--mycosis fungoides and relatives, and, of course, node based as in the present case. In the last category we have T-zone lymphoma, peripheral T cell lymphoma, T immunoblastic sarcoma, pleomorphic T cell lymphoma, T cell lymphoma with multilobated cells, T cell lymphoma with hypercalcemia (HIV-1 associated), Lennert’s lymphoma (T cell lymphoma with high content of epithelioid histiocytes), etc. In general, T cell lymphomas cannot be distinguished strictly on morphologic grounds without immunophenotyping and/or genetic studies. However, by light microscopy T cell derivation can be suspected if a lymphoma shows complex, irregular nuclei, giant forms and pleomorphism. Indeed, confusion of Hodgkin’s disease with T cell lymphomas can be a real diagnostic problem. Many T cell lymphomas are apparently functionally active; often there is a large population of reactive plasma cells and, in some examples, large numbers of eosinophils or histiocytes (Lennert’s). It is suspected that the neoplastic clone retains the capacity to secrete cytokines which attract the benign elements. Another characteristic of T cell lymphomas is their prominent vascularity--they show a striking content of high endothelial venules.

In relatively early nodal involvement, the neoplastic cells involve the paracortical areas of the node; in the spleen, this is seen as periarteriolar involvement. Of course, with progression of the tumor, the node and spleen are overrun by neoplastic cells and this distribution is obscured.

REFERENCES


THE SPECIAL OF THE DAY

CASE 20: METASTASIZING, MALIGNANT PHEOCHROMOCYTOMA

Adrenal pheochromocytomas are rare tumors although it is always taught to medical students to remember them as a treatable cause of hypertension. Malignant pheochromocytomas are extremely unusual and range from 2-15% of these tumors. However, true malignancy must be differentiated from multifocality especially in the setting of multiple endocrine tumor syndromes, etc. The histologic atypia which can be found in pheochromocytomas would force a malignant diagnosis in most other tumor types; however, in pheochromocytomas, atypia or mitoses alone are insufficient to diagnose malignancy. In addition, the finding of capsular and vascular invasion alone or together is insufficient also. The only criterion which can be used to make a malignant diagnosis is the presence of metastases; only about 5% of pheochromocytomas then can be considered malignant. This case fulfills these criteria, with metastases to mediastinum and lung.

Another unusual feature of the present case is the finding of a small cell component in the tumor which in other areas certainly is acceptable as a pheochromocytoma. The concern in our case was that we were dealing with a collision tumor, i.e., she had a small cell lung cancer that metastasized to the mediastinum and to the adrenal pheochromocytoma. However, complete autopsy did not disclose a primary in the lung; indeed, one metastasis in the lung showed the larger cells of the more readily recognizable pheochromocytoma.

Some authors have considered finding smaller cells in pheochromocytoma as a concern for malignant behavior; however, this small
cell neuroblastoma-like area was not what they had in mind. Medeiros et al. described certain cytologic differences between the benign and malignant pheochromocytomas in their series of 60 cases. The only good criterion was the presence of large amounts of necrosis in malignant varieties; mitoses were also more frequent but they could be seen in benign lesions as well. These authors also found that malignant tumors tended to be larger (759 g. versus 159 g.).

Our case may be compared to the case reported by Balazs of a mixed pheochromocytoma and ganglioneuroma of the adrenal in a 37-year-old woman with hypertension. The author postulated that the tumor arose from totipotent neuroectodermal cells derived from the neural crest.

REFERENCES

Following the seminar, additional history, follow-up or results added important information to the cases; I felt this information should be added for completeness.

Case 1: Thymic carcinoma. There was no lung mass or other known tumor in this patient. He is well about 1 year after surgery.

Case 2: Cirrhosis of liver - alpha-1-antitrypsin deficiency. Patient is well 1 year following transplant.

Case 3: Angiomyolipoma liver. Patient is well about 9 months postoperatively.

Case 4: Angiosarcoma-cholangiocarcinoma of liver. Patient had history of Thorotrust--for radiologic examination for lower extremity weakness 40 years ago. At autopsy had calcified spleen and angiosarcoma also in bone marrow.

Case 5: Crohn's disease, appendix. Patient had full radiologic work-up - no evidence of Crohn's elsewhere. Serologic evaluation for Yersinia was negative.

Case 6: Juvenile fibromatosis. Patient underwent complete surgical excision of mass, with preservation of the eye. He is well and without recurrence 4 years later.

Case 7: Glomangiomyoma. Patient had chest well excision and is free of disease at last follow-up (<1 year).

Case 8: Osteosarcoma. Patient was not given preoperative chemotherapy because of large size of lesion and fracture. Postoperative chemotherapy is being given; follow-up is short.

Case 9: Synovial sarcoma, abdominal wall. Following surgery and chemotherapy, patient has no evidence of disease at 1 year.

Case 10: Angiosarcoma, post-radiation. Patient was treated with chemotherapy, but deteriorated and died with widely disseminated tumor within 8 months of diagnosis.

Case 11: Cowden's disease, thyroid. Discussion centered on diagnosis of previous cases of thyroid cancer in this disease and absence of pathologic data in the reports in the literature. It was felt that the "invasive" appearance of the thyroid now was not consistent with cancer, but can be ascribed to prior surgeries and "implants." Patient's main problem is multiple oral and tracheobronchial papillomas.

Case 12: Polymorphous low-grade adenocarcinoma of minor salivary glands. History showed that initial lesion diagnosed when patient was 70 years of age was called adenoid cystic carcinoma (1982--this was the year before PLGA was first described). The tumor recurred at 7 years and destroyed the palate.
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invaded nasopharynx and was found in periaural spaces; wide local excision only was done and the patient is apparently well at 1 year (now age 78).

Case 13: Uterine leiomyoma with lymphoid infiltration. Patient's hysterectomy showed squamous carcinoma in-situ with microinvasion; she has no disease at 1 year.

Case 14: Gliosarcoma. The patient's original tumor was diagnosed as a grade 2 astrocytoma as was the initial recurrence two years later. After the L3 lesion was removed (seminar slide), a debulking of a further recurrence in the brain showed higher grade glioma with transition to a tumor histologically similar to the seminar slide. This was then gliosarcoma which metastasized to L3 area. The differential diagnosis of the L3 lesion without the historical data included malignant schwannoma which was ruled out by negative S100 staining.

Case 15: Small cell malignant glioma. The diagnosis of PNET was virtually ruled out by negative stain for synaptophysin (results returned following preparation of original handout). In addition, marked pleomorphism in this case (a previously untreated lesion) would argue against PNET diagnosis.

Case 16: Adenoma of liver in type I glycogen storage disease. Patient had multiple lesions and is 4 years post-transplant and is doing well since new liver corrected metabolic defect.

Case 17: Inflammatory pseudotumor of lymph node. Patient apparently doing well at 1 year. During discussion, it was pointed out that some of these lesions are associated with systemic symptoms which can regress on excision of mass; some have behaved in an aggressive manner even reportedly invading veins. Support for changing the name of "pseudotumor" was raised.

Case 18: Malignant lymphoma, T-cell type, in Wiskott-Aldrich syndrome. Detailed immunohistologic and flow cytometric studies on fresh tissue in this case showed T-cell phenotype: positive for CD2 and CD4 (T-cell markers) but negative for CD5 and CD7. The lack of staining for two pan-T-cell markers (CD5 and CD7) in the large pleomorphic cells represents an abnormal T-cell phenotype and is consistent with T-cell origin of the lymphoma. Gene rearrangement studies were not helpful.

Case 19: Dendritic reticulum cell sarcoma, lymph node. Patient received chemotherapy and local radiation therapy as well and is well at 1 year. Unfortunately, no fresh or frozen tissue was available for more detailed characterization of proliferating cell.

Case 20: Malignant metastasizing pheochromocytoma. The follow-up in the case showed that despite chemotherapy originally directed at pheochromocytoma (and after that didn't work) at small cell carcinoma, the patient died 6 months after diagnosis. At autopsy, the necrotic small cell component of the tumor was found in the retroperitoneum and mediastinal nodes and only the large cell component was found in 2 lung metastases. No primary lung small cell tumor was found and it was felt that there had only been one tumor, a malignant pheochromocytoma.