PEDIATRIC PATHOLOGY

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PEDIATRIC PATHOLOGY - DR. LOUIS P. DEHNER

CASE HISTORIES

Case 1. 11 year old white female with 3 month history of pain in right lower lumbar region. Treated for muscle sprain with only minimal relief. X-rays of low back and pelvis normal. Right kidney depressed and deviated laterally on IVP. At surgery, a large tumor was found, adherent to right 11th and 12th ribs, and invading psoas and paraspinal muscles and capsules of right adrenal and kidney.

Case 2. 15 year old white male with firm, slightly moveable subcutaneous mass on plantar surface of right foot for 1½ years. History of possible foreign body in this area at one time during childhood. Biopsy diagnosis of neuroma in 1975. Since biopsy, the mass gradually enlarged to 3 cm. in size. Minimal tenderness. At surgery, a subcutaneous fibrous mass was excised from area of metatarsal heads, adjacent to nerves but not attached to them.

Case 3. 4 year old white female who fell in March 1977 and rapidly developed an egg-shaped mass on right buttck. No evidence of ecchymosis. Mass failed to resolve, and two months later patient fell on same area with marked increased in swelling. Clinical impression of hematoma; X-ray was negative. Physical findings included a firm spleen, palpable 2 cm. below the left costal margin, and a non-tender ill-defined mass in right buttock with a prominent vascular pattern in the overlying skin. ACTA scan of right gluteal area showed a huge mass in right buttock with probable enlargement of right gluteus maximus. Excision of tumor performed, which was considered complete at the time.

Case 4. 13 year old female with 5 cm. mass involving the superficial lobe of the left parotid gland. No other significant findings.

Case 5. 8 year old black male with sore throat and fever in May 1977 treated with antibiotics. He developed ankle swelling with pain, leukopenia, fever, chills and skin rash. Additional antibiotic therapy did not produce clinical response, and pseudomonas was cultured from ankle area. Transferred, with diagnosis of pseudomonas necrotizing fasciitis. Treated with antibiotics and debridement. 10 days after debridement, he developed fever, leg pain, periosteal elevation over fibula. Additional surgery performed, including small window in fibula.

Case 6. 11 day old black male infant born 1/14/77 by emergency caesarean section. Pregnancy was complicated by abruptio placenta. Apgar of 2 at one minute and 3 at five minutes. Endotracheal tube placed. During the subsequent days, he suffered renal, hepatic and cardiac failure along with pulmonary hemorrhage and evidence of disseminated intravascular coagulation. Cardiopulmonary arrest on 1/25/77.

Case 7. 19 month old Caucasian male with sudden onset of vomiting, fever, chills. On day of admission, patient passed large watery bowel movement, and child's older brother also developed diarrhea. Liver 8 - 10 cm. below right costal margin. IV antibiotic therapy begun. On day after admission, motor seizure occurred followed by respiratory arrest. Hypotension after resuscitation. Blood and stool cultures grew out Salmonella. Disseminated intravascular coagulation developed. Clinical condition continued to deteriorate, and he died 4 days after admission with Salmonella septicemia and enteritis plus hepatomegaly of unknown etiology.
Case 8. Infant male, product of 41 week gestation. Immediately after birth the baby appeared flaccid, but this was thought to be secondary to sedation. As the day progressed cyanosis appeared, increased, and supportive therapy was begun. X-ray showed pneumomediastinum and no evidence of hyaline membrane disease. Right chest tube inserted with some air released from right thoracic cavity. Respirations appeared to improve, but soon the infant began to deteriorate. Left thoracotomy performed. Despite all efforts, the baby died 17 hours after birth.

Case 9. 16 year old female with one year history of increased nervousness, decreased ability to concentrate and decreasing grades in school. Physical exam: slight tremor of hands, slight lid lag, thyroid moderately and diffusely enlarged and non-tender. T3 and T4 elevated. No enlargement of pituitary fossa. Patient put on Lugol's iodine for 24 hours; then a subtotal thyroidectomy was performed.

Case 10. 1 month old male who developed symptomatology suggestive for necrotizing enterocolitis, which led to clinical evidence of rupture of the small intestine. This required emergency surgery.

Case 11. 13 year old white male with enlarged lymph nodes draining from right axilla for two months. Past history of febrile illness with cough and right upper lobe density 10 years ago. Lung biopsy and subsequent cervical node biopsy demonstrated granulomas. Slides are from axillary skin and nodes.

Case 12. 4 month old patient with palpable bluish mass on left anterior hard palate, present for 2 months. X-rays revealed a circumscribed osteolytic defect in the bone. Mass was excised and post-operative recovery uneventful. 18 months later parents noted a somewhat bluish, slightly tender mass beneath left eye. Clinical impression of hematoma. X-rays revealed large soft tissue mass with some clouding of left maxillary antrum. Biopsy performed, followed by an excision. Your section is from the partial maxillectomy specimen.

Case 13. 16 month old white male. Mass noted in right chest on chest X-ray for unrelated problem. Right thoracotomy performed with excision of mass. During post-op follow-up, left chest mass noted 13 days after excision of first mass. At surgery, a 3 x 2.5 x 1.5 lesion was found, paravertebral, at T11 - T12 level, adherent to but not invading aorta.

Case 14. 6 year old black male with 6 week history of a painless swelling of the left posterior mandible. Radiographs showed an expansile, lytic lesion which contained fine calcifications. The lesion extended from the premolar region to the coronoid notch. The developing second molar crown was displaced to the base of the condyle. After biopsy, the lesion was treated by curettage. Post-operative course was uneventful. In early 1977 (20 months after the first operation) a painless swelling was noted in the molar region. Radiographs showed a localized lytic and opaque lesion which was less than one-fourth the size of the original lesion. This was removed by curettage.

Case 15. 11 year old white male who had an episode of acute swelling over the angle of the left mandible. Radiographs showed a large lytic defect extending from the first molar area to the coronoid notch. The developing crown of the third molar was displaced to the lower border of the mandibular angle.

Case 16. 3 month old white female who became flaccid and pale 1 week prior to admission and developed episodic vomiting. Brain scan revealed a large mass in the right hemisphere, and arteriography showed large mass in right parietal area. Minimal left facial asymmetry and slight weakness in left arm. Right temporoparietal craniotomy performed.
Case 17. 10 year old white male with 6 week history of infraorbital mass. 2-3 cm. ill-defined mass present with some tenderness, slight pain, and no skin erythema. Radiographs showed poorly defined, deep mass in left infraorbital soft tissues without obvious involvement of underlying maxilla. Incisional biopsy performed. Later, an excision of the mass was attempted. Sections are from the excised tumor.

Case 18. 3 year old white female with three week history of respiratory distress. Symptoms began with non-productive cough and progressed to low grade fever, anorexia, irritability, increasing lethargy and right-sided chest pain. Stridor, tachypnea and grunting respirations noted on day of admission. Chest X-ray revealed near total opacification of the right lung field. Arterial blood gases showed pH of 7.38, PCO₂ of 30, and PO₂ of 70. Thoracentesis produced 3 cc of bloody fluid with white cell count of 20,900. Physical findings included palpable anterior cervical nodes, diminished breath sounds over entire right chest, and expiration prolonged on left. Hemoglobin 10.5 gm/dl, WBC 19,500 with 70% polys, 23% lymphs, 7% monocytes. Platelet count 600,000; sed rate 40 mm/hr. 24 hr. urine VMA elevated at 9.3 micrograms per milligram creatinine. Normal electrolytes, BUN, protein electrophoresis, coagulation studies and liver function tests. At surgery a large extrapleural tumor was present in the anterior mediastinum, extending from the superior vena cava to the diaphragm.

Case 19. 13 year old female with "cyst" on back of neck, at hairline, for 10 months. Recent enlargement. 1 cm. mobile lesion present on physical examination.

**DIAGNOSES**

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As noted from the protocol, this 11-year-old child had a large tumor in the retroperitoneum associated with the ribs and paraspinal muscles. Microscopically, the tumor is arranged in poorly circumscribed nests which blend into more diffuse foci. Hemorrhage and necrosis are readily identifiable especially at the periphery. At somewhat higher power, the nests consist of cells which are loosely cohesive. An alveolar pattern with cells lining the periphery and aggregates in the center is the striking feature of this neoplasm. There are numerous degenerating tumor cells in these nests but the viable cells are moderately large, polygonal and have round to slightly ovoid nuclei. The cytoplasm has a clear to acidophilic appearance. A sheet-like or syncytial formation is prominent in many areas. Some tumor cells showed a definite tendency to "spindle" out and a tapered tail of acidophilic cytoplasm was appreciated. The presence of the multinucleated tumor giant-cells with the brightly acidophilic cytoplasm was an extremely helpful finding in this tumor. At this point, there should be little question in anybody's mind that we are dealing with a malignant neoplasm. The anatomic location presents some obvious differential diagnostic considerations as well as the histology.

To analyze each of these possibilities plus additional ones that you may have thought about could occupy the remainder of the seminar. Let me say that I do not think that this tumor is a neuroblastoma or its better differentiated variants such as the ganglioneuroblastoma. The multinucleated cells are not ganglion cells and I failed to identify pseudorosettes, dystrophic calcification, nor a neurofibrillary background. Adrenal cortical carcinoma can be a fooler because it is so poorly differentiated. It, like renal cell carcinoma, malignant melanoma, alveolar soft part sarcoma, paraganglioma and alveolar rhabdomyosarcoma may have a striking alveolar pattern. Correlative functional laboratory data and electron microscopy may be required in such cases. The tumor was adherent also to the capsule of the kidney. Could we conceivably be dealing with a Wilms' tumor or a variant? There are infrequent variants of Wilms' tumor which are predominantly sarcomatous and most reminiscent of rhabdomyosarcoma. Wigger (1976) has described a "fetal rhabdomyomatous nephroblastoma" but I do not think that we are dealing with this neoplasm. Renal cell carcinoma is rare in children and anything can happen in a seminar. I excluded renal cell carcinoma because the tumor did not appear to originate from the kidney and there was no evidence of tubular formation nor clear cells. "Sarcomatoid" renal cell carcinoma can be an extremely difficult diagnosis by light microscopy alone. Your attention is directed to the excellent series of papers by Farrow and coworkers (1968) on this subject. Malignant lymphoma is another important tumor in our consideration. The "nesting" arrangement and the occasional multinucleated cells were features against this interpretation. There was one finding, infiltration of the fat, that made me think about that diagnosis more than anything else I encountered in the histology. Ewing's tumor arising in the rib, vertebra or soft tissues was a reasonable possibility. We are not told that the bone was involved although there were "attachments." Angervall and Enzinger (1975) have established the precedence for us to diagnose Ewing's
tumor in the soft tissues. The "alveolar" pattern and multinucleated cells diverted me from an interpretation of Ewing's tumor. I was not overwhelmed by the amount of cytoplasmic glycogen although a helpful feature in Ewing's tumor, it is not always demonstrable. The reasons for diminutive amounts of glycogen in a Ewing's tumor include little production by the tumor cells, anaerobic glycolysis by a highly necrotic tumor and "wash-out" of glycogen by the aqueous based formaldehyde. The necrosis in our tumor is another feature suggestive for Ewing's tumor. An endodermal sinus tumor or embryonal carcinoma were also considered but discarded. Retroperitoneal germ cell tumors or metastases from a testicular primary tumor are plausible but the histology was not compatible.

Rhabdomyosarcoma of the predominantly alveolar type was thought to be the most reasonable interpretation. The microscopic features including the alveolar pattern, large tumor cells and the multinucleated cells are the important findings. I thought that there were foci which also had an embryonal appearance. We usually think of the embryonal and alveolar rhabdomyosarcoma as distinct, separate neoplasms and in most cases they are. However, a small percentage of neoplasms will have hybrid features and this case is highly suggestive in that regard.

Riopelle first described the alveolar rhabdomyosarcoma but it was not until Enzinger and Shiraki (1969) reported the AFIP experience that this diagnosis caught hold. These authors pointed out some important clinicopathologic differences from embryonal rhabdomyosarcoma, namely, an older age, a peripheral soft tissue distribution and the poorer prognosis. The recent preliminary results of the Intergroup Rhabdomyosarcoma Study are demonstrating the lack of response of alveolar rhabdomyosarcoma. An interesting feature of alveolar rhabdomyosarcoma is its high rate of metastasis to the lymph nodes and heart. Other soft tissue sarcomas which metastasize to lymph nodes are embryonal rhabdomyosarcoma, synovial sarcoma, malignant fibrous histiocytoma, clear cell sarcoma of tendon sheath, and alveolar soft part sarcoma. The prognosis for this child is thought to be very poor.

CASE ONE

DIFFERENTIAL DIAGNOSIS

1. Adrenal
   Adrenal cortical carcinoma, neuroblastoma and variants.

2. Kidney
   Wilms' tumor and variants, renal cell carcinoma.

3. Lymph node
   Malignant lymphoma.

4. Soft tissues
   Malignant lymphoma, paraganglioma, malignant teratoma, soft tissue sarcoma (rhabdomyosarcoma, Ewing's tumor, fibrous histiocytoma (histiocytes variant), alveolar soft part sarcoma).

5. Bone
   Ewing's tumor, malignant lymphoma, metastatic tumor.

Case 2. Soft Tissue, Right Foot - Juvenile Aponeurotic Fibroma (Cartilaginous Analog of Fibromatosis) Versus Soft Tissue "Chondroma".

The history as given is that of a 15-year-old boy with a minimally tender subcutaneous mass on the plantar surface of the foot. An excision was performed of the mass which was adjacent to the metatarsal head.

There should have been no difficulties with the identification of this mass as being composed of lobules of reasonably mature fibrocartilage. The chondrocytes were more or less evenly distributed in the hyalin matrix with foci of chondrocyte cloning or aggregation. I did not see any binucleated chondrocytes, pleomorphic nuclei or mitotic figures. We are dealing with a benign soft tissue lesion composed predominantly of cartilage. At the margins of the original sections which I examined some months ago in preparation for this seminar, there was a striking component of cellular fibrous tissue which blended into the surrounding soft tissues. This feature led me to consider this tumor a highly cartilaginous variant of the juvenile aponeurotic fibroma originally reported by Keasbey in 1953. It is imperative, however, to consider other possibilities.

In addition to the juvenile aponeurotic fibroma, is this tumor a soft tissue chondroma? With the sections that you had to examine, I think that I would have placed that interpretation near the top of the list. Dahlin
and Salvador (1974) have reported their experience of 70 such lesions of the hands and feet. It is an unusual tumor of childhood in that 2 of the 70 cases occurred in the first two decades of life. There were 16 tumors of the foot, six near the metatarsal. An important point to keep in mind about cartilaginous lesions of the hands and feet is that they can be very disturbing histologically yet benign. True chondrosarcomas of the hands and feet are extremely uncommon. Synovial chondromatosis is yet another possibility, however, we have no information about this tumor residing within the joint space. The previous statement about the disquieting histology of soft tissue chondromas applies equally to synovial chondromatosis. Hensinger and coworkers (1974) have described multiple chondromatous hamartomas in a child and briefly discuss cartilaginous lesions in children.

Juvenile aponeurotic fibroma is one of the special histopathologic variants of the fibromatoses. The subject of fibromatosis has been somewhat confused by the overabundant terminology and uncertainty about the nosology of these lesions. Mackenzie (1972) has defined a fibromatosis as "an infiltrating fibroblastic proliferation showing none of the features of an inflammatory response and no features of unequivocal neoplasia." He goes on to point out that they can be fatal and as most of you are aware, they may be locally aggressive. Fibromatoses have been classified into two general groups, those occurring preferentially in children and a second group in children and adults (Table). There have been approximately 60-80 cases of juvenile aponeurotic fibroma reported to date with the AFIP series by Allen and Enzinger (1970) one of the largest. These lesions occur in the deep soft tissues, fascia, aponeuroses, tendons and muscles. As the name of the lesion indicates, they appear in childhood usually as a circumscribed mass measuring no more than 4 cm. in greatest dimension. Local recurrence is a problem in 40-50% of cases. Poorly circumscribed islands of cellular fibrous tissue infiltrating the fat and focal chondroid differentiation with calcification are the characteristic findings. I have seen only one other case with as advanced chondroid differentiation as this lesion which I thought represented juvenile aponeurotic fibroma.

There is one other form of fibromatoses in which the lesion has chondroid features and that is the juvenile hyalin fibromatosis. This disorder is rare and the tumors tend to the multiple.

# Table

## Classification of Fibromatoses

### Childhood Fibromatosis
- Congenital fibromatosis (so-called "infantile fibrosarcoma")
  - A. Localized
  - B. Generalized (documented spontaneous regression)
- Fibrous hamartoma of infancy (Reye, Enzinger)
- Fibromatosis colli (sternomastoid tumor)
- Recurring digital fibrous tumor (Reye)
- Infantile-juvenile fibromatosis (cellular)
- Juvenile aponeurotic fibroma (Keasbey)
- Hereditary gingival fibromatosis
- Juvenile hyalin fibromatosis (Murray)
- Nasopharyngeal fibroma (?)

### Primarily Adult
- Palmar-plantar fibromatosis
- Musculo-aponeurotic fibromatosis (aggressive)
  - A. Familial (Gardner's syndrome)
    1. Abdominal
    2. Extra-abdominal
  - B. Non-familial
    1. Abdominal
    2. Extra-abdominal
- Peyronie's disease (?)


The theme of this case is somewhat similar to Case 1 with a neoplasm of the soft tissues composed of "small blue cells" (Table). When the patient was admitted to the University Hospitals, a post-traumatic, non-neoplastic mass was the impression. A thorough pre-operative evaluation only confirmed the presence of the mass in the right buttock without osseous involvement. The splenomegaly was apparently a "red herring" since it has been of no consequence in the patient's course. An incisional biopsy was performed with a frozen section. The only reason for doing a frozen section was to confirm the presence of diagnosable tissue on permanent sections. Do not freeze everything! There was no thought of instituting immediate therapy. It has been our experience that surgeons are following this routine for suspicious bone and soft tissue tumors before a definitive procedure. There is absolutely no evidence to date that a patient's prognosis is compromised. Our diagnosis on the basis of the incisional biopsy was that of an undifferentiated small cell tumor and we favored an embryonal rhabdomyosarcoma. Two days later a wide local excision of a 13.5 x 8.5 x 5 cm. mass was performed. It appeared from the gross and microscopic examination that the surgeon was successful, however, your sections should have demonstrated conspicuous vascular invasion at the periphery.

Microscopically, the low power shows a well circumscribed but non-encapsulated tumor with a lobulated contour. Extensive hemorrhage and necrosis were apparent in the central portions of the mass. At higher magnification, the tumor cells were reasonably compact and for the most part, they were larger than the original biopsy seemed to indicate. A round to polygonal outline characterized the cells. The cytoplasmic rim was well defined and the cytoplasm was clear to slightly acidophilic. We were struck at this point that the tumor did not resemble the typical embryonal rhabdomyosarcoma. Another feature which lead us to our eventual conclusion was the focal presence of hyalin or myxoid material between aggregates of tumor cells. Special stains were performed including a negative PAS for glycogen
but the colloidal iron with hyaluronidase digestion was positive. We were impressed at this point with the chondroid features of the tumor. The lobulated appearance was another supporting feature. Other interpretations in addition to those already mentioned were soft tissue Ewing's tumor, malignant teratoma (sacroccocygeal), malignant lymphoma, alveolar rhabdomyosarcoma, chordoma and malignant peripheral neural tumor (neurofibrosarcoma).

The Mayo Clinic experience with soft tissue sarcomas in children indicated that the second largest group (first, rhabdomyosarcoma -55.7%) of neoplasms are "sarcomas of undetermined histogenesis" (20%). More recently, the Intergroup Rhabdomyosarcoma Study (IRS) has examined over 400 neoplasms entered into the IRS resulting in the confirmation of 83% as rhabdomyosarcomas. The other 17% of cases were "special Type I and II neoplasms" of the soft tissue Ewing's type or undifferentiated sarcomas.

Chondrosarcomas of the bone or soft tissues are unusual in children. There are distinctive subtypes of chondrosarcomas as listed below. The well differentiated

1. Well differentiated chondrosarcoma
2. Chondrosarcoma with dedifferentiation
3. Clear cell chondrosarcoma
4. Mesenchymal chondrosarcoma
5. Myxoid chondrosarcoma (chordoid sarcoma)

Chondrosarcoma, the clear cell variant and the dedifferentiated chondrosarcoma occur primarily in bones. Mesenchymal chondrosarcoma originates in both soft tissues and bones and is a tumor which appears in children. Most myxoid chondrosarcomas have been described in adults. Our tumor is a poorly differentiated chondrosarcoma which comes closest to the mesenchymal chondrosarcoma except well formed nests of cartilage were not apparent. Kauffman and Stout (1963) reported 7 cases of extraskeletal chondrosarcomas in children, one having very poorly differentiated features.

<table>
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<th>Laboratory</th>
<th>Anatomic Site</th>
<th>Histology</th>
<th>E/M</th>
<th>Special Studies</th>
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<td>Neuroblastoma</td>
<td>+</td>
<td>+</td>
<td>Rosettes, Fibrils,</td>
<td>Granules, Neurites</td>
<td>Tissue Culture, Fluorescence</td>
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<td>Malignant Lymphoma</td>
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<td>+</td>
<td>Lymphoblasts, &quot;Burkitt Cells&quot;</td>
<td>Lymphoid Features</td>
<td>Membrane and Cytoplasmic Immunoglobulins</td>
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<td>+</td>
<td>Small, Spindle Cells, 40% Striations</td>
<td>Myofibrils</td>
<td>PAS (+)</td>
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<td>Ewing's Tumor, Osseous &amp; Soft Tissue</td>
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Case 4. Parotid, Left, Excision - Malignant lymphoma, Histiocytic or "Large Lymphoid Cell Type".

This case should prove to be one of the more interesting ones in the seminar since sufficient time has elapsed to give us some type of answer. First of all, a 5 cm. mass was present in the superficial lobe of the left parotid. The section shows a diffuse infiltration of the gland by cells that have a lymphoid appearance. Most of the acinar architecture has been obliterated but small glandular structures are still identifiable. There were no myoepithelial islands of the type seen in the 'benign lymphoepithelial lesion' or Mikulicz's syndrome. Could this infiltrate represent a chronic inflammatory reaction without any significant sequela? I did not think so. The infiltrate is neoplastic and therefore, a malignant lymphoma although at that time, the patient did not have any other signs of disease. In addition to malignant lymphoma, I have also seen embryonal rhabdomyosarcoma infiltrate from the soft tissues into the parotid. An important differential feature, in addition to the cytology of the cells, is the pattern of infiltration. Embryonal rhabdomyosarcoma tends to invade along the septa of the gland rather than spill into the glandular parenchyma. Both lymphoma and embryonal rhabdomyosarcoma will course through the adjacent fat in a similar fashion.

Malignant lymphoma presenting in a salivary gland, usually the parotid, is distinctly uncommon and represents no more than 1-2% of malignant salivary gland lymphomas (Nime, et al., 1976; Hyman and Wolff, 1976). One of the problems is the site of origin of the tumor since in some cases, an intra-parotid lymph node seems to be the source. Most patients are adults and histiocytic lymphoma is the most frequent type of lymphoma. There is more than a passing association between the 'benign lymphoepithelial lesion' and malignant lymphoma.

I have avoided discussing the classification of the lymphoma other than implying that it is a non-Hodgkin's lymphoma. The application of the standard Rappaport scheme has been difficult to the childhood non-Hodgkin's lymphomas. In our case, we are dealing with a tumor composed of rather large lymphoid cells that in the old days would have been designated as "histiocytes". It is not necessary to beat the subject into the ground other than to say that the so-called histiocyte probably represents a transformed lymphocyte of either B- and T- cell type.

**NON-HODGKIN'S LYMPHOMA IN CHILDHOOD**

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<th>T-cell</th>
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<td>Malignant lymphoma, histiocytic (large lymphoid cell)</td>
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</table>
This summary represents the state of the art today but who is to say about tomorrow. Our patient probably fits into the last category. Patients, even children, with histiocytic lymphoma will not infrequently present with extra-nodal disease. In a recent tabulation of various series of non-Hodgkin's lymphomas in children, we found that 1/3 of cases had been classified as histiocytic lymphoma (Dehner, 1977). It is extremely difficult to say at this point what the prognosis will be for her without further information about the stage.


Case 5. Bone, Fibula - Acute Leukemia.

Although this case is the fifth one in the seminar, it was the last one for which I prepared the notes. The 8-year-old boy presented with a clinical picture of infection and then developed a skin rash and ankle swelling. A necrotizing fasciitis which contained Pseudomonas was cultured. X-rays of the leg revealed periosteal elevation of the fibula and an open biopsy was performed. I was told that he was leukopenic and that one week after the biopsy, he began to show abnormal circulating cells. Even from the abbreviated history, it is not difficult to appreciate the problems that faced the clinicians who were taking care of this child. They were presented with a patient who was presumably well until May, 1977, and then developed an acute illness with an infectious backdrop. His immune system had been drastically altered or overwhelmed by some process.

The biopsy discloses unremarkable cortical bone, however, the cells in the intraosseous or intertrabecular spaces are obviously abnormal. These cells lack cohesion and there is a diffuse quality about this infiltrate. I make this point to differentiate the type of pattern in a metastatic tumor such as neuroblastoma or embryonal rhabdomyosarcoma. These cells look malignant to me and I believe that we are dealing with a hematopoietic neoplasm without restrictions on that term. Ewing's tumor may present as this child did with signs and symptoms of an infection especially an acute osteomyelitis. The cells in this infiltrate are not the "small blue cells" of Ewing's tumor. There is generally more aggregation of the cells and some evidence of necrosis in Ewing's tumor. The PAS stain was negative but this finding does not rule out Ewing's tumor. Percolation through the intertrabecular spaces is a frequent feature of this tumor as well as a marked periosteal reaction because of the infiltration of the subperiosteum. Malignant lymphoma of bone usually creates an osteolytic defect with or without a periosteal reaction (Boston, et al., 1974). I can not totally exclude malignant lymphoma on the basis of the limited biopsy but I am assisted by knowing that abnormal circulating cells were present. Histiocytosis X is ruled out on the basis of history and the histology. Should we consider malignant histiocytosis? There are some similarities
such as the skin rash and fever but involvement of the skeleton is most uncommon especially at the onset (Dehner, 1977). With everything considered, I think that we are looking at a child with acute leukemia but I am uncertain whether it is lymphocytic or myelocytic. Bone pain occurs in 50% or more of patients with acute leukemia and it is more common in acute lymphocytic than acute myelocytic leukemia (Thomas, et al., 1961). There is no obvious correlation with the presence of bone lesions in a child with the prognosis according to Aur and coworkers (1972). The various skeletal manifestations of leukemia include metaphyseal lines, generalized and focal demineralization and periosteal new bone formation (Simmons, et al., 1968). The focal lesions can mimic metastatic tumor such as neuroblastoma. Resolution of all of these changes will occur during remission.


The history as given in the protocol is abbreviated and fails to note that this infant's mother was an insulin-dependent diabetic. An emergency caesarean section was performed because of placental abruption. The amniotic fluid was blood tinged and a large blood clot was suctioned from the trachea shortly after birth. From the very moment that this child was born, clinical difficulties began to multiply and were then compounded. Hypotension, hypoglycemia, hyperkalemia, acute renal failure, jaundice (total bilirubin, 27 mg./dl.), congestive heart failure and evidence of disseminated intravascular coagulopathy were some of the definable events. When the child came to autopsy, many of the anatomic findings were not surprising.

Your section shows a portion of kidney with the anticipated histology of an 11-day-old infant at least in the cortical zone. There is some persistent glomerulogenesis beneath the surface. The major abnormality is represented by the hemorrhagic and necrotic medulla and papilla. Through the sea of erythrocytes, residual irreversibly ischemic tubules are noted with some difficulty. There is a rather sharp zone between the ischemic papilla and the viable parenchyma. A fibrous and vascular response has already occurred and it is interesting to note that there are relatively few inflammatory cells. In my section, I was unable to identify any major vascular thrombosis. The tubules away from the necrotic zone were swollen and possibly some changes of acute tubular necrosis. In addition to the section of kidney, I also examined the liver which revealed extensive hemorrhagic necrosis. There were only a few foci of viable parenchyma and in these zones, bile duct proliferation has already begun. In summary, we have a child with acute organ necrosis of the hemorrhagic type who was the victim of severe perinatal stress.

Renal papillary necrosis is generally considered a pathologic change occurring primarily in adults who are diabetic, alcoholic, analgesic abusers or victims of acute obstructive pyelonephritis. Davies and coworkers (1969) reviewed 3516 pediatric autopsies and identified 16 cases of medullary-papillary necrosis (0.5%). A retrospective examination of the hospital charts revealed that none of the children were diagnosed as having papillary necrosis before death. A variety of perinatal-neonatal disorders were seemingly related to the change including asphyxia neonatorum, hemorrhage, shock, sepsis, diarrhea and dehydration, DIC, renal artery or vein thrombosis and hyperosmolar radiological contrast material. One can readily identify combinations of these events in our patient. Clinically, these children will develop an acute, short oliguric phase (2-3 days) followed by polyuria if they survive that long. Occasional red cells are seen in the urine but surprisingly there is very little else. The blood urea nitrogen rises to 60-100 mg./dl. and there may be severe sodium loss.

Pathologically, some children may have cortical necrosis in addition to the papillary necrosis (Sanerkin and Evans, 1965). The renal veins are generally patent in the bilateral, yet segmental disorder. Acute hemorrhagic necrosis of the liver and adrenals are other findings at autopsy. It is important to realize that not all children die and there is an increasing number of survival reports. Survival is not without its complications which include severe hypertension and concentration defects. The calyces show a bizarre pattern and histologically, there is severe atrophy and scarring.
Microscopic similarities exist between the segmental changes in medullary necrosis to segmental hypoplasia (Ask-Upmark kidney).


Case 7. Kidney - Medullary Cystic Complex Associated With Congenital Hepatic Fibrosis (? Variant of infantile polycystic disease, Type I).

If there has been a topic in pediatric pathology that has received as much attention as "cystic disorders of the kidney", I am hard pressed to name one other. Despite the flood of words, there still exists a great deal of confusion which will not be cleared entirely with this case.

The patient in the seminar was apparently well until the day of admission when he vomited, became febrile and developed diarrhea. Hepatomegaly (8-10 cm.) was present. Salmonella (group C2) was grown from the blood and stools. Hypotension and disseminated intravascular coagulation preceded his death 4 days after admission. At autopsy, the liver weighed 840 gms. and on cut surface, numerous small nodules (0.3-0.4 cm.) were present. The consistency of the liver was described as "increased." Both kidneys were large (right 140 gm.; left; 130 gm.) and the cut surfaces revealed multiple cysts restricted to the medulla which measured 0.1 to 0.3 cm. in diameter. Microscopically, the liver disclosed widespread changes in the portal regions characterized as a peculiar dysplastic transformation of the bile ducts accompanied by fibrosis. There was obvious expansion of the portal tracts and bands of connective tissue containing the ducts extended into the lobules. The ducts were lined by a simple cuboidal epithelium and many were filled with neutrophils indicative of a cholangitis. As noted in the gross examination of the kidneys, there were aggregates of dilated collecting ducts in the medulla with mild periductular fibrosis. Some dilatation of tubules was appreciated in the cortex but not the typical radial, elongated dilatation which is a feature of infantile polycystic kidneys (Potter, Type I). The changes in the kidney are more consistent with the "medullary cystic complex" whatever that is. From the clinical standpoint, it would be unusual for a child with infantile polycystic kidney disease to enjoy good health through the first 19 months of life. Many of these children are dead by 19 months of age if they have not been transplanted. Those who are surviving have hypertension and chronic renal failure. There is absolutely no evidence of atrophy and interstitial fibrosis in these kidneys. The hepatic changes in
this case have been characterized as either "infantile polycystic liver" or congenital hepatic fibrosis (Lieberman, et al., 1971). There is an element of interpretation and preference as to the diagnostic assignment of this case.

Some of the major cysts of the kidney have been summarized in the Table. In childhood, unilateral multicystic renal dysplasia is the most common form of renal cysts (Kissane, 1976). It is the most frequent etiology of an abdominal mass in the newborn period. There are no heredo-familial implications. The simple renal cyst is the most frequent form of cyst in the adult. One other point is that "adult polycystic kidneys, Potter Type II" have been described in childhood (Ross and Travers, 1975; Stickler and Kelalis, 1975).


SIMPLIFIED CLASSIFICATION OF RENAL CYSTS IN CHILDHOOD

I. Simple renal cyst

II. Multicystic renal dysplasia, total or segmental

III. Polycystic kidney disease
   A. Infantile (Potter, Type I)*
   B. Adult (Potter, Type III)*

IV. Medullary cystic complex
   A. Medullary sponge kidney*
   B. Medullary cystic disease (juvenile nephronophthisis)*

V. Unilateral multilocular cystic kidney (cystic nephroma)
   + Primarily adult disorder
   * Associated with "polycystic" liver or congenital hepatic fibrosis.
Case 8. Lung-Interstitial Emphysema

This newborn male is another example of an emergency situation in the delivery room. The differential diagnosis of respiratory disorders in the neonate can be conveniently divided into the non-surgical and surgical problems. Most children fall into the former category and, of course, in the neonatal period, so-called hyalin membrane disease is at the top of the list. The child in seminar was in difficulty from the very onset and therefore, hyalin membrane disease as the primary disorder can be excluded. Meconium aspiration, congenital pneumonia and the surgical disorders should be considered in the differential diagnosis (Table). An x-ray was taken and it demonstrated pneumomediastinum and pneumothorax. Unfortunately, the child responded poorly and died 17 hours after birth.

The seminar slide from the lung shows evidence of diffuse alveolar septal thickening without an exudative reaction in the alveoli. There was an excessive number of cells in the septum and so I thought that there was an interstitial pneumonia. The primary event is identified in the interlobular septa where there are dilated cysts and spaces without an endothelial lining. There was no evidence of a significant reaction such as inflammatory cells, giant cells or fibrosis. I believe that these spaces represent air and thus we are observing interstitial emphysema of the lung. I saw no sign of hyalin membrane disease in the section. The giant cells which I mentioned as not being present are noted on occasion partially lining the air cysts. It is a similar type of response which can occur in pneumatosis cystoides intestinalis and emphysematous cystitis.

What is the current state of understanding of interstitial emphysema, pneumothorax and pneumomediastinum in the newborn? Some confusion exists in the literature regarding associated factors presumably exercising some role in the pathogenesis and etiology of this "air-leak" syndrome in the neonate. It was previously thought that the full-term newborn without hyalin membrane disease was most prone to the "air-leak" syndrome (Kirschner and Strauss, 1964; Grosfeld, et al., 1970). During the period when this statement was enjoying acceptance, the relationship with renal malformations and hyalin membrane was appearing in the literature (Liberman, et al., 1969; Campbell, 1970, Renert, et al., 1972; Stern, et al., 1972). Yu and coworkers (1975) reported an incidence of neonatal pneumothorax in 3/1000 live births and 68% of cases were associated with hyalin membrane disease. These authors made an important point in that the 11 term infants without obvious pulmonary pathology presented very early (9 within minutes of birth). The children with hyalin membrane disease developed pneumothorax much later (mean, 45 hours) and many of these children were assisted with ventilators. Emery (1956) has studied the anatomic events of interstitial emphysema in the newborn with the conclusion that an alveolar ruptures and air dissect toward the hilum along connective tissue planes in interlobular septa. The air enters the areolar tissue of the mediastinum where it extends into the base of the neck. Meanwhile, the vessels in the hilum are compressed producing an "air block" phenomenon. Small leaks occur in the mediastinal pleura and produce pneumothorax. Air also dissects peripherally to the subpleural connective tissue. The peripheral cysts of the lung as noted at autopsy in our case are the major findings. Askin (1975) has summarized the factors which may contribute to alveolar rupture in the newborn.


SURGICAL DISORDERS IN THE NEWBORN ASSOCIATED WITH RESPIRATORY DISTRESS*

Extrathoracic airway obstruction

Choanal atresia
Retroplaced tongue (Pierre Robin syndrome)
Nasopharyngeal teratoma
Sublingual dermoid
Lingual thyroid
Congenital subglottic stenosis
Subglottic hemangioma

Intrathoracic airway obstruction

Cystic hygroma
Duplication cyst of bronchus
Esophageal atresia and T-E fistula
Vascular rings and related anomalies

Compression of pulmonary parenchyma

Pneumothorax-pneumomediastinum
Congenital lobar emphysema
Esophageal duplication
Cystic adenomatoid malformation
Diaphragmatic hernia (Bochdalek)
Gastric perforation-pneumoperitoneum

Case 9. Thyroid - Treated Diffuse Hyperplasia with Lymphocytic Thyroiditis.

The history indicates that this adolescent female had all the clinical signs of hyperthyroidism and on physical examination, the thyroid was diffusely enlarged and non-tender. She was placed on Lugol's iodine to suppress the gland and a subtotal thyroidectomy was performed.

A weight was not provided for the gland and when a treated hyperplasia is examined, the weight may be one of the few objective parameters of hyperplasia. If you were struck microscopically by the fact that the thyroid looked like lymphocytic or Hashimoto's thyroiditis rather than diffuse hyperplasia, do not be surprised. The section discloses a marked lymphocytic infiltration with conspicuous germinal centers throughout. Rather than the alternating large, dilated follicles and smaller, atrophic ones as usually found in a treated hyperplasia, nearly all follicles are small and have a pronounced oxyphilic appearance. There were occasional follicles in which some attenuated papillary infoldings were present. Overall, the features of hyperplasia were completely overshadowed by the lymphocytic (Hashimoto's) thyroiditis. Can we reconcile what is encountered in the thyroid with the clinical symptomatology? This possible association between thyroiditis and hyperplasia was posed by Spjut and coworkers (1957) with a more or less negative conclusion. Catz and coworkers (1973) examined the relationship between lymphocytic thyroiditis and other thyroid lesions. They felt that the administration of iodides in the pre-operative period was responsible for the occurrence of the lymphocytic infiltrates, a conclusion which is challengable. In their series of 64 patients with hyperthyroidism, 37 (58%) had classic diffuse lymphocytic (Hashimoto's) thyroiditis. Hargreaves and Garner (1968) have correlated a higher frequency of post-operative hypothyroidism in those patients with moderate to marked lymphocytic infiltration. A significant report which bears upon our patients is by Fatourechi, et al., (1971) who described a group of patients with clinical evidence of Graves' disease but whose thyroids showed lymphocytic thyroiditis. These authors raise the possibility that these two diseases may in fact be one.

Hyperthyroidism due to diffuse hyperplasia (Graves' disease) constitutes 10-15% of all thyroid disease in childhood and between 1-5% of all cases of thyrotoxicosis occurs in children. There is an overwhelming female predilection (3:1) and the peak ages are between 11-15 years (Vaidya, et al, 1974). Similarly, lymphocytic thyroiditis is frequent in children. In a compilation of 6 pediatric series of thyroid enlargement and/or nodules, lymphocytic thyroiditis was diagnosed in 26% of cases and diffuse hyperplasia in 19% (Dehner, 1975). The lesson in our case is that the line separating Graves' disease and lymphocytic thyroiditis is often sharper clinically than it is morphologically.

Case 10. Small Intestine - "Hypoplasia of Muscularis."

We are given essentially no information about this 1-month-old infant until the acute presentation with apparent signs of intestinal perforation-obstruction. Whether we could make any more sense from this case with additional clinical information is debatable. Nonetheless, the child had an emergency laparotomy at which time approximately 60 cm. of small bowel were resected. The bowel was described as having multiple dilated segments up to 3 cm. in length and the wall of the intestine was reported as "paper thin". At least 3 separate foci of perforation were identified in these ectatic segments.

Microscopically, the mucosa was congested and markedly flattened presumably the result of the dilatation. There were a few scattered inflammatory cells in the lamina propria but no evidence of a necrotizing inflammatory process nor pneumatosis cystoides intestinalis. From the history, we were told that necrotizing enterocolitis was considered in the diagnosis. The most remarkable finding is the marked attenuation or absence if you wish of the muscularis to the extent that the lamina propria is juxtapositioned to the serosa. The sections stained with trichrome were not available at the time of this writing but the process did not appear totally circumferential. I did not appreciate an acute peritonitis in the area. As far as I could ascertain, the ganglia were intact and ganglion cells were present.

The legitimate question can be raised about the significance of the apparent absence of the small bowel muscularis in the areas of perforation. Does this constitute the primary or secondary event? From what data is available to us, there was no obvious reason for this child presenting with obstruction-perforation. The patient is 1-month-old and we would have expected that the commonest cause of intestinal obstruction in the neonate, stenosis- atresia of the small intestine, would have long since become manifested (Long, 1967; Guttman, et al., 1975). These children develop vomiting and obvious signs of obstruction within hours or a few days of birth. Hirschsprung's disease can vary in its onset of symptoms and, in fact, some cases may go unrecognized until later childhood or adulthood. I obviously cannot exclude this possibility since we do not have any rectal biopsies. We have certainly seen children present at 1 month or later with obstruction and obvious megacolon. Meconium ileus, the earliest sign of cystic fibrosis, would present in the neonatal period and so we will exclude this diagnosis.
Necrotizing enterocolitis (NEC) was mentioned as a clinical impression and at the age of this child, it would occur with an anatomically obstructive lesion such as Hirschsprung's disease or a partial stenosis. The gross description in this case certainly corresponds with what has been seen at surgery with NEC. Most of you are aware that NEC presents in the first few days of life in a premature or low weight for dates infant (Santulli, et al., 1975; Touloukian, 1976). Polin and coworkers (1976) have described eight term infants who developed NEC between the 26th and 67th days of life after protracted periods of diarrhea. For this reason, it would be important to know whether there were any significant antecedent events in our patient. Additional sections of the bowel would also be required to exclude NEC in this patient. Congenital absence of the intestinal musculature is a final possibility and one which is supported by the morphology. This rare disorder has been reported as a cause of neonatal obstruction and it like NEC usually presents in the first few hours after birth (Steiner, et al., 1969; Carroll 1973). It is a segmental disorder which again would correspond to the findings in this case. Carroll (1973) appropriately concludes that "it is possible that a segment or segments of intestine with only mucosa and serosa present and the musculature 'congenitally absent' could be a state just prior to the rupture of the small intestine." I could not summarize my impression of this case any better.


The history as given in the protocol and the presence of the granulomatous inflammation in the lymph node would immediately warrant a search for tuberculosis and a variety of fungal agents (histoplasmosis, blastomycosis, coccidioidomycosis, etc.). All special stains have been negative for acid fast organisms and fungi. Some of the "granulomas" have more of a stellate abscess appearance with a central neutrophilic reaction rather than caseous necrosis. Therefore, cat scratch disease and tularemia should be included in the differential diagnosis. The workup for these infectious diseases was negative.

If one looks carefully at the lymph node in the areas around the granulomas, there are pigmented histiocytes with brownish cytoplasm. These histiocytes contain ceroid and if seen in a Romanowsky-Wright stained section, they would have a "sea-blue" appearance. The reaction in the skin is a deep acute and chronic inflammatory response without a granulomatous appearance. His lung and cervical lymph node biopsies also showed granulomas.

Landing and Shirkey (1957) described a syndrome in young boys and characterized it as "recurrent infection and infiltration of viscera by pigmented lipid histiocytes." Today, we know this disorder as chronic granulomatous disease of childhood, a hereditary defect of neutrophilic function (Good, et al., 1968; Quie, 1972). The disease appears to be transmitted usually as a sex-linked recessive trait but there are examples of autosomal recessive transmission. These children present in early life with suppurative cervical-axillary lymphadenitis, recurrent pulmonary infiltrates, granulomatous and eczematoid skin lesions, visceral abscesses (hepatic and subphrenic) and osteomyelitis. The neutrophilic defect involves the failure to destroy catalase positive microorganisms once phagocytized. Ultrastructurally, the organisms sit in the cytoplasm totally unscathed. The nitroblue tetrazolium reduction test is used in the screening for the disorder but as Lace and coworkers (1975) indicate, it is not absolutely diagnostic. Staphylococcus aureus is primarily responsible for the recurrent adenitis but as the septic deaths are usually the result of gram negative infection. Overwhelming salmonella septicemia has been reported (Lazarus and Neu, 1975).

Chronic granulomatous disease of childhood is considered one of the inborn lysosomal diseases (Hers, 1973). The disease requires laboratory confirmation but as previously noted, the combination of caseous granulomas resembling tuberculosis and the pigmented histiocytes is very suggestive of the diagnosis. These same histiocytes are found in the red pulp of the spleen and in the portal tracts and sinusoids of the liver. The cutaneous manifestations are less specific and the skin biopsies only provide the type of information which was seen in this case (Windhorst and Good, 1971). Honeycomb lung, renal amyloidosis, and infiltration of the lamina propria of the colon are other morphologic findings. The prognosis is poor since these children respond dismally to antibiotic therapy. Most children have died by adolescence. Interestingly, the mothers who are carriers have a lupus-like disorder.
Case 12. Maxilla - Malignant Melanotic Neuroectodermal Tumor of Infancy.

The clinical course of the neoplasm is this child was unfortunately completely anomalous for what has been reported for the melanotic neuroectodermal tumor of infancy. When this patient was first seen at 4 months of age with a firm mass on the anterior hard palate, it was thought to represent some type of inflammatory process. A biopsy was performed and it disclosed features very similar to those in the seminar section. The tumor was composed of small nests of cells, many of which had been crushed in the sectioning, scattered within a densely fibrous stroma. Some of the better preserved nests revealed a peripheral rim of larger, pale cells and smaller basophilic cells aggregated in the center. Brownish granules were present in the larger cells and this feature was accentuated with the Fontana-Masson stain. This stain may be necessary especially if tissue blocks have gone through the process of decalcification which tends to bleach the melanin. Many nests seem to blend into the fibrous stroma whereas others are intimately associated with the islands of bone. It was concluded when the tumor was originally excised and later when it had recurred locally for the first time that its features were consistent with a typical melanotic neuroectodermal tumor of infancy. The parents had been told that there was a chance of recurrence but after 18 months, the subsequent events were indeed extraordinary.

When the patient returned with the bluish mass beneath the left eye, a biopsy was performed confirming the presence of tumor and a subtotal maxillectomy was done. The margins of resection all contained tumor and within a few weeks, a mass reappeared and a radical maxillectomy was performed but again the margins were all positive. As you can see from the diagram (Figure), the tumor pursued an unrelenting course with the development of cervical lymph node metastasis, extension into the neck and death 34 months after the original resection. At autopsy, tumor had replaced the left side of his face (maxilla, orbit) and there were metastases in the liver, lymph nodes, lung and bones. The adrenals were atrophic and contained no tumor (Dehner, et al.).

Serial ultrastructural and tissue culture studies were performed. Both the melanocytes and neuroblast-like cells were identified until the left neck mass developed. At that time, only the neuroblast-like cells were noted by electron microscopy and tissue culture (Sibley, et al.). Terminally, the tumor was not only looking, but behaving like a typical Stage IV neuroblastoma.

Krompecher first described the melanotic neuroectodermal tumor of infancy as a congenital melanoma in 1918. Since that time, there have been approximately 80-85 cases reported in the literature under a variety of terms reflecting the lack of concensus about the histogenesis. Some of these appellations include pigmented ameloblastoma, melanotic ameloblastic odontoma, pigmented congenital epulis, retinoblastic teratoma and the more popular melanotic progonoma and retinal anlage tumor. It has been accepted by most authors that this tumor is derived from the neural crest. Ultrastructural studies and the infrequent documentation of elevated catecholamine levels have provided some of the strongest evidence for such a derivation. Bolande
(1974) has included this tumor with neuroblastoma, pheochromocytoma and carcinoid as one of the "simple neurocristopathies."

Most melanotic neuroectodermal tumors of infancy present in the first year or so of life and the anterior maxilla is the most frequent site (Stowens and Lin, 1974). About 15% of tumor will locally recur but there has been only one report of a putatively metastasizing melanotic neuroectodermal tumor and this tumor was described in a stillborn (Lindahl, 1970). Our case represents the first one to have a course documented in the fashion as we have. The reason for the obvious malignant transformation is unknown.


Figure. Clinical Course of Malignant Melanotic Neuroectodermal Tumor of Infancy.

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**BIOGENIC AMINES**

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A - Left maxillary gingival swelling
B - Biopsy and excision of mass
C - Bluish mass beneath left eye and fever; partial maxillectomy
D - Recurrent left infra-orbital and maxillary mass; radical maxillectomy
E - Recurrent left facial mass, proptosis and contralateral cervical lymphadenopathy; local radiation therapy (5750 rads)
F - Biopsy of right cervical lymph node with metastatic tumor; chemotherapy
G - Progressive enlargement of facial mass and destruction of left orbit
H - Biopsy of left supraclavicular area with metastatic tumor; chemotherapy altered
I - Death of tumor

VMA - vanillylmandelic acid $\sigma (N=1-6.2 \text{ mg/24 hrs})$, $\delta (N=1.3-8 \mu g \text{ VMA/mg creatinine})$
HVA - homovanillic acid $\text{mg/24 hrs} (N=0-15 \text{ mg/24 hrs})$
Metanephrine $\text{mg/24 hrs} (N=0-1.3 \text{ mg/24 hrs})$
CAT - catecholamine $\mu g/24 \text{ hrs} (N=0-135 \mu g/24 \text{ hrs})$

A tumor of neurogenous derivation should have been the clinical diagnosis of choice on the basis of a paravertebral mass in the posterior mediastinum. As you noted from the history, the patient had at least 2 tumors and not necessarily a metastasis from one site to the other. Apparent multifocal primary tumors have been reported. It was not stated whether either one of these tumors entered an intervertebral foramen.

Histologically, the tumor is readily identifiable as a malignant neoplasm belonging to the neuroblastoma group. The tumor cells are scattered irregularly in a lacy, fibrillar background. There are abundant incomplete fibrovascular septa. At the periphery, foci of dystrophic calcification are noted. Necrosis was not apparent in my section. Lymphoid aggregates with reactive germinal centers were noted but I could not be certain if this mass represented a lymph node with metastatic tumor.

This case raises the questions about the grading of neuroblastomas and whether there is any significance to such an exercise. Makinen (1972) in a reasonably careful paper graded neuroblastomas into 4 categories based upon the following signs of maturation: 1) enlarged nuclei and presence of a single, large vesicular nucleus, 2) appearance of nucleoli, 3) cytoplasmic development, 4) cytoplasmic processes (neurofibrillary background), 5) clumping of cells, 6) formation of Homer-Wright pseudorosettes, 7) bands of stroma separating the cells into units and 8) presence of mature ganglion cells. One can appreciate from the section that our case would rate a positive response to most of these features. The larger tumor cells are not well differentiated ganglion cells and I would estimate that these cells represent only 5-10% of the total population. Using the following system of grading which I think is more simple, I have diagnosed this tumor as a differentiating neuroblastoma.

I. Neuroblastoma, NOS (poorly differentiated) Diffuse small dark cells, no differentiating features.

II. Neuroblastoma, differentiation (poorly differentiated ganglioneuroblastoma) Focal Homer-Wright pseudorosettes, neurofibrillary material, 5-10% larger tumor cells with ganglionic features.

III. Ganglioneuroblastoma Ganglion cells (15-25%), abundant neurofibrillary material, numerous Homer-Wright pseudorosettes.

Approximately 60% of all mediastinal tumors in childhood are neurogenic and 15-20% of all neuroblastomas occur in the mediastinum, typically the posterior mediastinum. There are occasional exceptions. Without question, the prognosis for a mediastinal neuroblastoma is far better (85%) compared
to an overall survival of 20-25%. These tumors are more readily resectable en toto plus they tend to be better differentiated as this case illustrates. The poorest prognosis is associated with an intra-adrenal neuroblastoma.


The osteolytic lesion with punctate calcification in the mandible of this 6-year-old boy presents the problem of 'fibro-osseous lesions', their histogenesis, pathogenesis, nosology and prognosis. There has been a great deal written in the literature about these lesions but less consensus and thus the debate continues.

Microscopically, the tissue consists of osseous trabeculae with irregular geographic outlines which are set in a background of cellular fibroblastic tissue. Many of these trabeculae have the appearance of immature or woven bone rather than mature lamellar bone. I polarized the bone and, indeed, the birefringence pattern consisted of irregular swirls and not an orderly parallel or lamellar appearance. Some osteoblasts were present at the periphery of the trabeculae. The orderly and regular arrangement of osteoblasts typical of ossifying fibroma was not seen. There is another feature in this case which is worthy of comment. Small circular "osseous" islands were present and these resembled what has been described as cementum. As a general pathologist, I have always been intrigued with cementum and how the oral pathologist can always recognize it. Giansanti (1970) has demonstrated some differences in osteoid and cementum by polarizing microscopy but I am still vague and I guess will continue to be.

The differential diagnosis of this lesion includes the other fibro-osseous lesions, cementifying fibroma and ossifying fibroma. Well-differentiated osteosarcoma may closely resemble fibrous dysplasia microscopically but not roentgenographically nor biologically. Chronic osteomyelitis can simulate a fibro-osseous lesion in an edentulous area of the jaw. For the fibro-osseous lesions of the jaws, I have taken somewhat of a "lumper's" attitude because of the frequent overlap in microscopic features. If a lesion has a predominant pattern, I will designate the lesion in the following manner:

I. Fibro-osseous lesion, fibrous dysplasia type.

II. Fibro-osseous lesion, ossifying fibroma type.

III. Fibro-osseous lesion, cementifying fibroma type.

or

IV. Fibro-osseous lesion, mixed type

In the long bones, the situation at least by convention is less confusing since most fibro-osseous lesions are reasonably typical fibrous dysplasias. There have been two reports of tibial ossifying fibromas which roentgenographically resembled fibrous dysplasia or adamantinoma. Friedman and Goldman (1969) have described two "cementomas" of the femur and humerus, respectively.
We had the opportunity to study 46 benign lesions of the jaws in children with the fibro-osseous lesions representing one-third of the series (Dehner, 1973). There were 11 lesions in the maxilla and 4 in the mandible. As best as we could, we designated these lesions as fibrous dysplasia (7 cases), cementifying fibroma (4 cases) and ossifying fibroma (4 cases). Interestingly, one of the cementifying fibromas was associated with an aneurysmal bone cyst. Although not germane to this case, it appears in an ever increasing percentage of cases that the so-called aneurysmal bone cyst is a secondary phenomenon in a primary bone lesion such as solitary bone cyst, giant cell tumor, osteosarcoma, fibrous dysplasia, chondroblastoma, hemangiomia and giant cell granuloma. Some of our other findings in this study of fibro-osseous lesions was the prominent cellularity of the fibroblastic tissue in younger children with fibrous dysplasia and the inability to differentiate the monostotic from the polyostotic fibrous dysplasia. Persistent or recurrent disease was not uncommon even in children with monostotic lesions. A skeletal survey is warranted in patients with a biopsy proven fibrous dysplasia. The vast majority of patients with cranio-facial fibrous dysplasia will only have monostotic disease. Another finding in our study was the occasional locally aggressive behavior that a cementifying fibroma may pursue. Extensive wide local excision may be required to control the tumor.

I have shared with you some of my experiences with this rather frustrating group of lesions with some philosophical thoughts but without any real insight. It is even difficult to answer the question whether we should consider these lesions as neoplasms or some type of developmental anomaly in bone formation.


Case 15. Mandible - Ameloblastoma, Cystic (arising in dentigerous cyst).

Acute swelling and presumably pain at the angle of the jaw brought this 11-year-old boy to clinical attention. A huge lytic defect extended from the first molar area to the coronoid notch. The developing crown of the third molar was displaced to the lower border of the mandibular angle. An excision was performed and it revealed a cyst with a polypoid lesion. The surface of the cyst and the nodule are lined by a type of stratified epithelium that has an odontogenic appearance. There is budding and proliferation of this epithelium into the underlying fibrous stroma. The cells at the periphery of the anastomosing and proliferating epithelium show palisading. The differential diagnosis is ameloblastoma arising in a dentigerous cyst or mural proliferation of odontogenic epithelium in a dentigerous cyst.

For the general pathologist, the interpretation may seem like so much hair splitting but the natural history of the ameloblastoma is that of a tumor which locally recurs in approximately one-third of cases (Small and Waldron, 1955). The dentigerous cyst is one of the odontogenic cysts and not considered a neoplasm. In one scheme of odontogenic cysts, the dentigerous cyst is considered an inflammatory cyst with the odontogenic keratocyst (Figure). Most ameloblastomas occur in adults (average 35-40 years). Only 31 cases in children under 9 years of age were reported through 1962 (Young and Robinson, 1962). Additional cases have appeared in the literature since that date but usually in the form of individual case studies. Odontogenic tumors in general are infrequent in children but there are some with a predilection in early life including the adenomatoid odontogenic tumor (adenoameloblastoma), ameloblastic fibroma, odontogenic fibroma, ameloblastic odontoma and odontoma (Pizer and Hammer, 1967). The remaining odontogenic tumors are curiosities in children.

The differential diagnostic problem presented by this case is a recurrent one as judged by the reports in the literature of "ameloblastomas" in the pediatric age group. There is one series from Nigeria of 16 cases in patients between 5 and 17 years of age (Daramola, et al., 1975). These children appeared to have classic ameloblastomas and were treated as such.

The dental literature contains a number of references which attempt to settle the question of the "ameloblastomatous" potential of the dentigerous cyst. Gorlin (1957) examined 200 mandibular dentigerous cysts which were usually lined by non-keratinizing stratified squamous epithelium. Odontogenic
epithelium was found in only 3% of cases. Bhaskar, however, feels that 25-30% of ameloblastomas originate in dentigerous or follicular cysts. If one peruses the reports of the pediatric ameloblastomas, there is the recurrent theme of proliferating odontogenic epithelium or a true ameloblastoma (Bingham and Boyle, 1971; Sinclair, 1977). Vickers and Gorlin (1970) have defined the earliest neoplastic changes which they will accept as an ameloblastoma arising in a cyst: 1) hyperchromatism of basal cell nuclei of lining epithelium of cyst, 2) palisading and polarization of basal cell nuclei in the lining epithelium and cytoplasmic vacuolization of the basal cells. I do not know whether all oral pathologists follow these criteria. There is sufficient ameloblastic proliferation for me to consider this case an ameloblastoma which should be managed as such.

### CLASSIFICATION OF ODONTOGENIC CYSTS

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>MAIN TYPE</th>
<th>SUBTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental Cysts</td>
<td>Dental Cyst</td>
<td>Radicular Cyst</td>
</tr>
<tr>
<td></td>
<td>Lateral Peridontal Cyst</td>
<td>Residual Cyst, Gingival Cyst</td>
</tr>
<tr>
<td></td>
<td>Dentigerous (Follicular)</td>
<td>Eruption Cyst</td>
</tr>
<tr>
<td>Inflammatory Cysts</td>
<td>Odontogenic Keratocyst (Primordial)</td>
<td>Primordial Cyst</td>
</tr>
</tbody>
</table>

Case 16. Brain - Glioblastoma Multiforme.

Tumors of the central nervous system represent the second largest group of neoplasms in childhood following the leukemias (Young and Miller, 1975). They thus constitute the largest category of solid tumors in children. Our case illustrates one of the many interesting aspects of CNS neoplasms in the pediatric age group. First of all, many probably would consider the occurrence of a primary CNS tumor supratentorially as highly unusual in a 3-month-old child. The patient was apparently well until one week before admission when she became flaccid, pale and developed episodic vomiting indicating increased intracranial pressure. We would anticipate that the mass was quite large because the fontanels and sutures are still open. Indeed, a large mass was identified in the right cerebral hemisphere.

Microscopically, the tumor is composed of relatively small uniform cells with oval to spindle configurations. Mitoses were found without difficulty. There is a faint eosinophilic fibrillary background and at low power, a suggestion of rosettes or cells arranged about a central fibrillary focus. I did not identify any true rosettes with a central lumen. The vascular component was quite prominent to the point of endothelial hyperplasia. An important feature of the tumor was the presence of "palisading" necrosis.

The tumor is an obviously malignant one and primary in the brain. My differential diagnosis included in addition to my final diagnosis, a "primitive neuroectodermal tumor of the brain" or intracerebral neuroblastoma and cellular ependymoma. Not all ependymomas are adjacent to the ventricles and the cellularity with apparent rosette formation can make that diagnosis very difficult. The "palisading" necrosis is an unusual feature for an ependymoma. Therefore, I eliminated this possibility. The "primitive neuroectodermal tumor of the brain" is a term used by Hart and Earle (1973) to designate highly undifferentiated neoplasms of the cerebrum in young patients which have also been referred to as "cerebral medulloblastomas" or "cerebral neuroblastomas" by other authors (Rubinstein, 1972). Despite the fact that these tumors are highly undifferentiated, they may show glial and/or neuronal differentiation. I believe that there is glial differentiation in our tumor. There is enough similarity between the seminar case and some of the conventional glioblastomas to justify that diagnosis although I would not quarrel who wished to use the term "primitive neuroectodermal tumor of the brain". Semantics do not affect the prognosis and for this patient unfortunately, the prognosis is very likely to be extremely poor.

We ordinarily think of CNS tumors in childhood as presenting in the posterior fossa which is true for 55-65% of cases. This case illustrates the point that the younger the patient (less than 2 years), the greater the likelihood that the neoplasm will be supratentorial either in the hemisphere or basal ganglia. Most of these tumors are either astrocytomas or very primitive neoplasms which are difficult to classify into one of the conventional categories. Most intracranial tumors occurring in the first weeks of life are, in fact, located in the cerebral hemispheres.


Case 17. Bone, Maxilla - Osteosarcoma (post-irradiation).

As the history stated, this child presented with a left infraorbital mass which was difficult to palpate. A series of diagnostic studies were performed and finally it was determined that there was a tumor in the maxilla. It was decided that a biopsy was in order, and after a definitive diagnosis, a radical maxillectomy was performed. The patient is 10 months post-surgery and has been receiving methotrexate and Adriamycin on schedule.

Grossly, the tumor involved the anterior maxillary wall and the major macroscopic component was present in the soft tissues of the cheek. Microscopically, the neoplasm consists of bizarre mononuclear and spindle cells with conspicuous acidophilic material deposited among the tumor cells. This material is interpreted as osteoid of an abnormal type. Much of the reaction in the section is probably the result of the recent biopsy. The margin of resection contained infiltrating tumor primarily in the soft tissue.

The diagnosis of osteosarcoma in a child of this age should not evoke any great surprise but the anatomic site is unusual. This situation should raise some questions and the most important one is about the past history. The patient was originally seen at the University Hospitals at 4 months of age when his parents noted that the right eye failed to respond normally to light. The right eye seemed to be larger also. A tumor was identified in the posterior chamber of the right eye and a two small ones in the left eye. An enucleation of the right eye was performed and the 2 small tumors in the left eye were photocoagulated. Irradiation therapy was also given to the left eye (1,500 rads). Two years later (1969) without evidence of interval disease, a mass developed in the left cheek. A biopsy was performed and it showed a highly undifferentiated tumor interpreted as metastatic retinoblastoma. There was no evidence of osseous involvement. He was treated with 3,000 rads of cobalt followed by cyclophosphamide. There were no interval difficulties until early 1977 when the osteosarcoma was diagnosed.

Retinoblastoma is one of the so-called 'embryonic neoplasms' because its morphologic features simulate the embryogenesis of the parent organ. The other tumors in this same category include the medulloblastoma, neuroblastoma, Wilms' tumor (nephroblastoma) and pulmonary blastoma. Retinoblastomas represent a rather small percentage of childhood malignancies (2-3%), occur in 1:14,000-20,000 birth except in Mexico where the frequency is 1:2000 infants. The average age at diagnosis is 16-18 months (90% less than 3 years old) except that the age is much younger in the child with bilateral retinoblastomas (2-4 months). It ranks with the neuroblastomas as the most common congenital tumor. Approximately 70% of retinoblastomas are unilateral. Although our patient had bilateral tumors, this is the situation in 30% of sporadic cases. It has been estimated with 6% of all retinoblastomas are inherited through a dominant autosomal gene with a high penetrance or expressivity (70-95%). One-half of the familial cases are bilateral. The prognosis of the retinoblastoma is dependent upon the stage of the disease. In general, the overall survival is very good (85-90% - 3 years).

Morphologically, the retinoblastoma is located in the posterior chamber where it usually grows as an exophytic mass often producing retinal detachment. Multifocal tumors are not uncommon. It may seed the vitreous
and aqueous humors and form deposits on the iris and chamber angles. The tumor will also invade the subretinal space, choroid and optic nerve. There was no evidence of involvement of the optic nerve in our patient. Flexner-Wintersteiner rosettes, necrosis, calcification and DNA precipitation around the blood vessel (Azzopardi effect) are the principal histologic features.

What about the relationship between the development of the osteosarcoma in our patient and his retinoblastomas? The association between retinoblastoma and a second primary malignancy in the head or neck region has been appreciated for some time (Sagerman, et al., 1969.) All patients, of course, have received irradiation therapy to the area but more strikingly, the child with bilateral tumors and a positive family history has the maximum risk. Whether the known chromosomal instability (deletion of long arm of chromosome 13) in some cases is a factor remains a speculative point. Schimke and coworkers (1974) have reported siblings with bilateral retinoblastomas who developed osteosarcomas. Osteosarcoma is by the way the most frequent second malignant tumor in these patients. There is nothing unusual about the morphology and behavior of these osteosarcomas. Approximately 4% of all osteosarcomas in the Mayo Clinic experience are related to prior irradiation therapy (Table).

# Varieties of Osteosarcoma

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Conventional</td>
<td>75%</td>
</tr>
<tr>
<td>Osteoblastic</td>
<td>50%</td>
</tr>
<tr>
<td>Chondroblastic</td>
<td>25%</td>
</tr>
<tr>
<td>Fibroblastic</td>
<td>25%</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Jaw bones</td>
<td>6%</td>
</tr>
<tr>
<td>Paget's disease</td>
<td>3%</td>
</tr>
<tr>
<td>In other conditions</td>
<td></td>
</tr>
<tr>
<td>Post radiation</td>
<td>4%</td>
</tr>
<tr>
<td>Dedifferentiated chondrosarcoma</td>
<td>3%</td>
</tr>
<tr>
<td>Multicentric</td>
<td></td>
</tr>
<tr>
<td>Telangectatic</td>
<td>3%</td>
</tr>
<tr>
<td>Well differentiated</td>
<td>1%</td>
</tr>
<tr>
<td>Periosteal</td>
<td>1.5%</td>
</tr>
<tr>
<td>Parosteal</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Case 18. Anterior Mediastinum (Thymus) - Malignant Mesenchymal Tumor (? Thymoblastoma).

This anterior mediastinal tumor was unique in our experience and at the time we were presented with this case, our best effort was to indicate what it was not. The surgeon described the mass as residing in the anterior mediastinum and was definitely extrapleural. As you noted from the section, the tumor is obviously malignant and fails to display any significant differentiation. The tumor cells are moderately large and consist mainly of a hyperchromatic nucleus and moderate numbers of mitoses. Some ill-defined aggregation of cells is noted and the background stroma has a myxoid quality. That myxoid quality was also apparent in the gross in that the fragments of tumor were greyish-white and slimy. The tumor was excised in a piecemeal fashion. We sampled extensively from the multiple fragments and other features of the tumor emerged including lobules of neoplastic cartilage, foci resembling embryonal rhabdomyosarcoma, blastomatous nests in a loose background reminiscent of the nephroblastoma, glandular areas and compressed but otherwise normal thymus. We were struck by the similarity to the Wilms' tumor or alternatively, that pulmonary tumor which has been designated the 'pulmonary blastoma.'

Since we encountered this tumor, we have seen two other cases with Drs. Ralph Franciosi and Robert Drake of the Minneapolis Children's Health Center and Hospital with very similar clinical and pathologic findings. These children have presented with fever and respiratory insufficiency and on chest x-ray, there was a large mass in the anterior chest. Foci of neoplastic cartilage and embryonal rhabdomyoblastic areas have been identified in these tumors. We have been perplexed as to the classification of this neoplasm, since these tumors appear to originate in the anterior mediastinum. Why isn't it a malignant germ cell tumor? Malignant germ cell tumors in the anterior mediastinum are either seminomas (germinomas), embryonal carcinomas, endodermal sinus tumors, choriocarcinomas or mixtures. There was very little in the histology of the tumor to strongly support a germ cell origin. It is certainly not a conventional type of thymoma. Although the rare thymoma in a child varies somewhat in its morphology and also behavior to the thymoma in the adult, this tumor is well outside our experience (Dehner, et al., 1977). Another possibility that we considered at the time was a metastasis to the anterior mediastinum from a nephroblastoma because of the superficial similarities. This suggestion failed to yield positive results. We were then left with the distinct possibility that we were observing a tumor which has not been characterized in the literature. Because of its very embryonal appearance and the location in the thymus, we have proposed the term of "thymoblastoma."


This case illustrates the fact that all age groups and slide seminars have been enveloped by the lesion diagnosed as malignant fibrous histiocytoma. Although I did not have a complete gross description, the lesion is probably represented en toto in the microscopic section. The circumscribed nodule is seemingly surrounded by a fibrous envelope with scattered lymphocytic aggregates at the periphery. I looked twice at the section to be certain that I was not looking at a lymph node. Large, histiocytic cells are scattered among more fibroblastic appearing cells. Occasional bizarre giant cells are also present. A storiform pattern consisting of cellular bands radiating into a central hypo- or acellular zone is identified without much difficulty.

The malignant fibrous histiocytoma is but one tumor in a spectrum of lesions presumably derived from the fixed tissue histiocyte (Table). There is a close correlation between the depth in the skin and soft tissue of the fibrohistiocytic lesion and its prognosis. The size of the tumor is also an important prognostic consideration.

Although the malignant fibrous histiocytoma is one of the commonest soft tissue tumors in adults, it is distinctly unusual in childhood. These tumors have a predilection for the lower extremities, retroperitoneum and buttock, however, there is no apparent limitation as to the anatomic localization. The local recurrence rate is rather high (60-70%) and a metastatic rate of 30-40%. Metastases rarely occur before one or more local recurrences.

The differential diagnosis of malignant fibrous histiocytoma may pose some problems since this tumor must be distinguished from pleomorphic liposarcoma, pleomorphic rhabdomyosarcoma, hemangiopericytoma, fibrosarcoma, metastatic renal cell carcinoma, metastatic melanoma and reactive lesions such as nodular fasciitis and malakoplakia. It is appreciated that most of these tumors and reactive processes are problems encountered mainly in the adult. An important stain to perform is the PAS with diastase digestion since it will provide some clues and direction in a diagnosis.

I do not have the follow-up available in this case but I suspect that this young girl should do well.


THE FIBROUS HISTIOCYTOMAS: TUMORS COMPOSED OF CELLS RESEMBLING FIBROBLASTS AND HISTIOCYTES

A. BENIGN (may recur) AND REACTIVE

1. Subepidermal nodular fibrosis
2. Juvenile xanthogranuloma
3. Nodular tenosynovitis
4. Xanthofibroma (fibroxanthoma)
5. Pigmented villonodular synovitis
6. Reticulohistiocytoma
7. Xanthomas
8. Atypical fibroxanthoma of the skin

B. LOCALLY AGGRESSIVE AND POTENTIALLY MALIGNANT

1. Storiform fibrous histiocytoma
   (dermatofibrosarcoma protuberans)
2. Atypical fibroxanthoma of the skin

C. MALIGNANT

1. Fibroxanthosarcoma
2. Inflammatory fibrous histiocytoma
   (xanthosarcoma)
3. Malignant giant cell tumor of the soft parts
4. ? Epithelioid sarcoma
5. Malignant fibrous histiocytoma, unclassified

(From Kempson, R. L., 1977)