MINNESOTA SOCIETY OF CLINICAL PATHOLOGISTS
FALL SEMINAR
OCTOBER 25, 1986

JUAN ROSAI, M.D.
Professor and Director, Anatomic Pathology
Department of Pathology
Yale University, School of Medicine
New Haven, CT
CONTENTS

CASE HISTORIES AND CONTRIBUTORS ........................................... 1

DISCUSSION AND REFERENCES

Case 1. - Breast - Intraductal carcinoma .................................. 6

Case 2. - Kidney - Wilms' tumor (with mucinous epithelium) .......... 9

Case 3. - Peritoneum - Multiple peritoneal inclusion cysts (so-called multicystic benign mesothelioma) .................. 11

Case 4. - Soft tissue, thumb - Fibrolipomatous hamartoma of nerve ........ 13

Case 5. - Brain - Malignant astrocytoma (anaplastic astrocytoma; small cell glioma; isomorphic glioblastoma) ................. 14

Case 6. - Oral cavity - Peripheral ameloblastoma ...................... 17

Case 7. - Soft tissue, neck - So-called angiomatoid malignant fibrous histiocytoma ............. 19

Case 8. - Skin - Angiomatosis (Kaposi's sarcoma-related) .......... 21

Case 9. - Testis - Mature teratoma and intratubular germ cell atypia 23

Case 10. - Pleura - ? Malignant fibrous mesothelioma .......... 26

Case 11. - Spleen - Systemic mastocytosis ......................... 28

Case 12. - Pancreas - Solid and papillary epithelial neoplasm ...... 30

Case 13. - Meninges - Papillary (malignant) meningioma ............ 32

Case 14. - Thyroid - "Mixed" carcinoma (papillary, Hurthle cell, clear cell, and poorly differentiated) ....................... 34

Case 15. - Thyroid - Undifferentiated (anaplastic) carcinoma arising in Hurthle cell carcinoma .................. 36

Case 16. - Kidney - Multilocular cyst (multilocular cystic nephroma) .... 38
Case 17. - Bone, Sacrum - Sinus histiocytosis with massive lymphadenopathy (SHML) .............. 40

Case 18. - Bone, Scapula - Chondrosarcoma with poorly differentiated areas (so-called dedifferentiated chondrosarcoma) .................. 42

Case 19. - Thymus - Thymoma with anaplastic transformation ("carcinosarcoma") .................. 44

Case 20. - Skin - Malignant pilar (trichilemmal) tumor ................................................. 46
Case 1

The patient is a 52-year-old female with a suspicious nodule which was detected by mammography. The past history was remarkable for breast cancer in a maternal grandmother, an aunt and possibly her mother. A breast biopsy was performed. (Contributed by Dr. Charles Horwitz, Minneapolis, MN)

Case 2

A newborn infant was found to have a tracheo-esophageal fistula, imperforate anus and bony defects in the sacrum. Her fistula was repaired and a colostomy was performed as a first stage in the repair of the imperforate anus. She was released from the hospital at 6 weeks of age; she appeared to be progressing well until 6 months of age when a left lower abdominal mass was palpated on a follow-up examination. The mass was located in the lower pole of the left kidney. (Contributed by Dr. Ralph Franciosi, Minneapolis, MN)

Case 3

A 42-year-old female was admitted for the performance of a tubal ligation. At laparoscopy, multiple peritoneal cystic lesions were found in the pelvis. At laparotomy, numerous thin-walled cysts containing clear fluid were found attached to the bowel, uterus, ovaries and parietal pelvic peritoneum. The largest cysts measured 2 cm in diameter, the aggregate dimensions of the multicystic mass was 20 x 10 x 2 cm. (Contributed by Dr. Juan Rosai, New Haven, CT)

Case 4

The patient is an 18-year-old left-handed college student with enlargement of the right thumb and thenar eminence. There is no history of familial diseases. The onset of the disorder was first noted at age 2 shortly after the patient experienced an insect bite. Digital enlargement has been progressive with a general increase in stature. Biopsy two years prior to resection of the lesion showed adipose tissue with possible traumatic neuroma. Neurologic examination at the time of admission showed massive but painless enlargement of the thumb with some diminished cutaneous sensation. Hypopigmentation was noted at the periphery of the enlarged digit. A physical examination was otherwise unremarkable. X-rays showed marked soft tissue enlargement but no abnormality of the bones of the thumb. (Contributed by Dr. B. W. Scheithauer, Rochester, MN)

Case 5

An infant, a 6-week-old female, was the product of an uncomplicated pregnancy. She was discharged home after a normal nursery examination. Several hours before admission to the hospital, the parents noted that she seemed excessively drowsy and was irritable when aroused. Shortly after the onset of a seizure, she was taken to the emergency room where obvious bulging of the fontanelles was noted. Papilledema was difficult to establish. Emergent imaging studies were performed; a large mass in the left hemisphere was identified. A craniotomy and biopsy were performed. (Contributed by Dr. Thomas Swallen, Robbinsdale, MN)
Case 6

This 66-year-old male presented with a painful swelling in the back of the mouth for several months. His past medical history was significant for a previous diagnosis of sarcoidosis which was established on the basis of a biopsy of mediastinal lymph nodes. After a period of steroid therapy, his disease stabilized. Physical examination revealed a moderately firm mass in the soft tissues along the left inner mandible. The mass was discrete from the bone which was confirmed by X-rays of the region. A biopsy was followed by a resection. (Contributed by Dr. Carlos Manivel, Minneapolis, MN)

Case 7

A 21-year-old male presented with mass of unknown duration in the soft tissues of the posterior neck. A total excision was carried out. Grossly, the mass measured 8 X 7 X 5 cm. It was delimited by a thick fibrous capsule, and surrounded on one side by skeletal muscle. The cut surface showed a large cystic space filled with clotted blood. The gross appearance was very much like that of a hematoma, except for the presence of a solid grayish area of granular appearance measuring up to 1.5 cm. in diameter, surrounded by blood except for an area of attachment to the fibrous capsule. (Contributed by Dr. Juan Rosai, New Haven, CT)

Case 8

The patient is a young, gay male with a history of fever and weight loss over several months. He developed cutaneous and subcutaneous nodules over his entire body; one large nodule radiographically eroded a portion of the humerus. The patient died two months after biopsy. Autopsy disclosed cutaneous and subcutaneous lesions throughout his skin and soft tissues, in retroperitoneal lymph nodes and the liver. A large mass surrounding his duodenum showed the same histology. (Contributed by Dr. Arthur Cohen, Charlotte, NC)

Case 9

The patient is a 29-year-old male with an uneventful past medical history. Approximately one week before admission, he noted a painless swelling in the right testicle. Examination revealed a firm, 2 cm. mass in the right testicle. There were no other abnormal findings on physical examination. Clinical laboratory studies including hemogram and urinalysis were within normal limits. Following a biopsy of the right testicle, a radical orchietomy was performed. A well circumscribed, cystic lesion measuring 2 cm. occupied a portion of the testis. (Contributed by Ronald Fuglestad, Waconia, MN)

Case 10

In 1982, this 36-year-old woman, who was being evaluated for menstrual irregularity and infertility, was found to have a cystic mass in the right middle lobe of the lung. The cystic mass had first appeared as an infiltrate in 1979. A retrospective review of previous chest X-rays showed the lesion to have been present as early as 1975. As the lesion appeared to be slowly enlarging since 1979, the right middle lobe was resected. There was a peripheral 15 cm. pleural cyst filled with hemorrhagic fluid. Within the cyst arising from the surface of the lung there was a polypoid tumor (4 X 3 X 2.5 cm) which was attached by a stalk. (Contributed by Dr. H. A. Carpenter, Rochester, MN)
Case 11

A 79-year-old white male presented with lethargy, mild weight loss, and left upper quadrant pain of unspecified duration. The principal abnormality on physical examination was splenomegaly in the absence of hepatomegaly and lymphadenopathy. There were no cutaneous changes. The white cell count was elevated (22,000); the hemoglobin was 12 gm.% and the indices were microcystic. Bone marrow biopsy was interpreted as "chronic myeloproliferative syndrome". A splenectomy was performed which yielded a 1040 gm specimen. (Contributed by Dr. Martin L. Lipschultz, St. Paul, MN)

Case 12

The patient is an 18-year-old female who presented in mid-1983 for a routine school physical examination. Mild splenomegaly was confirmed on ultrasound. A computer assisted tomographic scan of the abdomen revealed a 10 cm. mass separate from the spleen and presumably involving the tail of the pancreas or retroperitoneum. A serum amylase was elevated three times the upper limit of normal. At surgery, a soft discrete tumor was found within the tail of the pancreas. On cut section the solitary lesion was yellow-tan and unaccompanied by extrapancreatic spread or lymph node involvement. (Contributed by Dr. L. H. Weiland, Rochester, MN and Dr. D. W. Ohrt, Sioux Falls, SD)

Case 13

The patient is a 66-year-old former fireman who in 1975 presented with a 3 cm. left parietal-dural neoplasm. The discrete mass was grossly totally resected. Over the ensuing 11 years, he underwent four additional resections for recurrence. Following the first recurrence in 1980, he underwent radiotherapy (6075 rads via a 5 cm. port). Invasion of brain substance was noted on the third recurrence in 1984. The fourth recurrence was heralded by intratumoral hemorrhage. As before, "excellent margins" were achieved at the time of resection. The most recent recurrence was associated with worsening of his long-standing hemiparesis as well as the onset of aphasia. At surgery the globular tumor mass was accompanied by a 3 mm. thick shelf of tumor extending laterally into the subdural space. Brain invasion was again noted. Excision was subtotal. The patient is presently receiving chemotherapy. (Contributed by Dr. B. W. Scheithauer, Rochester, MN)

Case 14

A 23-year-old female had a history of radiation therapy to the neck three years previously for Hodgkin's disease. The radiation field included the thyroid gland. She now presents with a thyroid nodule. At operation, the entire thyroid gland was found to be multinodular and adherent to adjacent structures. According to the surgeon, small amounts of neoplasm or thyroid tissue were left in the operative field. Grossly, the cut surface of the thyroid showed multiple nodules ranging from 0.2 to 1.8 cm. in diameter. They varied in color from dark red to tan. (Contributed by Dr. Juan Rosai, New Haven, CT)

Case 15

The patient is a 78-year-old male who presented in February 1978 with a 3 cm. nodule in the left thyroid gland. An infiltrative neoplasm was resected.
Six months thereafter a nodule, presumably metastatic, was resected from the right sternocleidomastoid muscle; 5600 rads were administered to this region. One year thereafter, a second 3 cm. mass was resected from the same sternocleidomastoid. The patient remained well until September 1980 at which time chest X-ray revealed a 4 cm. left upper lobe mass. Lobectomy was performed. The patient remains well and is gainfully employed in 1978. He attributes his longevity to his capable surgeon and vitamin C. (Contributed by Dr. F. E. Nora, Medford, OR)

**Case 16**

This 51-year-old woman was first seen in 1978 complaining of a progressively enlarging mass in her right abdomen first noticed five months previously. Radiologic studies showed a filling defect in the right renal pelvis associated with a large mass which extended through the retroperitoneum to the dome of the bladder. The patient felt well and had no history of urologic disease. A 15 x 14 x 7.5 cm. cystic mass was resected from the right kidney. (Contributed by Dr. H. A. Carpenter, Rochester, MN)

**Case 17**

A 19-year-old female complained of deep aching pain, bad enough to awaken her at night, in the low back for three months. X-rays showed a destructive lesion of the sacrum. Rectal examination revealed a tender mass in the sacrum. A sacral biopsy was done. Three months later the patient developed chills, fever and enlarged neck nodes. The material provided is from the sacrum. (Contributed by Dr. K. K. Unni, Rochester, MN)

**Case 18**

The patient is a previously healthy 54-year-old white male who presented with intermittent sharp stabbing left shoulder pain in July, 1985. He was treated for bursitis without relief of symptoms. X-ray studies at the time were negative. In December, 1985, the imaging studies were repeated because of continued symptoms and at that time, a lytic lesion in the left scapula in the area of the coracoid process was identified. The physical examination was basically negative. No mass was palpable in the region of the left scapula. Following routine laboratory studies, all negative, an open biopsy was performed followed by a scapulectomy. (Contributed by Dr. Mark Wick, Minneapolis, MN)

**Case 19**

A 68-year-old Japanese-American female presented with a very slowly enlarging anterior mediastinal mass for at least 25 years. On several occasions in the past, she had refused surgery. Earlier this year she became febrile and developed a pleural effusion. At thoracotomy, a huge mediastinal tumor was found occupying the majority of the lower half of the chest, with multiple adhesions to the lung and pericardium. Several nodules within the left upper lobe were also palpated. On gross examination, the mass measured 18 x 11 x 9 cm. and weighed 810 grams. It was bosselated with an irregularly nodular external surface varying in color from grey-pink to yellow-grey. The latter areas had a myxoid appearance. The cut surface had a variegated appearance, consisting of multiple nodules separated by thin, grey-white, fibrous strands. Some of the nodules had a glistening, pale grey appearance with an encephaloid quality. Other areas were firmer, grey-yellow and granular. Finally, some
nodules were hemorrhagic and contained yellow-grey necrotic centers.
(Contributed by Dr. Juan Rosai, New Haven, CT)

Case 20

A 78-year-old female presented with a skin tumor in the scalp for over 20 years. The mass increased in size during the past few months. At the time of presentation, the tumor measured 6 cm. in diameter, was polypoid and centrally ulcerated. A wide local excision with regional lymphadenectomy was performed.
(Contributed by Dr. Juan Rosai, New Haven, CT)
CASE 1 - BREAST - INTRADUCTAL CARCINOMA

Most of the breast tissue seen in this biopsy has a somewhat atrophic appearance. The stroma is of dense fibrous type, including the intralobular portion. The lobules themselves are relatively small and dissociated by the fibrous overgrowth. Some of the lobules show cystic involution, a change to be regarded as physiological and not constituting cystic disease. In addition, there is a medium-sized duct with a marked epithelial proliferation surrounded by a mild lymphocytic infiltrate. The proliferating cells are cuboidal, with vesicular nuclei, relatively inconspicuous nuclei, little if any mitotic activity, and very well-defined cell membranes. The cytoplasm varies in staining quality from acidophilic to pale. There is individual cell necrosis, with nuclear pyknosis and foamy changes or shrinkage of the cytoplasm. Some of these foamy cells are clearly of epithelial nature. The myoepithelial layer is preserved, a fact confirmed with actin stain. There is no evidence of stromal invasion.

The changes seen in this duct raise the difficult and controversial differential diagnosis between atypical intraductal hyperplasia and carcinoma in-situ. I prefer to regard this particular lesion as an example of carcinoma in-situ of non-comedo type in view of the monotonous appearance of the cell proliferation, the pallor of the cytoplasm, the sharply outlined cell membranes and the presence of individual cell necrosis. The persistence of the myoepithelial cell layer in no way invalidates the diagnosis of cancer, as Azzopardi has pointed out in his book(1).

He also commented that carcinoma cells usually do not have the "syncytial" character of epitheliosis. He stated that sharp cell edges are very suggestive of malignancy in a borderline lesion and that the marked pallor of the cytoplasm, sometimes even apparent at low magnification, should alert the observer as to the possibility of carcinoma. He also warned about slight cytoplasmic granularity arising one's suspicion. Most of these features are present in the Seminar case.

The most important practical question raised by this case is the treatment to be instituted following this biopsy, in relation to the probability of this patient developing invasive breast cancer if no additional therapy were to be instituted at this time.

Retrospective studies of in-situ ductal carcinoma treated by biopsy only have revealed an incidence of subsequent invasive carcinoma in about 30-40% of the patients (2,3,6,7,8,9). When mastectomy was performed for in-situ ductal carcinoma at the time of the initial diagnosis, unsuspected invasion was found in 6% of the cases in one of the series. Because of these findings, the usual recommendation is to treat in-situ
ductal carcinoma by ipsilateral general mastectomy with low axillary dissection and to perform a contralateral breast biopsy.

Because of the controversial issues raised by the various terms used to define proliferative breast disease, the American Cancer Society recently convened a group of pathologists in an attempt to achieve a consensus regarding the terminology to be employed and the recommendations to make(4). The groups defined in the study in relation to the relative risk for invasive breast carcinoma were the following:

1. No increased risk: Nonproliferative disease.
2. Slight increased risk (1.5-2x): Epithelial proliferative disease without atypia.
3. Moderately increased risk (4-5x): Atypical hyperplasia.

To these, one could add as a fourth category a High risk group, in which the incidence is 10 times or more that of the normal population; this would include both lobular carcinoma in-situ and the non-comedo type of ductal carcinoma in-situ(5). Using this scheme, I would place Case 1 into the latter category, and I would have therefore recommended the performance of a mastectomy. In this particular case, the family history of breast carcinoma increases further the risk of invasive carcinoma, and the indication for a mastectomy becomes even stronger.

REFERENCES


CASE 2 - KIDNEY - WILMS' TUMOR (WITH MUCINOUS EPITHELIUM)

The overall microscopic appearance of this renal neoplasm is characteristic of Wilms' tumor. All of the usual elements of this malignancy are present, including primitive renal blastema, spindle stroma, immature tubules, and developing glomeruli (2,3,4). The epithelial structures stain strongly for cytokeratin, whereas vimentin shows staining only in scattered cells located in the central portion of the developing glomeruli, suggesting early mesangial differentiation. The blastematous portion shows high mitotic activity, but this tumor does not show the features thought to be associated with an unfavorable prognosis, i.e., anaplasia or sarcomatous stroma.

The most interesting morphologic feature of this particular case is the presence of ductal type epithelium with extensive branching, resulting in a fibroadenoma-like appearance. An article describing fibroadenomatous-like structures in nephroblastoma was published by Delemarre at al. recently (5). They found 23 cases with this distinctive growth pattern in a review of 889 patients with Wilms' tumor from the files of the SIOP Nephroblastoma trials and studies. When they compared this subgroup in terms of recurrence, free survival and actuarial survival with the entire series of SIOP nephroblastomas, they found that the subtype with the fibroadenomatous-like structures was associated with a more favorable prognosis: only one 3-year-old child with stage IV tumor had died.

In the Seminar case, this tubular epithelium has the additional striking feature of a marked degree of mucinous differentiation. This epithelium is highly positive for mucicarmine stain, and it also shows isolated cells positive for chromogranin, consistent with endocrine differentiation. The presence of mucinous epithelium and argentaffin cells in nephroblastoma was described by Hou and Azzopardi in 1967 (6); they viewed these components as derivatives of collecting tubules. There is no indication that Wilms' tumors with this feature behave differently from the others. Interestingly, Ater et al. (1) described cases of Wilms' tumor associated with the presence of a mucinous material in the serum which behaved in an aggressive fashion. However, those neoplasms were not morphologically dissimilar from the usual Wilms' tumors, and therefore it is not clear whether this phenomenon bears any relation with the microscopic features seen in the Seminar case.

REFERENCES


CASE 3 - PERITONEUM - MULTIPLE PERITONEAL INCLUSION CYSTS
(SO-CALLED MULTICYSTIC BENIGN MESOTHELIOMA)

This distinctive pelvic lesion is characterized by the formation of variously sized cysts lined by flattened, cuboidal and low columnar epithelium. The content of the cysts varies from clear to mucinous. The wall is of fibrous type and usually contains a mild to moderate amount of inflammatory infiltrate. The epithelium shows the typical morphologic, immunohistochemical and electron microscopic features of mesothelium. It is positive for keratin and negative for Factor VIII related antigen. Electron microscopically, it is characterized by the presence of numerous tonofibrils, complex desmosomes, and long and slender microvilli. Focally, this epithelium has a mesonephroid appearance due to the location of the nuclei in the apical portion of the cytoplasm. In addition, there are submesothelial glands with the typical appearance of endosalpingiosis. One of the fallopian tubes show characteristic changes of salpingitis isthmica nodosa.

This case is typical of an entity which has been generally reported as multicystic benign mesothelioma(2,4). However, there is very little evidence that the disease is neoplastic. It does not resemble any of the known types of bonafide mesotheliomas. Instead, it is often accompanied by inflammatory infiltrates and fibrin deposition, and it is nearly always seen in the pelvis of females, sometimes associated with obvious pelvic inflammatory disease. The largest series on this entity is in the process of being written up by Dr. Robert Scully and his colleagues, from Massachusetts General Hospital. Through his courtesy I was able to obtain data regarding this series, which is comprised of 24 cases. All of the patients were female. Three were in the late second decade, eight in the fourth decade, two in the fifth decade, and three in the sixth decade at the time of presentation. The average age at the time of diagnosis was 33 years. The lesions presented mostly as pelvic masses that were often attached to or engulfed pelvic organs. Almost two thirds appeared to be confined to or practically confined to the pelvis. Some of them appeared inoperable on exploration. Fourteen of the patients gave a history of a previous operation involving the pelvis, nine had endometriosis, and four had pelvic inflammatory disease. Sixteen patients had follow-up examination for one year or more. Four were alive and well with no evidence of recurrence 1.5 to 12 years (average 8 years) post-operatively. Twelve had recurrences. Of these, five had recurrences that were successfully treated so that the patients were alive and well, free of clinical evidence of disease, 3 to 16 years after the initial operation. Several patients were alive with recurrent disease 1 to 17 years after their initial operation. Of the total 12 patients who had recurrences, six had one recurrence, five had two recurrences, and one had three recurrences. The first recurrence varied in the post-operative interval from less than one to 15 years. No patient has died of the disease;
one died of a cerebral disorder, the nature of which is not clear. Grossly, the size of these lesions was up to 16 cm. They were composed of multiple cysts filled with clear to gelatinous fluid separated by fibrous tissue. Inflammation, hemorrhage, and deposits of fibrin in the fibrous component of the lesion was a constant and sometimes prominent feature, greater than what one would expect in a true mesothelial neoplasm. These microscopic observations, in addition to the essentially benign course of the disease, suggested to the authors that the lesion was not a neoplasm but rather a mesothelial reaction to an inflammatory process.

Although nearly all cases of this entity have occurred in the pelvis of females, isolated cases in males or with involvement of the entire peritoneal cavity have been reported.

The most important differential diagnosis of this entity is with cystic lymphangioma. In a series by Carpenter et al from the Mayo Clinic on multilocular cystic lesions of the peritoneum(1), eight were examples of the lesions represented by the Seminar case, and 25 were classified as cystic lymphangiomas. The latter lesion occurs most often in males, often develops in children, and recurrence is extremely rare. It differs from the mesothelial process because of the presence of smooth muscle in the wall of some of the cysts, focally prominent collections of lymphocytes (sometimes forming follicles), and the fact that the lining cells of the cysts are negative for keratin and do not show epithelial features ultrastructurally.

Also of interest in the Seminar case is the coexistence of endosalpingiosis and salpingitis isthmica nodosa. Although both of these conditions are of controversial histogenesis, many authors regard them as of metaplastic nature related to inflammation(5); this fits well with Scully's proposal that this peritoneal lesion is of reactive rather than neoplastic type.

Occasionally, these mesothelial cysts have been found incidentally during the course of laparotomy lying free in the peritoneal cavity(3).

REFERENCES

CASE 4 - SOFT TISSUE, THUMB - FIBROLIPOMATOUS HAMARTOMA OF NERVE

This lesion is composed of thickened nerve bundles surrounded by mature adipose tissue and dense fibrous tissue. The nerves show thickening of the epineurium and perineurium. The bulk of the lesion is made up of an admixture of fibrous tissue and fat, with no morphologic abnormalities of significance.

This case is a typical example of the lesion described by Silverman et al (4) as fibrolipomatous hamartoma of nerve. Their article included 26 cases of this entity, 19 of them without macrodactyly and 7 associated with macrodactyly (as seen in the Seminar case). Twenty-five involved the hand, wrist, palm, and finger, and one case involved the foot. Four of the nine patients with neurologic symptoms of pain or paresthesias had physical findings compatible with compression neuropathy, and two others were described as having the carpal tunnel syndrome. Most patients had been aware of a mass for several years; in ten of the cases the lesion had been present at birth or had developed within the first two years of life, suggesting a congenital origin. In many of the patients the lesion was slowly progressive, as it was the case in the Seminar example.

Microscopically the lesion was characterized, as in the Seminar case, by fibroadipose enlargement of the nerve with massive epineurial and perineural fibrosis. In two of the cases this nerve enlargement was associated with overgrowth of bone and surrounding subcutaneous tissue. In one additional case there was metaplastic bone formation. Follow-up in 18 cases revealed a benign course following biopsy, limited excision, or division of the flexor retinaculum in the wrist. Previous cases have been reported as intraneural lipoma, perineural lipoma, lipofibromatous hamartoma, and macrodystrophia lipomatosa (1,2,3). This abnormality is virtually confined to the median nerve, but isolated involvement of other nerves has been reported.

REFERENCES


This primary malignant tumor of the CNS has a rather monomorphic appearance. It is composed of relatively small cells, having round or oval nuclei which are normochromatic and associated with a very modest degree of mitotic activity. Necrosis is essentially absent. The cytoplasm is scanty and has a vaguely fibrillary quality; cytoplasmic borders are indistinct. Vascularity is prominent, a few of the vessels being lined by plump endothelial cells. Rosettes, giant cellular forms, and perivascular formations are absent. Stain for glial fibrillary acidic protein (GFAP) shows strong cytoplasmic staining in a small proportion of cells which seem to be of neoplastic nature. The staining is mainly in the perikaryon, but sometimes extends to thin cytoplasmic prolongations. Staining for neurofilaments and neuron specific enolase shows occasional positive cells and nerve fibers surrounded by tumor cells. These cells do not show nuclear atypicalities and are interpreted as entrapped non-neoplastic neurons.

The diagnosis of this tumor is malignant astrocytoma in view of its morphology and positivity for GFAP. One of its most striking features is the uniformity of the cell population, which sets it notably apart from the most common malignant glial tumor in the adult brain, i.e., glioblastoma multiforme. In the classification of tumors of the central nervous system proposed by Del Rio Hortega, there was a major category of neoplasms made up of cells recapitulating the structure of glioblasts. He included into this category two subsets, which he designated as heteromorphic and isomorphic. The former is usually known as glioblastoma multiforme. It is likely that del Rio Hortega's isomorphic form of glioblastoma multiforme is the tumor represented by the Seminar case, i.e., a neoplasm which is now recognized as exhibiting astrocytic derivation because of its positivity for GFAP. Actually, the extensive fibrillary background present between the nuclei of the tumor cells suggests that this tumor might have also been positive with the classic gold and silver impregnation techniques for astrocytes.

The value of GFAP for the diagnosis of malignant astrocytoma has been corroborated in numerous studies(3). In a large series from England, Marsden stained 366 primary brain tumors in children for this marker(6). They detected GFAP in 76 of 121 juvenile astrocytomas, 34 or 78 adult type astrocytomas, 0 or 8 malignant gliomas, 2 of 4 other astrocytic tumors, and in 0 of 101 medulloblastomas. One should be careful in not misinterpreting as positive the stain in entrapped astrocytic elements or the phenomenon of nonspecific absorption by tumor cells of nonglial type of GFAP liberated by necrotic astrocytes.
Approximately 25% of childhood brain tumors are gliomas of high grade malignancy, i.e., malignant astrocytoma and glioblastoma multiforme (4,9). 51% of them arise in the cerebral hemispheres (as in the Seminar case), less commonly in the brain stem (37%), and rarely in the cerebellum. The clinical presentation relates to size, location, and rapidity of growth. Focal seizures may be the presenting symptoms in over 30% of the cases, especially when the tumor arises in cortical locations of the temporal or frontal lobes. Following radiation the prognosis for malignant cerebral astrocytomas in children is somewhat better than in adults, with about 25% of the patients surviving five years. Adjuvant multidrug chemotherapy may improve survival for children. A randomized trial to study the potential benefit of adjuvant chemotherapy was started in 1976 and closed in June 1981 (1,2,5). Patients receiving adjuvant chemotherapy had a greater disease-free-survival than those receiving radiation therapy alone: at 30 months the DFS was 43.1% for the chemotherapy arm and 21.3% for the radiation therapy arm. The degree of surgical resection also influenced outcome. Patients who had a subtotal partial resection lived longer than those who had a biopsy only. Other variables such as age, sex, conventional pathology grading, and radiation dose and volume did not appear to influence DFS. Whether these encouraging results seen with multidrug chemotherapy mean that a cure has been achieved in many of these patients or simply that the time to relapse has been simply postponed is not yet clear.

This improved survival following chemotherapy has also been shown by the group of Phuphanich et al., from the University of California in San Francisco (8). Fifteen of their 27 patients had been treated by radiation therapy alone. Fourteen had tumor progression, with a median time to tumor progression (MTP) of 65 weeks. Twelve patients were treated with chemotherapy as an adjuvant to radiation therapy, and of these only 7 had tumor recurrence, with an MTP of 130 weeks.

It should be pointed out that a good proportion of supratentorial astrocytomas in children are well-differentiated and associated with a good prognosis. In a series of 41 cases of hemispheric supratentorial astrocytoma in children reported from Rome, Italy (7), 76% were still alive 5 to 27 years after surgery. The best results in terms of survival and quality of life were obtained in cases of cystic astrocytoma, especially of the pilocytic variety.

REFERENCES


This tumor is located in the oral cavity, in close proximity with the overlying squamous mucosa and minor salivary glands. It is clearly of epithelial nature and is growing in a complex pattern of anastomosing strands and trabecula having a geographical configuration. These formations are surrounded by a very well-defined basement membrane and show prominent peripheral palisading. The stroma has a loose fibrous quality and is focally abundant. The tumor cells have oval or spindle nuclei, and there is focal evidence of keratinization. Some of the nests show some lack of cohesiveness of the tumor cells, which acquire as a result a polygonal or stellate shape. PAS stain shows extensive accumulation of cytoplasmic glycogen. In one area there is a clear cut connection between the overlying squamous epithelium and the tumor.

The appearance of this neoplasm fulfills the criteria for the diagnosis of ameloblastoma. The differential diagnosis includes tumors of minor salivary gland origin, but the morphologic features of this neoplasm are clearly pointing to an odontogenic rather than a salivary gland type of differentiation. The most interesting aspect of this case is its apparent origin in the soft tissues of the oral cavity. In the presence of a tumor with an ameloblastoma-like morphology in the soft tissues around the jaw, the most likely interpretation is that it represents an extension of a bony lesion, a fact that can usually be demonstrated with radiographic studies. However, in this case the mass was said to be separate from the bone and the x-rays were described as normal. Furthermore, there is a connection with the overlying epithelium suggesting that this tumor represents an example of so-called peripheral ameloblastoma. The implication behind this diagnosis is that the tumor is arising not from tissue associated with odontogenic apparatus in the jaw but rather from epithelium in the oral cavity that has the capacity to differentiate towards odontogenic structures(3,6).

Some cases of this entity have been reported as basal cell carcinoma of the gingiva(4,5). Gardner(2) reviewed 21 cases of peripheral ameloblastoma and commented upon the fact that this lesion may exhibit nearly all of the many histologic patterns found in the intraosseous ameloblastoma, but that it has a marked tendency to be acanthomatous. In his experience, these lesions proved to be relatively innocuous, lacking the persistent invasive features of their intraosseous counterpart. He suggested for them to be excised with a small margin of normal tissue and that the surgical site be re-examined periodically. Focal continuity of the tumor with the surface epithelium was clearly illustrated in his article. Bony involvement was absent in all of these cases, although three of them exhibited a type of bony lesion referred to as "cupping" or "saucerization", and which was
interpreted as representing pressure resorption of the underly­
ing bone rather than invasion by tumor. Some of the lesions were
thought to arise from remnants of the dental lamina within the
gingiva (so-called rests of Serres), but the others appeared to
originate from the surface epithelium, in some cases at one
specific site and in others in a multifocal fashion(1).

REFERENCES

1. Balfour RS, Loscalzo LJ, Sulka M: Multicentric peripheral

2. Gardner DG: Peripheral ameloblastoma: A study of 21 cases,
including 5 reported as basal cell carcinoma of the gingiva.


4. Peters RA, Gingrass RP, Reyes CN, Hintz CS: Basal cell

5. Simpson HE: Basal-cell carcinoma and peripheral ameloblas­

6. Yazdi I, Nowparast B: Extroselective adenomatoid odontogenic
tumour with special reference to the probability of the
basal-cell layer of oral epithelium as a potential source
CASE 7 - SOFT TISSUE, NECK - SO-CALLED ANGIOMATOID MALIGNANT FIBROUS HISTIOCYTOMA

This soft tissue tumor shows at its periphery a deposition of fibrous tissue heavily infiltrated by lymphocytes, many of which are arranged in the form of lymphoid follicles with germinal centers. The center of the lesion shows extremely cellular foci alternating with large areas of fresh and old hemorrhage. Some of the cavities have a telangiectatic appearance. High power examination of the more cellular foci shows a relatively monomorphic population of cells with medium-sized nuclei of round to oval shape growing in a solid fashion, associated with numerous capillaries. The cytoplasm is moderately abundant, eosinophilic, and occasionally vacuolated. A sprinkling of eosinophils is present focally, and there are collections of hemosiderin-laden macrophages. Mitotic figures are present in small numbers. Pleomorphism is minimal.

The features are typical of the entity which Enzinger described as angiomatoid malignant fibrous histiocytoma (1,3). His 41 cases occurred primarily in the extremities of young individuals between the ages of 5 and 25 years, with a median of 13 years. They manifested in the form of nodular soft tissue growth which were sometimes tender or painful and which were clinically often mistaken for hematomas or hemangiomas. Grossly, they presented as hemorrhagic masses with a multinodular or multicystic appearance that ranged in size from 7 mm. to 10 cm. (median 2.5 cm). The three major microscopic components were solid nests of fibroblasts and histiocyte-like cells, sometimes containing hemosiderin or lipid; focal areas of hemorrhage, often arranged in cyst-like spaces; and aggregates of chronic inflammatory cells, chiefly lymphocytes and plasma cells. On follow-up, 21 patients were found to be alive, 11 of them with recurrence, 1 with recurrence and metastasis, and another with metastasis. Three patients had died of metastasis, 1, 3, and 13 years respectively after the initial surgical therapy. Enzinger interpreted this tumor as most likely of fibroblast and histiocyte-like origin akin to malignant fibrous histiocytoma but different in its age incidence, microscopic appearance and behavior.

Comparison of these cases with those of conventional malignant fibrous histiocytoma and its several other well described variants actually shows very few features in common between them. Angiomatoid MFH has an age distribution, microscopic appearance, and ultrastructure which are distinctly different from those of all other forms of MFH and which raise serious doubts about its inclusion into this family. Instead, many of its features are suggestive of a vascular derivation. The plump appearance of the proliferating cells, their occasional vacuolated cytoplasm, and the fact that they are surrounded by a heavy inflammatory infiltrate containing eosinophils and well-defined germinal centers are reminiscent of the features seen in histiociytoid hemangiomma (epithelioid hemangiendothelioma) (4). Two recent electron microscopic studies of
angiomatoid MFH have suggested that the cells making up this
tumor are modified endothelial cells with histiocytic or histio-
cytoid features rather than true histiocytes(2,6). Both articles
concluded that the tumors were of vascular rather than fibrohis-
tiocytic derivation. However, the tumor cells of the present
case did not stain for Factor VIII related antigen or Ulex euro-
paeus lectin, the two most commonly used markers for endothelial
differentiation. Therefore, the histogenesis of this tumor
remains to be determined, although there is little question that
the lesion represents a distinct clinical and pathological
entity.

Angiomatoid MFH should also be distinguished from a
variant of benign fibrous histiocytoma of the skin associated
with marked hemorrhagic or telangiectatic changes(5). This is a
benign tumor usually seen in adults which has all of the features
of the usual dermatofibroma or histiocytoma of the skin except
for the presence of marked hemorrhagic changes.

REFERENCES

1. Enzinger FM: Angiomatoid malignant fibrous histiocytoma: A
distinct fibrohistiocytic tumor of children and young adults

2. Kay S: Angiomatoid malignant fibrous histiocytoma: Report
of two cases with ultrastructural observations of one case.

3. Leu HJ, Makek M: Angiomatoid malignant fibrous histiocyto-

4. Rosai J, Gold J, Landy R: The histiocytoid hemangiomas: A
unifying concept embracing several previously described
entities of skin, soft tissue, large vessels, bone and heart.

5. Santa Cruz DJ: Aneurysmal ("angiomatoid") fibrous histio-

6. Sun CJ, Toker C, Breitenecker R: An ultrastructural study of
CASE 8 - SKIN - ANGIOMATOSIS (KAPOSI'S SARCOMA-RELATED)

The tumor present in the skin and subcutaneous fat of this patient is clearly of vascular nature. Its architecture is vaguely lobular. The neoformed vessels have well-defined lumina, are lined by plump endothelial cells, and surrounded by equally plump cells of perithelial appearance. Red blood cells are not very numerous, but those present are usually within the lumen of the vessels rather than in the interstitium. Focal thrombosis is present. The stroma contains collections of neutrophiles, with abundant "nuclear dust". In addition, a prominent feature seen focally is the deposition of an extracellular amorphous eosinophilic substance which is moderately PAS positive. Its appearance suggests the deposition of a material analogous to that seen in conditions associated with immune mechanisms. It probably contains fibrin and perhaps also antigen-antibody complexes, and it may be related to the pathogenesis of this particular lesion. Factor VIII and Ulex stain show strong positivity in the endothelial cells of the vessels surrounding the lesion. However, only a minority of the cells within the lesion stain for these markers. Instead, stain for actin shows strong positivity in most of the cells located outside the basement membrane of the neoformed vessels, suggesting a perithelial nature.

The combination of architectural, cytological, and immunocytochemical features of this case suggests that this tumor belongs into one of the several categories of angioma, and are somewhat reminiscent of the type recently redesignated as "lobular capillary hemangioma", of which pyogenic granuloma is its most typical example(2,3,4,5,8). The plump cytoplasmic appearance of the endothelial cells and the occasional cytoplasmic vacuolation also suggest a link with the vascular proliferative lesion designated as histiocytoid hemangioma.

Naturally, the background disorder in this patient and the fact that these vascular lesions are multiple suggests strongly the possibility of Kaposi's sarcoma. However, this particular lesion does not fulfill the morphological criteria of Kaposi's sarcoma. The question then arises whether it should be designated as Kaposi's sarcoma because it is occurring in an AIDS patient and behaving as such, or whether it would be designated according to its morphologic appearance. Although most of the vascular lesions of the skin in AIDS patients have morphologic features equivalent to those seen in the classical form of Kaposi's sarcoma, others have an appearance which is more in keeping with other benign and malignant vascular tumors, including lobular hemangioma, histiocytoid (epithelioid) hemangioma, and angiosarcoma(6). In our limited experience with this group of diseases in this population, we have seen that their clinical presentation, multicentricity and rapid progression are similar regardless of their microscopic appearance. Therefore, from a practical standpoint, perhaps they should be all regarded as belonging to a spectrum of histogenetically related lesions despite their morphologic diversity(7).
The difficulty in making or ruling out the diagnosis of Kaposi's sarcoma in atypical vascular proliferations of skin has been commented upon by several authors. In a review of 106 biopsies clinically thought to be suspicious for Kaposi's sarcoma, Blumenfeld et al. listed 7 cases showing a vascular proliferation that did not easily conform to the usual categories of benign vascular proliferations. The author termed these lesions "atypical vascular proliferations" and stated that the changes were not diagnostic of even early Kaposi's sarcoma. They thought that current available follow-up information was insufficient for determining whether such cases may develop Kaposi's sarcoma at a later time.

REFERENCES


CASE 9 - TESTIS - MATURE TERATOMA AND INTRATUBULAR GERM CELL ATYPIA

This testicular germ cell tumor has the typical appearance of a mature teratoma. Several well-differentiated tissues are present, including skin and skin appendages, glia, cartilage, and bone. The keratin liberated from one of the cysts has elicited a strong foreign body reaction. An intriguing aspect of this case is the presence of an additional component, the histogenesis of which I was not able to ascertain. It is composed of well-defined nests of cells with oval nuclei having prominent grooves, arranged in clusters, gland-like formations, and small papillary structures. In some of the glands there is a distinct polarity to this proliferation, in the sense that one side is lined by columnar cells, whereas the other is lined by extremely flattened cells. Focally, this component is intimately adjacent to islands of cartilage. Since this unidentified component has a somewhat proliferative appearance and disorganized pattern of growth, one may consider naming this tumor an "immature teratoma" because of it. From a practical standpoint this makes no great difference, since the treatment and outlook for these two tumors are probably the same. It is now widely accepted that testicular teratomas in adults have metastatic potential no matter how well-differentiated, and this needs to be taken into consideration for the purpose of treatment(1,2). This is different from the mature teratomas seen in the prepubertal testis, for which no documented instances of metastatic behavior have been reported, and which therefore can be safely treated with orchiectomy alone.

The nomenclature of the largely mature teratoma of the testis is somewhat controversial because of the inconsistencies noted in the definition of the terms in the major publications on the subject. Terms such as "immature teratoma", "teratoma with maturation to tissue level", "organoid differentiated teratoma", "teratoma with malignant change", and "teratoma with malignant transformation" have been variously used in a loose fashion, as pointed out by von Hochstetter et al(10).

When metastases from mature teratomas of the testis develop, they may have the appearance of teratocarcinoma, embryonal carcinoma, or mature teratoma(6). Three theoretical possibilities exist to explain to explain the metastases from teratomas which appear entirely mature: (a) The teratomas may have the biologic potential for metastatic spread despite their microscopic appearance of maturity; (b) The sampling missed areas of immaturity or malignancy; (c) The tumor in the testis matured after it metastasized. The opposite phenomenon has also been observed, i.e. that of metastases from an embryonal carcinoma or a teratocarcinoma appearing completely mature(11).
In the Seminar case, the tumor is separated from the testis by a thick fibrous capsule. The few seminiferous tubules present around the tumor capsule are atrophic, almost devoid of signs of spermatogenesis, and surrounded by a thick basement membrane. Some of them contain cells with large atypical hyperchromatic nuclei with prominent nuclei, suggesting the presence of intratubular germ cell neoplasia. This abnormality is frequently seen in testes harboring germ cell tumors of all types and is thought to represent the precursor in situ stage of germ cell tumors (3, 4, 5, 7, 8, 9). However, the slides I had the opportunity to study from this case contained so few tubules that I would prefer to make only a diagnosis of intratubular germ cell atypia.

REFERENCES


CASE 10 - PLEURA - ? MALIGNANT FIBROUS MESOTHELIOMA

This neoplasm shows areas of extreme cellularity alternating with others showing a hypocellular and edematous appearance. Often the hypercellular areas center around blood vessels. The tumor cells are generally oval, but round or spindle forms are also present. The nuclei are generally normochromatic, and mitotic figures are easily identified. Areas of degeneration with cholesterol granulomas are also present. Immunohistochemically, a small proportion of the tumor cells stain for vimentin, but actin stain is totally negative. Both S-100 protein and epithelial membrane antigen stains show positivity in the tumor cells located in the hypocellular areas, and even more so at the interface between the hypercellular and hypocellular elements. Keratin stain shows strong positivity in isolated cells, but it is difficult to determine whether these are neoplastic elements or entrapped mesothelial cells.

I found the diagnosis of this lesion very difficult. It is clearly neoplastic, and it should be regarded as malignant (although probably of a low grade) because of its cellularity, mitotic activity, and necrosis. The possibility of a metastasis should be considered, but the long clinical history makes this option a very unlikely one. The location within the pleura obviously suggests the possibility of a mesothelioma, a diagnosis which I would like to favor despite the fact that this tumor does not have the typical features of this entity(1,2,5). In the fibrous mesotheliomas that we have examined, we have not found positivity for S-100 protein or epithelial membrane antigen, and instead we have often found positivity for actin. The S-100 positivity in the hypocellular areas of the Seminar case suggests the development of cartilaginous metaplasia, a feature which is also vaguely suggested by the morphologic features in these foci. This brings to mind the possibility of mesenchymal chondrosarcoma, a tumor characterized by a biphasic pattern consisting of aggregates of small cells alternating with islands of well-differentiated cartilage(3). However, in this case the small cell component of the tumor does not show hemangiopericytoma-like foci, and areas of well-differentiated cartilage are not identified. Another possibility, in view of the S-100 positivity, is that of a malignant neurogenic tumor. However, I found no morphologic features to support this diagnosis. Still another possibility, in view of the EMA positivity(4), is that of synovial sarcoma, but once again the morphologic features are not supportive of this diagnosis.

REFERENCES


CASE 11 - SPLEEN - SYSTEMIC MASTOCYTOSIS

This spleen shows ill-defined areas of fibrosis, most of them surrounding medium-sized vessels. Many are located at the periphery of the malpighian follicles and partially encircle them. Whenever the vessels are cut in a transversal fashion, it becomes clear that the fibrotic and inflammatory process is surrounding their walls. Close examination within the areas of fibrosis shows that there are several cell types embedded in the fibrous tissue, including lymphocytes, occasional eosinophils, and cells with a round regular nucleus and an ill-defined clear cytoplasm, which is occasionally granular. Staining with the Leder technique (chloroacetate esterase) shows that many of these cells react positively, identifying them as mast cells and the disease as systemic mastocytosis (1, 3, 5). Interestingly, metachromatic stains did not show these cells convincingly, and the Leder stain needed to be done several times before clear cut positive results were obtained. It is not unusual for cases of mastocytosis to present problems in the specific staining of the proliferating cells, perhaps due to technical factors or perhaps because of an abnormality in the secretion by the neoplastic elements. Recently, an immunoperoxidase technique for the identification of mast cells using tryptase was described (2). Other authors have reported the use of monoclonal antibodies having specificity for the granule components of human mast cells (4).

In a review of 14 patients with systemic mastocytosis, Brunning et al (1) found that half of the patients did not have recognizable cutaneous lesions, whereas the other half had evidence of urticaria pigmentosa. There were no major clinical differences between the two groups except for splenomegaly, which was much more common in the patients without skin disease. The other major difference was in regard to the median age at the time of diagnosis, which was higher in the patients without skin manifestations. The appearance of the mast cells varied considerably from site to site. Some were typical, others were spindle-shaped, and some others resembled histiocytes. Bone marrow involvement was present in all of the 13 specimens studied, the involvement being either focal or diffuse. The focal involvement was frequently in a perivascular and paratrabeicular location, whereas the diffuse involvement simulated the appearance of myelofibrosis. One of the most striking radiographic features was the presence of diffuse x-ray bone changes, either osteoblastic or osteolytic, which closely simulated the appearance of metastatic disease, particularly from the prostate. The involved lymph nodes exhibited prominent sinusual and pericortical infiltration by mast cells. The splenic involvement was practically identical to that seen in the Seminar case, and characterized by ill-defined areas of fibrosis, some of them having a granuloma-like configuration. The liver specimens showed prominent portal fibrosis.
The features of hepatic involvement in systemic mast cell disease were well described by Yam et al (6) in a study of 13 patients with this condition. They pointed out the difficulties in making the histologic diagnosis on the basis of a liver biopsy, and the fact that this diagnosis can be facilitated in biopsy specimens embedded in plastics such as methacrylate. In their series, the severity of the histologic changes in the liver did not correlate well with the size of the liver or the biochemical changes in the blood. They concluded that the prognosis of systemic mast cell disease was more closely related to the systemic effect of mast cell involvement in the other organs and not to hepatic involvement per se.

Systemic mastocytosis has a relatively slow evolution, but some patients develop a poorly differentiated lymphoreticular tumor which may be the result of "dedifferentiation" or blastic transformation of the mastocytosis (1,3).

REFERENCES
CASE 12 - PANCREAS - SOLID AND PAPILLARY EPITHELIAL NEOPLASM

This pancreatic tumor is a typical example of a distinctive tumor entity of this organ which has been variously called solid and papillary, papillary and solid, and papillary-cystic epithelial neoplasm. (1,2,4,6,7,8). It is composed of small, relatively uniform round to cuboidal cells, arranged in a predominantly solid pattern, but also showing a distinctive perivascular distribution resulting in a pseudopapillary configuration. Equally characteristic is the fact that the space between the vessels and the neoplastic epithelium is often occupied by an abundant extracellular basophilic material which stains strongly for mucin stains. Mitoses are rare, and pleomorphism is minimal. The differential diagnosis includes islet cell tumor, acinar cell tumor, and pancreatoblastoma (5).

Several series have been written on this tumor entity, but unfortunately the largest remains unpublished. This deals with the A.F.I.P. experience, which I have obtained through the kindness of Dr. John Compagno (3). He studied 54 cases of this entity. The tumors were usually large (mean diameter 10 cm.), encapsulated, and often hemorrhagic. The patients presented often with a gradual enlarging abdominal mass, frequently in the left upper quadrant, with some associated and progressive abdominal discomfort and pain. The tumors were predominantly found in the tail of the pancreas, chiefly in young women (mean age 24 years). Microscopically, some limited evidence of aggressive behavior in the form of capsular invasion and extension of tumor cells into the adjacent parenchyma was found. The authors commented that this neoplasm had often been misclassified as islet cell tumor, cystadenoma, or cystadenocarcinoma, and added that it had not been clearly distinguished from the infantile pancreatic carcinoma (pancreatoblastoma). Their electron microscopic study verified the absence of secretory granules and showed, instead, features consistent with those seen in cells of the small pancreatic ducts. Follow-up data (mean period of 7.1 years) indicated that these are very low grade malignant neoplasms. Only one patient was known to have died as a result of metastases, and none of the other patients had a recurrence despite histologic evidence of local aggression.

Additional reports have concentrated on the histogenetic aspects, with one author suggesting the possibility of an acinar derivation (6), and others reporting the presence of isolated endocrine cells as a component of the tumor (7).

REFERENCES


CASE 13 - MENINGES - PAPILLARY (MALIGNANT) MENINGIOMA

This neoplasm is composed of oval and spindle cells which show a characteristic arrangement around blood vessel and a pseudopapillary configuration probably resulting from lack of cohesiveness. The pattern of growth could actually be described more as peritheliomatous than as a true papillary growth. The nuclear appearance is relatively bland, with relatively scanty mitotic activity and minimal pleomorphism. In the more solid areas the cells grow in solid sheets or nests consistent with a meningothelial derivation. Stains for epithelial markers are negative, whereas stains for vimentin show strong positivity in the cytoplasm of many tumor cells (2,3).

The appearance of this tumor is characteristic of the variant of meningioma which Ludwin et al (4) named papillary meningioma. In their study describing 17 cases, they found that this pattern was invariably associated with other features of malignancy. The tumors often displayed aggressive clinical behavior, characterized by a high rate of local recurrence or the appearance of distant metastases. The author suggested that this variant of meningioma was sufficiently characteristic to justify its separation as a distinct clinicopathological entity. This tumor variant showed no predilection for any particular site of origin that differed from that of meningiomas in general. The sites of metastatic spread included lungs, liver, and cerebrospinal pathways. Forty-seven percent of the patients were children, and the authors commented that meningiomas in young children are apt to be malignant or histologically atypical.

In a more recent article, Pasquier et al (7) confirmed the markedly aggressive behavior of papillary meningioma, with 5 of their 7 cases dying within 1.4 to 9 years after the original operation. They stated that 46 papillary meningiomas had been identified in the literature up to 1985.

Meningiomas are negative for keratin, but recently Schnitt and Vogel (8) have described positivity for epithelial membrane antigen in all the 22 tumors they studied, which however did not include the papillary variety. Similar results were obtained by Meis et al (5). In our case the epithelial membrane staining was interpreted as negative, the only cells showing some apparent staining being located at the very edge of the specimen.

It should be emphasized that the majority of clinically aggressive meningiomas do not have a papillary pattern, and that they do not differ microscopically a great deal from the benign types (1,6,9).

REFERENCES


CASE 14 - THYROID - "MIXED" CARCINOMA (PAPILLARY, HURTHLE CELL, CLEAR CELL, AND POORLY DIFFERENTIATED)

This thyroid malignancy shows a remarkable combination of morphologic patterns. Focally both the architectural and cytologic features are typical of papillary carcinoma because of the formation of branching papillae with fibrovascular stalks and the presence of optically clear overlapping nuclei. In most other areas the pattern of growth is follicular, trabecular, or solid. Some of the nodules are composed of cells with abundant granular acidophilic cytoplasm characteristic of Hurthle cells. Other nodules are composed of cells with a strikingly clear cytoplasm, in which some focal granularity is preserved. Close examination of these nodules show a sometimes obvious transition from the Hurthle cells to the clear cells. Still other nodules have a distinctly nesting arrangement and marked nuclear atypicality in the tumor cells, approaching but not reaching the appearance of an anaplastic carcinoma. Of all these patterns, the one prognostically more important is the latter, which we like to refer to as "poorly differentiated". This is a marker of bad prognosis and aggressive clinical behavior, somewhat intermediate between that of well-differentiated follicular and papillary tumors and the totally undifferentiated (anaplastic) thyroid carcinomas. Some of these poorly differentiated tumors have a distinctly "insular" appearance, but this is not the case in the present example.

The existence of a poorly differentiated type of thyroid carcinoma with an intermediate degree of morphology and behavior has been recently recognized by other groups.

Another interesting aspect about this case is the presence of nuclear abnormalities in the non-neoplastic gland, which are in all likelihood the result of the previous radiation therapy to the area. It is typical of thyroid glands subjected to external radiation therapy or radioactive iodine to show abnormalities in the form of irregularly shaped follicles lined by cells which vary a great deal in size, particularly in regard to the nuclei, some of which are markedly hyperchromatic. Although the large majority of thyroid malignancies arising within this background are papillary carcinomas and therefore of low malignant degree, other tumor types have been described, including anaplastic carcinoma and malignant lymphoma. Three cases of papillary thyroid carcinomas after high dose external radiation therapy for Hodgkin's disease were reported by McDougall et al. The radiation dosage of the neck overlying the site of thyroid cancer was 3000, 4000, and 4100 rads respectively, probably similar to that received by the patient in the Seminar case. Bakri et al. reported a case of adenosquamous carcinoma of the thyroid after radiation for Hodgkin's disease, but we would interpret this tumor as well as others which have been reported under this heading as examples of papillary carcinomas with extensive squamous and mucinous metaplasia.
REFERENCES


CASE 15 - THYROID - UNDIFFERENTIATED (ANAPLASTIC) CARCINOMA ARISING IN HURTHLE CELL CARCINOMA

The bulk of this tumor is composed of very anaplastic, sarcoma-like cells growing in a diffuse fashion, sometimes in a storiform arrangement. Most of the cells are spindle-shaped and of mesenchymal appearance; some are extremely pleomorphic, with giant hyperchromatic nuclei. Vascular invasion is prominent, and there is extensive stromal invasion. The appearance in these areas is characteristic of so-called undifferentiated or anaplastic thyroid carcinoma. In addition, there are areas of better differentiated tumor characterized by a nesting pattern of growth, occasional follicles and papillary formations, and cells with granular acidophilic cytoplasm characteristic of Hurthle cells. Thyroglobulin and cytokeratin stains show positivity in the better differentiated areas but total negativity in the anaplastic component.

This tumor is to be interpreted as an undifferentiated carcinoma arising from anaplastic transformation or "dedifferentiation" of a pre-existing better differentiated neoplasm which seems to have the features of a Hurthle cell carcinoma. In our experience with 70 cases of undifferentiated carcinoma(2,5), we found a combination of morphologic patterns, which we designated as spindle cell, pleomorphic (giant cell), and squamoid. High mitotic activity, high cellularity, foci of necrosis with palisading of tumor cells at the edges, and vascular invasion were constant features. Ultrastructurally, evidence of epithelial differentiation was seen in less than half of the cases studied. Of all the immunocytochemical reactions tested, stain for low molecular weight cytokeratin proved most useful, with nearly 50% of the tumors giving positive results. Other authors have obtained even better results, claiming a positivity of nearly 100%(3). Instead, we have found thyroglobulin stain consistently negative in the anaplastic areas; this is in contrast with other authors, who claim to find positivity in over 70% of the cases. Care should be exercised not to misinterpret areas of entrapped normal thyroid tissue, residual better differentiated tumor, or nonspecific absorption by the tumor cells of thyroglobulin liberated by entrapped follicles. In our study(1) we were also unable to confirm a recently made suggestion that most anaplastic carcinomas represent undifferentiated variants of medullary carcinoma.

The most remarkable feature about the Seminar case is the fact that this patient is still alive 8 years after removal of the primary tumor, despite the fact that this tumor invaded the sternomastoid muscle and that it apparently metastasized to the lung. In our series of 57 patients in whom follow-up information was available, we found that all patients had died of tumor, the longest survival being 2.5 years. It is very likely that most
reported cases of long survival in undifferentiated thyroid carcinoma are the result of mistaken inclusion of cases of malignant lymphoma, medullary carcinoma, or poorly differentiated (insular) carcinoma. It is now widely accepted that the tumors formerly designated as the small cell diffuse type of anaplastic thyroid carcinomas are malignant lymphomas(4). Nevertheless, bonafide cases of patients with undifferentiated carcinomas who have survived for several years are on record(1), and the Seminar case seems to be an unquestionable example of this exceptionally rare event.

REFERENCES


CASE 16 - KIDNEY - MULTILOCULAR CYST (MULTILOCULAR CYSTIC NEPHROMA)

This is a multilocular cystic mass located in the kidney. The cysts are lined by an epithelium which varies in height from flat to low columnar. This epithelium stains strongly for keratin and epithelial membrane antigen. The septa which separate the cysts are markedly cellular and contain numerous vessels. The cells in these septa have a spindle shape and are strongly positive for vimentin. There is no evidence of heterotopic tissue such as cartilage or skeletal muscle, or of developing nephrons.

This case is a typical example of the rare lesion variously called multilocular cyst or multilocular cystic nephroma(1,3). Out of 165 primary renal tumors in children, Gallo and Penchansky(3) found 143 cases of Wilms' tumor and only 4 cystic nephromas. Although probably most of them arise in early infancy, it is not infrequent for them to present clinically during adult life. They are nearly always unilateral and appear as a well-circumscribed encapsulated mass. The size usually ranges between 5 and 15 cm., and the outer surface is coarsely nodular. The individual cysts measure from 1 mm. to 3 cm., although occasionally larger cysts may be seen. The walls are very thin, translucent, and lack papillary projections. The fluid within the cysts is usually serous. The lining of the cyst is of epithelial nature, but it can be so flattened as to simulate endothelium. When this happens, the lesion may be misdiagnosed as a lymphangioma of the kidney. The stroma is usually nongrdescribable, but it may contain smooth muscle, striated muscle, or cartilage. Occasionally, immature nephroblastomatous tissue is found in the septa having an appearance indistinguishable from that seen in Wilms' tumor. This suggests that this lesion is histogenetically related to Wilms' tumor and that it is perhaps represents a fully differentiated variant of the latter(2,5). This fact was recognized by Joshi et al(4), who preferred to designate this entity as cystic partially differentiated nephroblastoma. These authors believe that the cysts are simply an expression of tubular differentiation of the metanephrogenic blastema, with subsequent cystic changes. They regard the presence of differentiated, undifferentiated, or partially differentiated renal elements in the septa of the loculi as the criterion to distinguish between this entity and multilocular cyst of the kidney. Although this distinction may be reasonable and even useful on practical grounds, it seems likely that we are dealing with a continuous spectrum of lesions.

REFERENCES


CASE 17 - BONE, SACRUM - SINUS HISTIOCYTOSIS WITH MASSIVE LYMPHADENOPATHY (SHML)

This nodule is surrounded by a complete fibrous capsule and is composed of tissue which on low power examination shows alternating light and dark areas. Closer inspection shows that the light areas correspond to accumulation of cells of histiocytic appearance, characterized by large vesicular nuclei with occasional prominent nucleoli and an abundant pale cytoplasm with generally ill-defined cytoplasmic margins. The shape of these cells is irregular and sometimes stellate. The darker areas correspond to accumulations of lymphocytes and mature plasma cells. Lymphoid follicles with germinal centers are present, but they are not prominent. The cytoplasm of some of the histiocytic cells contains phagocytosed lymphocytes and other lymphoid elements. These histiocytes are moderately positive for S-100 protein. Stains for kappa and lambda light chains show a polyclonal population of mature plasma cells.

The appearance of this nodule is characteristic of the entity known as sinus histiocytosis with massive lymphadenopathy, and the diagnosis is supported by the subsequent appearance of cervical lymphadenopathy(6). The remarkable aspect about this case, duplicating several others from our series, is the fact that the tissue (said to be obtained from within the sacrum) recapitulates to perfection the structure of a lymph node.

We now have 332 cases of SHML entered in our informal registry. The basic clinicopathologic features remain very similar to those that we described in our previous articles on the subject. The etiology remains unknown, although it has become increasingly clear that the process is not of neoplastic nature. No organisms have been identified, despite the fact that the clinical course often suggests an infectious etiology. In about 35% of the cases there is evidence of extranodal involvement, which in some instances may be the predominant or exclusive site of disease. The extranodal sites most commonly involved are skin, upper respiratory tract, orbit, skeletal system, and central nervous system, but we have also seen involvement of the thyroid, gastrointestinal tract, kidney, and testis. The lesions within the skeletal system may be multiple or solitary, and radiographically they may simulate the appearance of histiocytosis X(5,8). Most of the neurologic symptoms seen in this condition are the result of involvement of the vertebral canal, probably by extension from a destructive lesion in the vertebral body. Some patients manifest signs of cord compression as a result(1,3).

The microscopic differential diagnosis of this disorder includes histiocytosis X, storage diseases, a variety of inflammatory processes (particularly rhinoscleroma and leprosy) and metastatic tumors (particularly melanoma). Although the disease is largely self-limited, a long protracted course is seen in some
of the cases. Fourteen deaths have been documented in our registry, but SHML infiltrates were clearly the cause of death in only two patients(2). In another four cases, persistent SHML was prominent at death. The other deaths were the result of complications of either defined immunologic abnormalities in five cases or of unusual infections in three(4). We have not seen an example of cytologic malignant transformation of SHML, although we have been told that one such case has been documented. The treatment should be conservative because of the usually favorable outcome; however, in some cases chemotherapy may be necessary because of extensive involvement by the disease. In some instances, administration of chlorambucil and prednisone has resulted in resolution of the lesions(7).

REFERENCES


Most of this bone tumor is formed by large lobules of well-differentiated cartilage, sometimes approaching the appearance of normal tissue. However, close examination shows some features of malignancy, such as presence of two or more cells per lacuna and presence of cells with two or more nuclei. These features justify the designation of these areas as well-differentiated chondrosarcoma. There is in addition a poorly differentiated component at the periphery. This component is very cellular and composed of cells with a marked degree of pleomorphism and mitotic activity. In some of these foci there is hardly any intercellular stroma, but focally there is deposition of intercellular material with the appearance of cartilaginous matrix, which is seen to undergo ossification.

This lesion has the feature of the entity interpreted by Dahlin et al (1) as "dedifferentiation" of low grade chondrosarcomas. In their study of 370 well-differentiated chondrosarcomas, the authors found 33 which had "dedifferentiated" zones of fibrosarcoma or osteosarcoma. Most of the cases were located in the iliac bone, but they also had three examples in the scapula. The "dedifferentiated" portion was described as being typical of fibrosarcoma admixed with cartilaginous components. The malignant cells produced osteoid in 11 cases, and 4 of these had zones of chondroblastic differentiation. These "dedifferentiated" areas usually abutted abruptly against the distinctly different cartilaginous tumor. Of the 28 patients with long term follow-up, 23 were dead, usually with known metastatic disease. This poor prognosis contrasted sharply with the expected five year survival of more than 70% for patients who had ordinary chondrosarcomas that were adequately treated. Eighteen additional cases were reported by McCarty et al (4). Thirteen of the 14 patients on whom there was follow-up died of their tumor, with an average survival of 6 months. The average age was 61, and the most common location of the lesion was the distal femur. In their series the "dedifferentiated" area had the appearance of a high grade sarcoma, usually with features of a malignant fibrous histiocytoma.

Another large series was reported from the M.D. Anderson group (2, 6). In this study the poorly differentiated component was designated as MFH, rhabdomyosarcoma, fibrosarcoma, osteosarcoma, or undifferentiated sarcoma. The cells of the nonchondroid portion stained for alpha-1-antichymotrypsin in 12 of 20 cases. Staining for S-100 protein was consistently negative, whereas the chondrosarcoma component stained in 14 cases. Six tumors were reactive for desmin; 4 of the 6 were also positive for myoglobin, and 2 for smooth muscle myosin. In 4, a rhabdomyosarcomatous component had been identified in the H&E stained sections.
The term "dedifferentiation" has been criticized on biological grounds. It has been stated that cells, whether normal or neoplastic, do not dedifferentiate but rather fail to differentiate. According to this view, a clone of spindle cells from this tumor would fail to differentiate into neoplastic chondrocytes and acquire the features of a high grade sarcoma.

Another issue raised by this case is the proper designation of the poorly differentiated areas, in view of the fact that they seem to be making both cartilage and bone(3). Since most of the osteoid and bone being formed seems to be made through an interposition of neoplastic cartilage, one could regard this particular case as a well-differentiated chondrosarcoma with poorly differentiated areas. The positivity for S-100 in many of the poorly differentiated areas further supports the interpretation that this tumor is basically of chondrosarcomatous nature, even in its anaplastic component(5). However, in a few foci there seems to be osteoid formation without interposition of cartilage, a feature traditionally regarded as diagnostic of osteosarcoma(7).

REFERENCES


CASE 19 - THYMUS - THYMOMA WITH ANAPLASTIC (SARCOMATOID) TRANSFORMATION

This mediastinal tumor has two distinctly different components. One has the typical architectural and cytologic features of thymoma(1). The epithelial component is predominantly spindle-shaped and is admixed with a large number of mature and slightly immature lymphocytes. It is incompletely divided into lobules by thick bands of fibrous tissue, with a sharp interface between the tumor lobules and the stroma. Embedded within these fibrous septa and occasionally within the tumor itself, there are gland-like spaces lined by flattened epithelium. In these areas atypicality is absent, and mitotic figures are very scanty. The spindle and oval cells stain positively for keratin. If the entire tumor had looked like this, the diagnosis of benign thymoma would have been appropriate. However, there is a second component with a very malignant appearance characterized by a biphasic pattern of carcinoma and sarcoma-like elements. The carcinomatous components are made up of solid islands, sometimes sharply outlined by a thick basement membrane, and composed of cells with large vesicular nuclei with prominent nucleoli. The sarcoma-like areas are generally spindle-shaped and nondescript, with an appearance that could be designated as resembling that of fibrosarcoma of malignant fibrous histiocytoma. However, there are also areas of clearly identifiable cartilage. This component could be designated descriptively as carcinosarcoma, or—if one believes that the entire neoplasm is of epithelial derivation—as a sarcomatoid or anaplastic carcinoma. In this particular case, the long history and the presence of a well-differentiated component suggests that we are in the presence of a malignant or anaplastic transformation of a benign thymoma.

Malignant thymomas can be divided into two main categories, allowing for some overlap between them. The first and more common is constituted by cases that cytologically are not significantly different from the benign tumors but which are designated as malignant because of their invasive pattern and/or metastatic behavior(3). These tumors share with benign thymomas most of the morphologic features of this entity, including the formation of perivascular spaces, the very intimate admixture with non-neoplastic lymphocytes, and the occasional presence of myasthenia gravis or other immune-mediated disorders. The second category is composed of tumors which are clearly malignant on cytologic grounds. Some authors reserve the term "thymic carcinoma" for this second category only(4). Despite their rarity, several morphologic variants of thymic carcinoma exist, the two most common being keratinizing squamous cell carcinoma and non-keratinizing carcinoma with a lymphoepithelioma-like appearance. Less common types are clear cell carcinoma, mucosidermoid carcinoma, basaloid carcinoma, and sarcomatoid carcinoma, of which the Seminar case represents an example(2). The sarcoma-like component of these tumors may be nondescript, or it may contain neoplastic cartilage or skeletal muscle. The differential diagnosis includes mediastinal germ cell tumors with a sarcomatous component, and malignant schwannoma with metastatic mesenchymal elements.
Often, the diagnosis of sarcomatoid thymic carcinoma becomes one of exclusion in view of the fact that no pathognomonic microscopic features are present. The Seminar case is therefore of great interest because it provides conclusive evidence that mediastinal tumors with a sarcoma-like appearance can indeed develop from the thymus.

The prognosis of thymic carcinoma is generally poor, except for the mucoepidermoid and basaloid variants. Sarcomatoid carcinomas are particularly aggressive, this aggressiveness being manifested by massive local extension and widespread distant metastases.

REFERENCES


CASE 20 - SKIN - MALIGNANT PILAR (TRICHILEMMAL) TUMOR

This skin tumor grows in the form of well-defined nests which are infiltrating the dermis and beginning to permeate the subcutaneous tissue. The invasion is mainly of the "pushing" type, and it is associated with some degree of stromal reaction. The epithelium of the tumor is of well-differentiated squamous type. The keratinization is of the pilar or trichilemmal type by virtue of its homogenous appearance, the lack of interposition of a keratohyaline layer, and its tendency to calcify. Nuclear atypicality and mitotic activity are focally prominent. Connection with the overlying skin is obvious in several areas.

The location, architecture and cytology of this case are typical of a distinctive type of hair follicle tumor which has been variously designated as pilar tumor, proliferating trichilemmal cyst, trichilemmoma, giant hair matrix tumor, trichilemmal pilar tumor, invasive hair matrix tumor, and proliferating epi-dermal cyst(1-10). This tumor occurs almost exclusively in the scalp or back of the neck, but exceptional examples have been reported in other sites. Multiplicity is not unusual. The patients are adults and most are women. The tumors can grow to an enormous size, as the clinical photograph in the case reported by Dabska(3) dramatically illustrates. Many arise from pre-existing pilar cysts or are seen associated with them. The most distinctive feature is the presence of pilar keratinization, which distinguishes them from tumors of the surface epidermis. The type of keratinization seen in these lesions is characteristic of follicular isthmus; however, many of them show a wider range of differentiation including features of the follicular infundibulum, the lower nonkeratinizing portion of the follicular outer root sheath and sebaceous cells(7). The tumors are predominantly composed of squamous rather than basaloid cells, a fact that sets them apart from pilomatrixomas. Some of these tumors, like in the Seminar case, exhibit a set of histological and/or cytologic features which justify the diagnosis of malignancy. However, it is well to remember that the behavior of pilar tumors as a whole is that of a very indolent neoplasm. Local recurrences have been described, but metastases are exceptionally rare. In our experience only one such tumor metastasized, and this was a very malignant-looking neoplasm microscopically.
REFERENCES


CASE 1: Fibrocystic change of moderate to high risk type
CASE 2: Intracystic Wilms' tumor with enteric differentiation, favorable histology
CASE 3: So-called benign multicystic mesothelioma
CASE 4: Fibrolipomatous hamartoma of nerve
CASE 5: Infantile small cell glioma
CASE 6: Peripheral ameloblastoma
CASE 7: Angiomatoid MFH vs. true vascular neoplasms of soft tissues
CASE 8: Histiocytoid hemangioendotheliomatosis
CASE 9: Mature cystic teratoma with intratubular germ cell neoplasia
CASE 10: Cellular, solitary mesothelioma, visceral
CASE 11: Systemic mastocytosis
CASE 12: Solid and cystic tumor of the pancreas
CASE 13: Malignant papillary meningioma
CASE 14: Thyroid - "Mixed" carcinoma (papillary, Hurthle, clear and poorly differentiated
CASE 15: Anaplastic carcinoma of the thyroid with metastases and long term survival
CASE 16: Multilocular cyst of the kidney
CASE 17: SHML of bone and lymph node
CASE 18: Dedifferentiated chondrosarcoma
CASE 19: Thymus - spindle cell thymoma and sarcomatoid thymic carcinoma
CASE 20: Skin, scalp - Malignant pilar tumor