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SLIDE SEMINAR - DR. JUAN ROSAI
PROBLEMS IN DIAGNOSTIC SURGICAL PATHOLOGY

DIAGNOSES

1. R76-747 - Thymus-Malignant thymoma (lymphoepithelioma-like)
2. R78-1128 - Spleen-Systemic mastocytosis
3. UH78-5867 - Lymph node, cervical - "Post-transplant malignant lymphoma"
4. 270767 - (SHML #115) Skin-Sinus histiocytosis with massive lymphadenopathy
5. R75-1187 - Stomach-Multiple carcinoid tumors (in a patient with multiple endocrine adenomatosis)
6. R78-1336 - Appendix-Goblet cell carcinoid
7. R78-1206 - (S78-1038) - Testis-Seminoma with trophoblastic giant cells
8. S56-235 & S58-2101 - Skin-Masson's hemangioma
9. R78-805 & R78-808 - Soft tissue - Myospherulosis
10. R79-156 - Spleen - Histiocytoid lymphangioendothelioma
CASE 1 -

This 27 year old Portugese cleaner presented to his doctor in August, 1975 with the gradual onset of hoarseness. He was given medication for this and it cleared up. He had some difficulty sleeping as well but there was no specific history of chest pain, shortness of breath or dyspnea. A chest x-ray was taken at that time. This showed a density in the anterior superior mediastinum extending to the left of midline at the level of the aortic arch. Clinically, an ill-defined left subclavicular mass could be palpated. On April 12, 1976 he underwent a mediastinoscopy and mediastinotomy and the mass was biopsied. This showed fragments of thymus with cysts, as well as fragments of tumour composed of nests of malignant cells in lymphoid tissue. Left tracheobronchial and subcarinal lymph nodes removed at the same procedure were negative. On April 26, 1976, the entire mediastinal mass was removed in two pieces -- a large 9 x 6 x 5 cm. mass representing the main tumour and a smaller lobulated 5.5 x 5 x 4 cm. mass felt by the surgeon to be residual thymus. Histologically, both specimens show thymic tissue with cyst formation and some epithelial proliferation. The yellow lobulated poorly defined area in the larger tumour and foci in the smaller also show a neoplasm similar to that seen at mediastinoscopy. A urological consultation was obtained and it was felt that he did not have a testicular tumour at this time. The Seminar section is from the second operation. (Courtesy of Dr. M.E. Platts, Toronto, Canada).

CASE 2 -

This 73 year old man was hospitalized because of pancytopenia, monocytosis and splenomegaly with weight loss. Towards the summer of 1977 he lost his appetite and has been losing weight (about 45 lbs) ever since. He was hospitalized in the fall of 1977 and was found to have splenomegaly. In March of 1978 he was found to have the hemoglobin in the range of 9.5, white count approximately 2,000 to 2,500 with up to 30% monocytes. He did have a bone marrow examination at that time, which showed some neutropenia and monocytosis. One of the sections of the aspiration material showed an epithelioid granuloma without necrosis.

During this hospitalization, the patient also had a liver biopsy which showed minimal round celled portal infiltrates. The patient had a T4 of 4.3 and had somewhat elevated alkaline phosphatase at 365. His platelet count ranged from 80,000 to 136,000 and sed rate was 115. His protime was slightly prolonged and he received vitamin K for that. He was then discharged but has continued to feel weak and continued to lose weight.

The patient gives no particular history of fever or night sweats. He has no definite history of any skin rash or arthralgias. No particular urinary symptomatology. There is no history of exposure to TB.

Physical examination reveals somewhat pale looking man who is oriented and in no acute distress. BP is 130/70. Neck is supple with no cervical lymphadenopathy. Abdominal exam reveals the spleen to be firm and about 2 1/2 to 3 fingerbreadths below the costal margin. Liver is not palpated. A splenectomy was carried out. The weight was 1,650 gm. It measured 20 x 16 x 9 cm. Cross sections showed ill-defined
fibrosis, but no definite nodules. The Seminar section is from the spleen (Courtesy of Dr. L.V. Crowley, Minneapolis, U.S.A.).

CASE 3 -

A 67 year old male had a renal transplantation on September 1970. He was immunosuppressed with prednisone and Immuran. In April 1978 developed an exophytic lesion at the base of the tongue, which gradually resolved in the following 3 months. In July 1978, serum titers of 32 for CMV (CF) and 160 for EBV were recorded.

In September 1978, enlargement of submandibular lymph nodes was noted. The virus titers at this time were CMV (CF) 32, (IF) 1280, EBV from 2560 to 5120. A lymph node biopsy was taken in October 1978. At this time, titers were CMV (CF) 8, (IF) 1280, EBV 1280. No therapy was instituted.

In January 1978, back pain developed. A filling defect was detected on liver scan; a liver biopsy was performed and combination chemotherapy was begun. In March 1979, the liver defect has markedly increased in size, judging from the scan. The specimen for the Seminar is a cervical lymph node biopsy.

CASE 4 -

A 48 year old male with asymptomatic dermal nodule in skin of shoulder, present for several months. The clinical diagnosis was lipoma. There are no peripheral lymphadenopathies, hepatomegaly, splenomegaly, other skin lesions or fever. Laboratory studies revealed a marked polyclonal hypergammaglobulinemia. The Seminar section is from the skin nodule (Courtesy of Dr. Juan J. Segura F., San Jose, Costa Rica).

Note: In some of the Seminar sets, this section corresponds to a skin biopsy from another patient with the same disease.

CASE 5 -

This 45 year old white male had come to medical attention on several occasions over a four-year period because of several episodes of renal lithiasis and a perforated duodenal ulcer. At his most recent presentation, the patient complained of the sudden onset of intermittent severe abdominal and costovertebral-angle pain which radiated into the scrotal and shoulder areas. Roentgenographic examinations revealed multiple bilateral renal calculi, marked thickening of the gastric rugal folds, and deformation of the duodenal bulb with a 1 cm. ulcer crater. Clinical laboratory examinations revealed increased levels of serum calcium (10.9 to 11.9 mg/dl), decreased levels of serum phosphorus (2.2 to 2.6 mg/dl), and elevated levels of serum parathyroid hormone (2.0 ng/ml; normal range = 0.0 to 1.5 ng/ml with normal serum calcium levels). Renal tubular reabsorption of phosphorus was 74%, while the blood level of ionized calcium was 2.9 mg/dl. The serum gastrin level was elevated to 2,554 pg/ml (adult normal up to 300 pg/ml), and correlated with large volumes of highly acidic gastric secretion. Blood and urine levels of histamine and of other biologically active amines were not determined. Selective celiac and superior mesenteric arteriograms were normal, as were roentgenograms of the hands. Esophagealduodenoscopy disclosed markedly enlarged rugae with active ulceration in a pattern highly suggestive of Menetrier's disease. The constellation of clinical findings described was felt to be highly suggestive of the Zollinger-Ellison variety of multiple endocrine adenomatosis, Type I.

Surgical exploration of the neck revealed a parathyroid adenoma in the left superior position and three apparently normal parathyroid glands. The adenoma weighed 2.2 grams, measured 3.8 x 1.5 x 1.1 cm., and was composed of dense sheets of chief and oxyphil cells compressing a narrow rim of normal cellularity. Nevertheless, the subjects serum calcium levels remained abnormally high in the post-operative period.
Subsequently, total gastrectomy was carried out. The stomach was massively enlarged, measuring 64 cm. along the greater curvature and 21 cm. along the lesser curvature. Its wall ranged in thickness from 0.6 to 4.5 cm. and was rigid to palpation. The mucosal surface bore numerous superficial ulcers which were most prominent over the largest areas of submucosal tumefaction.

It is noteworthy that the subject's sister died approximately 15 years prior to his presentation from a condition remarkably similar to his. The Seminar sections are from the gastrectomy specimen (Courtesy of Dr. J. Kyllo, Minneapolis, U.S.A.).

CASE 6-

A 56 year old male with symptoms of acute appendicitis. An exploratory laparotomy was carried out. A mass was found in the appendix, and a right hemicolectomy was carried out. Grossly, the appendix had a markedly thickened wall. The cross section showed a diffuse thickening, of a somewhat gelatinous appearance. The lumen was not dilated. The sections are from the appendiceal mass (Courtesy of Dr. H. Sumner, Minneapolis, U.S.A.).

CASE 7-

A 36 year old male with unilateral testicular swelling of 8 months duration. Laboratory studies showed marked elevations of serum HCG (beta subunit), as determined by radioimmunoassay. A radical orchectomy was performed. The tumor measured 7 cm in greatest diameter and replaced most of the testis. It was solid, gray-white and homogeneous, with several small foci of necrosis. The sections are from the testicular tumor.

CASE 8-

Adult male with life-history of angiomatous lesion involving most of the left upper extremity. This has been accompanied by the appearance of dermal and subcutaneous nodules over the years, overlying the angiomatous areas. Some of these have been biopsied (Courtesy of Dr. Bruce Webber, Bethesda, MD., U.S.A.).

CASE 9-

A 43 year old male from Costa Rica consulted for a cystic mass in the soft tissues of the gluteal region. The clinical diagnosis was "sebaceous cyst". A local excision was carried out. Grossly, there was a subcutaneous cystic mass measuring 2 cm in diameter, composed of a thick wall and a center occupied by a semisolid yellowish material. Smaller cavities of similar appearance were seen surrounding the larger one (Courtesy of Dr. Juan J. Segura F., San Jose, Costa Rica).

CASE 10-

A 13 year old girl was found to have a left upper-quadrant abdominal mass on routine preathletic physical examination. In retrospect, she had been aware of a mass in this region for at least six months. It was symptomatic only in that it occasionally "fell" from the left upper-quadrant to the midabdomen. At these times, she experienced a "tugging" sensation and was aware of a mass. She then would manipulate the mass into its normal position beneath the rib cage and would become asymptomatic.

There was no history of fever, infection, weight loss, or other systemic symptoms. Careful history showed absolutely no gastrointestinal, genitourinary, or hematologic symptoms. On admission, her weight was 54.5 kg (120 lb), and she appeared to be healthy.

Results of physical examination were normal, except for a mass in the left upper-quadrant of her abdomen. The mass was palpable 6 cm. below the left-costal margin and
extended across the midline. It was firm, irregular, and freely movable. The mass moved with respiration and did not transilluminate.

Results of laboratory studies on admission including platelet count, were within normal limits. Chest x-ray films were normal. Results of an upper-gastrointestinal tract series showed medial displacement of the stomach by an extrinsic mass. Examination by barium enema showed inferior and lateral displacement of the colon; an intravenous pyelogram demonstrated pronounced downward displacement of the left kidney.

After the preliminary evaluation, the patient underwent abdominal exploration and splenectomy.

Grossly, the spleen was enlarged and irregular in size and shape. Its weight (850 gm) was nine times the normal weight (93 gm). The outer surface showed four irregular nodules, each with a smooth surface. The cut surface showed that these four nodules were situated superficially immediately under the splenic capsule. A fifth nodule was found deep within the splenic tissue. The nodules were brownish-red, with a glistening surface and umbilications in the center. They were well circumscribed, but lacked gross capsules (Courtesy of Dr. Ala B. Hamoudi, Columbus, Ohio, U.S.A.).
CASE 1 - THYMUS - Thymic carcinoma (Lymphoepithelioma variant)

This is a good example of a type of thymoma that can be identified as malignant on microscopic grounds. Both the architecture and cytologic features are highly reminiscent of the so-called lymphoepithelioma of the upper respiratory tract. One of the most characteristic features of these tumor cells is their large vesicular nucleus of round or oval shape, smooth contours and a single, large, eosinophilic or amphophilic nucleolus.

We propose the following classification for malignant thymomas, a term that refers both to invasive thymomas that spread locally in the mediastinum and thorax to involve nerves, vessels, pleura, lungs, and myocardium and to the rare examples of typical thymoma that metastasize hematogenously or via lymphatics (Table). The designation thymic carcinoma is best reserved for cytologically malignant thymomas (regardless of gross pattern).

In category I we include thymomas that show at most only modest degrees of epithelial atypia. Mitotic counts are of little value, as these are in any event usually high in lymphocyte rich benign thymomas. Paucity of lymphocytes is said to be associated with aggressive behavior, but once again, in any one case, this is of little prognostic value. In the final analysis it is the finding at surgery of an encapsulated versus truly invasive lesion that determines the designation benign versus malignant thymoma. Encapsulated thymoma is adequately treated by surgery alone and recurrence is rare (2 per cent). Invasive thymoma is an indication for postoperative radiotherapy.

Thymomas are rare in children and usually carry a poor prognosis in this age group.

A review of the literature reveals that lymphatic or hematogenous spread from a category I malignant thymoma is extremely rare. Care must be taken to exclude the many cases of lymphoma, carcinoid, and germ cell tumor that have been erroneously
reported as metastatic thymoma. In 1978, when we reviewed the literature on the subject, we satisfied ourselves as to the validity of only some 15 cases of meta-
static typical thymoma.

Category II is constituted by thymic tumors that are obviously malignant
cytologically. These may be squamous carcinoma, emulate lymphoepithelioma of the
nasopharynx, or have an undifferentiated or sarcomatoid appearance (even with
rhabdomyosarcomatous areas). We have also encountered a glycogen rich, clear cell
thymic carcinoma that closely simulated renal carcinoma and a case of primary thymic
mucoepidermoid carcinoma. The true incidence of poorly differentiated thymic carcino-
ma is unclear, since most series of thymomas deliberately exclude such cases. The
series of Thomson and Thackray is a notable exception, for they reported 54 thymomas
of which 20 were "undifferentiated". These tumors can easily be confused with
histiocytic lymphoma. Without ultrastructural examination, immunoperoxidase or cell
surface studies, it is often difficult to reach a diagnosis other than "malignant
tumor, unclassified". If fresh tissue is available, the tumor cells should be examined
for possible lymphoid characteristics such as surface immunoglobulin, complement recep-
tors, and E rosetting capacity.

Thymic carcinoma may be encapsulated and apparent cure can be achieved by simple
resection. However, thymic carcinoma is more likely to be invasive and to metastasize.
Cure may be achieved even in cases that demonstrate local lymph node metastasis.

Although the diagnosis of thymic carcinoma can be made with certainty only after
metastasis to the anterior mediastinum, especially from the lung, is excluded, there
are enough well documented cases that verify the existence of a true thymic carcinoma.
The treatment of choice for malignant thymoma (including thymic carcinoma) is surgical
excision supplemented by radiation therapy.

CLASSIFICATION OF MALIGNANT THYMOMAS

I. With no or minimal cytologic atypia
   a. Locally invasive (usual form)
   b. With true lymphatic or hematogenous spread (rare)

II. Cytologically malignant (=thymic carcinoma); morphologic variants:
   a. Squamous cell carcinoma
   b. Lymphoepithelioma-like
   c. Clear cell carcinoma
   d. Mucoepidermoid carcinoma
   e. Sarcomatoid (electron microscopy often needed to distinguish from epithelial
tumors)
   f. Undifferentiated (electron microscopy often needed to distinguish from histio-
cytic lymphoma and germ cell tumors)
REFERENCES


Case 2 - SPLEEN - Systemic mastocytosis

The spleen shows widespread involvement by ill-defined nodules of granulomatoid appearance accompanied by fibrosis. The infiltrate is composed of a variety of cell types, among which cells of somewhat irregular nucleus, clear cytoplasm and well-defined cell border are prevalent. These are mast cells, as demonstrated by metachromatic stains and the von Leder's reaction.

Diseases of mast cells can be divided in three types: (1) urticaria pigmentosa arising in infancy or early childhood without significant systemic lesions; (2) urticaria pigmentosa arising in adolescence or adult life without significant systemic lesions; and (3) systemic mast cell disease. The Seminar case is an example of the third type. In this condition, there is progressive involvement of many organs, including the liver, spleen, intestinal tract, meninges, bones and bone marrow. Mast cells may be released into the blood, occasionally reaching the proportions of mast cell leukemia. Of a total of 29 cases of systemic mast cell disease reviewed by Mutter et al. in 1963, 11 had died at the time of reporting. In 5 of the 29 patients cutaneous lesions were absent. Although most cases of fatal systemic mast cell disease have been reported in adults, a fatal outcome may occur in children.

Microscopically, extensive aggregates of mast cells are present, with diffuse infiltration especially of lymph nodes, spleen, liver, intestinal tract, bones and bone marrow. Mild infiltration of the bones causes asymptomatic osteoporotic and osteosclerotic changes, whereas massive infiltration can cause collapse of several vertebrae.

The marrow lesions of systemic mastocytosis may be found as a direct result of search in a patient with urticaria pigmentosa or may be detected in a biopsy performed for some reason unrelated to suspected mastocytosis. In the latter instance, when there is no clinical suggestion of mastocytosis, the lesions of mast cell disease are frequently overlooked or misinterpreted because of the difficulty of identifying mast cells in routine sections and the changes inherent in the mast cells in this disease. Smears obtained by bone marrow aspirate may suggest the diagnosis of mastocytosis if large numbers of mast cells are present; the number should exceed 7% since up to that percentage has been reported in patients without mast cell disease. In many instances, the mast cells in the marrow in mastocytosis are associated with an increase in reticulin fibers and are not readily aspirated. As a result, the pathologist is not alerted to the possibility of mast cell disease from the smears.

The marrow infiltration in mastocytosis may be diffuse or focal. The focal lesions may take several forms: mast cell aggregates, fibrotic foci associated with mast cells, lymphocytic aggregates surrounded by a collar of mast cells or a focus of
mast cells surrounded by a collar of lymphocytes. Fibrotic foci may be found in a paratrabeucal location and nodular granulomatous foci may be present. A prominent perivascular arrangement of mast cells is sometimes noted; hyperplasia of the vessel wall and perivascular collagenous fibrosis may occur. Eosinophilia is usually prominent in the area of the mast cell aggregates and may be the most conspicuous morphologic finding. The bone trabeculae may show osteoblastic and osteolytic changes in the same section. Blood eosinophilia and hypocholesterolemia are frequently associated laboratory findings.

A major difficulty in the diagnosis of mast cell lesions results from the frequently abnormal morphology of the mast cells in this disorder. The cells often resemble histiocytes in that they possess abundant eosinophilic cytoplasm. The granules are difficult to identify even when the true nature of the lesion is suspected. In the fibrotic foci, the mast cells may have a spindly appearance and resemble fibroblasts. Large fibrotic lesions may be misinterpreted as idiopathic myelofibrosis. The identification of the mast cells is best accomplished with the Giemsa or toluidine blue 0 stains, the von Leder chloroacetate reaction or electron microscopy. With the toluidine blue 0 stain, the mast cell granules appear reddish purple; the staining of the granules can be enhanced in decalcified tissue by treatment of the section with potassium permanganate followed by oxalic acid prior to the staining procedure.

The marrow lesions in systemic mastocytosis are similar to the changes described as "the eosinophilic fibrohistiocytic lesion".
REFERENCES


Case 3 - LYMPH NODE, CERVICAL - "Post-transplant malignant lymphoma"

This is a typical example of the type of lymphoreticular proliferation that has been described with increasing frequency in transplant recipients under the term of "post-transplant malignant lymphoma". There is total effacement of the architecture by a pleomorphic infiltrate in which plasma cells, plasmacytoid cells and immunoblasts predominate. Immunoperoxidase stains showed a polyclonal pattern of cytoplasmic immunoglobulin in the proliferating lymphoid cells. Evidence of EBV infection was documented in the patient.

In 1977, we reviewed the clinical evolution, pathologic distribution, and morphology of 27 cases reported as "malignant lymphomas" to the ACS/HIH Organ Transplant Registry. The findings documented a distinctive clinicopathologic entity. The clinical evolution from the onset of symptoms to death tended to be extremely rapid without significant response to any mode of therapy. The onset could occur anytime in the post-transplant period, the shortest interval in this series being 1 month. Morphologically, the process was composed of a monotonous proliferation of large "immunoblastic" and plasmacytoid cells infiltrating organs in a diffuse pattern quite atypical for histiocytic lymphomas. Determination of intracellular immunoglobulins by the immunoperoxidase techniques indicated that the process represented, in virtually every case, a polyclonal proliferation of B-lymphocytes. Documentation of acute Ebstein-Barr virus infection was obtained in several cases, raising the possibility of a viral stimulus for this syndrome.

It is possible that we are in the presence of an EBV-induced B-lymphocyte proliferation which, by virtue of this patient's induced, defective T-cell response to EBV has progressed to a condition which has many of the features of neoplastic process.

This hypothesis fits nicely with the well-known statement made by Dameshek and Gunz to the effect that infectious mononucleosis is "a generalized proliferation of one of the white cell-forming tissues, that has many if not all of the features of acute leukemia with one notable exception, i.e., its reversibility".

Recent evidence indicates that this reversibility is dependent upon the presence of suppressor T-cells which control and eventually abolish the proliferation of EBV-infected B-lymphocytes. It is easy to conceive how, in the presence of an impaired T-cell function as the result of immunosuppression, the B-cell proliferation could proceed in an unrestrained fashion, acquiring in the process the morphologic and behavioral features of a neoplastic process. This interpretation, if correct, is a remarkable "experiment of nature" linking in humans a well-documented infection by an oncogenic virus with the neoplastic state. Obviously, this is a matter of great practical importance because, if this is indeed the case, chemotherapy may not be the best
therapy for these patients. Instead, discontinuation of the immunosuppression could prove a much more effective measure in that it might still revert the process.

It should also mention in this regard that many of the "lymphomas" developing in patients with natural immunodeficiencies have very similar morphologic and clinical features to the "post-transplant lymphomas", as we have found out in a recent review of the cases collected by the Immunodeficiency Cancer Registry at the University of Minnesota.
REFERENCES


The section shows a nodular dermal infiltrate of inflammatory appearance composed of lymphocytes, plasma cells, neutrophiles, and numerous histiocytes of large vesicular nucleus and abundant pale cytoplasm. Some of these histiocytes contain phagocytosed lymphocytes in their cytoplasm.

The microscopic appearance is consistent with the cutaneous manifestation of sinus histiocytosis with massive lymphadenopathy (SHML). This is one of ten cases that we have recently reviewed of SHML manifesting with skin lesions. Increasing experience with this disease has shown that SHML tends to involve extranodal structures more often than indicated in the original descriptions. The microscopic appearance in these sites is quite similar to that seen in the lymph nodes in terms of cellular composition of the infiltrate. On the other hand, the overall architecture is somewhat variable, mainly as a function of the type of tissues and structures involved. Foremost in this regard is the absence in the skin and most other extranodal sites of lymph node sinuses, whose alterations represent one of the most important hallmarks of SHML. It has thus become evident that the designation "sinus histiocytosis" is not appropriate when applied to most extranodal lesions, including those in the skin. The alternative designation that we have chosen to describe this phenomenon is that of "cutaneous involvement by SHML," analogous to the use of terms such as "cutaneous involvement by ulcerative colitis" or "cutaneous involvement by benign mucous membrane pemphigoid" to indicate skin involvement by conditions primarily affecting other organ systems.

The recognition of a cutaneous lesion of SHML is rarely a problem, since the nature of the disease is usually evident on the basis of the lymph nodal manifestations. However, it is important to describe the diagnostic criteria and differential diagnosis of this disease when located in the skin, since this not only may be the first source of biopsy material but, as the Seminar case demonstrates, it may also be the only obvious site of the disease. In this regard, it should be mentioned that we have now seen several other patients with SHML in whom an extranodal focus (such as an orbital mass) was the predominant manifestation of the disease, whereas the cervical nodal enlargement was minimal or absent. Thus, the designation of "massive lymphadenopathy" does not accurately describe this particular group of cases.

The cutaneous lesion of SHML can be defined as a dermal infiltrate predominantly composed of mature histiocytes (some foamy and/or multinucleated), lymphocytes, and plasma cells, with or without associated vascular proliferation and fibrosis and usually accompanied by relatively minor and nonspecific epidermal changes. Two additional features are the segregation between the histiocytes and the other
inflammatory cells, the former sometimes arranging in tissue spaces suggestive of lymph vessels; and the presence of lymphocytes and other inflammatory cells within the cytoplasm of the histiocytes. Unfortunately, these features were usually not as prominent in the skin as they were in the lymph nodes, and sometimes they were absent.

The following diseases should be considered in the differential diagnosis on microscopic grounds: dermatofibroma, xanthoma, Tangier disease, histiocytosis X, reticulohistiocytoma, juvenile xanthogranuloma, leprosy and Hodgkin's disease. The skin lesions of SHML had a tendency to involute spontaneously; this applied to all four cases in which we have follow-up information.

The other most common site of extranodal involvement by SHML are the upper respiratory tract, eye and adnexa (particularly orbit), and skeletal system. We have also seen cases located in the testicle, epididymis, central nervous system (extensions from peridural masses), trachea and thyroid.
REFERENCES


Case 5 - STOMACH - Multiple carcinoid tumors (in a patient with multiple endocrine adenomatosis)

The stomach from this case shows two lesions: a diffuse hyperplasia of the fundal mucosa consistent with Menetriere's disease, and multiple primary endocrine gastric tumors of carcinoid type, composed of argentophilic cells and associated with diffuse hyperplasia of mucosal argentophilic cells.

This is one of two patients with multiple primary tumors of the stomach, giant hypertrophic gastropathy, and elevated serum gastrin levels fulfilling the criteria for Zollinger-Ellison syndrome and suggestive of MEA I that we have recently studied. Gross examination revealed multiple submucosal neoplasms in one case and only hypertrophic gastric folds in the other. Microscopically, the gyriform pattern of growth, consisting of festoons and ribbons of small dark cells, was considered characteristic of that previously associated with gastrin-secreting pancreatic islet cell tumors. These neoplasms were also uniformly argentaffin-negative and argentophil-positive. An independent pancreatic tumor in one patient lacked the gyriform appearance and was both argentaffin and argentophil-negative. Immunohistochemical techniques failed to localize intracytoplasmic gastrin within the gastric tumors. Ultrastructural studies revealed the presence of large numbers of membrane-bound cytoplasmic granules of neurosecretory type. The granules in both gastric tumors were similar in that their outer electron-dense membranes encompassed homogeneous cores of variable intensity.

On the basis of our data, we have reached some conclusions regarding these novel gastric neoplasms. First, we have concluded that the gastric tumors represent multiple primary tumors rather than metastases from the neighboring pancreatic neoplasms. We feel that this conclusion is supported by the following evidence: (1) Isolated metastases from pancreatic neoplasms to the gastric submucosa without widespread metastatic dissemination elsewhere would be most unusual; (2) The in situ proliferation observed in the gastric glands argues strongly for an intrinsic gastric neoplastic process; (3) In both cases, the gastric tumors and the pancreatic tumors showed different histochemical characteristics when subjected to the argentrophil reaction; (4) There was a striking difference between the electron microscopic appearances of the neurosecretory granules identified in the gastric tumors when compared with those identified in the pancreatic metastases.

We think that these gastric tumors may be designated carcinoids. We have chosen this term in order to follow the nomenclature of the World Health Organization which defines "carcinoid" as a generic term for a tumor which has originated from any cell of the diffuse endocrine system, outside of the pancreas. We have also concluded that the available evidence suggests that these gastric neoplasms do not arise from
G or gastrin-producing cells. Our reasons for this conclusion are as follows: (1) The tumors and the hyperplastic argyrophil cells are present in the fundus of both stomachs, a site known to be poorly populated by G-cells; (2) The ultramicroscopic appearance of the granules from the one stomach tumor examined differ from those of known gastrin-producing tumors; (3) The immunoperoxidase reaction for gastrin was negative; (4) The serum gastrin level remained elevated after total gastrectomy in one patient studied.

There are four possible endocrine cells of the human stomach which may have given rise to these neoplasms. They comprise the G or gastrin cell, the E.C. or enterochromaffin cell, the E.C.-L. or enterochromaffin-like cell, and the D cell which resembles the D cell of the pancreatic islets. We have effectively excluded the G cell as the cell of origin of these tumors. The enterochromaffin cell is not a likely candidate, because of the fact that enterochromaffin cells are argentaffin-positive whereas the cells comprising our gastric tumors are uniformly argentaffin-negative. That leaves the enterochromaffin-like cell and the D cell as possible progenitors for these neoplasms.

It is possible that the diffuse gastric endocrine cell proliferation reported by some authors in association with the Zollinger-Ellison syndrome represents the precursor stage for the disease exemplified by Case 5.
REFERENCES


This is a good example of a specific type of primary appendiceal neoplasm of dubious histogenesis, but which is generally regarded as a morphologic variant of carcinoid tumor. According to this scheme, carcinoid tumors of the appendix can be roughly divided into three categories. The "classic" type is formed by solid nests of small monotonous cells with occasional acinar or rosette formation. Mitoses are exceedingly rare. A peculiar retraction of the tumor periphery from the stroma is evident. Some of the cells are found within intraappendiceal nerves. The second type, referred to as the "tubular type adenocarcinoid" by Warkel et al., is often misdiagnosed as primary or metastatic carcinoma. It is characterized by glandular formation without solid nests. Mucin stains are positive, whereas argentaffin and diazo reactions are negative. The lack of mitoses and atypia, orderly arrangement, and origin at the base of the glands with an otherwise normal mucosa should suggest the diagnosis. On occasion, the cytoplasmic granules of these cells are large and acidophilic, simulating those of Paneth cells, a feature also sometimes exhibited by normal Kultschitsky's cells. Electron microscopic examination will be diagnostic even with formalin-fixed material because of the presence of neurosecretory granules. The third type, represented by the Seminar case, is variously called mucinous carcinoid tumor, goblet cell carcinoid, goblet cell type adenocarcinoid and microglandular carcinoma. Grossly, it may be found in any portion of the appendix and appears as an area of whitish, sometimes mucoid induration without dilatation of the lumen. Microscopically, and like the other two carcinoid types, it is characterized by a predominantly submucosal growth. Extension into the muscle and serosa are common, but the mucosa is characteristically spared, except for areas of apparent connection between tumor nests and the base of the crypts. The tumor itself is formed by small uniform nests of signet ring cells, often arranged in a microglandular fashion, and sometimes accompanied by extracellular mucus. Focal resemblance to Brunner glands and Paneth cells has been noted. Acute appendicitis is a common complication. Mucicarmine stains are consistently positive, and argentaffin cells show cytoplasmic granules in about 88% of the cases. Electron microscopic studies have shown mucin droplets and neurosecretory type granules, although there is controversy whether they are located in the same cell. The behavior of this tumor is more aggressive than the other two types of carcinoid: metastases have been documented in 8 to 20% of the cases. Because of this, we favor the performance of a right hemicolectomy for this tumor type, especially if the neoplasm has spread beyond the appendix and/or shows a high mitotic count.
REFERENCES


Case 7 - TESTIS - Seminoma with trophoblastic giant cells

This testicular tumor has many of the features associated with classical seminoma, but in addition, it contains a good number of multinucleated giant cells with an appearance consistent with syncytiotrophoblast. Many of these cells are closely related to the wall of blood vessels. Immunoperoxidase stains shows presence of human chorionic gonadotropin in the cytoplasm of these cells, confirming their trophoblastic differentiation.

The presence of these cells does not indicate that this tumor has a component of choriocarcinoma. It should still be diagnosed as seminoma, but the presence of these cells and of elevated level of serum HCG should be taken as an indication that the tumor will probably run a more aggressive clinical course than in the usual case, and more akin to that of anaplastic seminoma. Anaplastic seminomas, as currently defined, comprise about 5% of all seminomas; they have the overall light and electron microscopic appearance of classical seminomas, but mitoses are more frequent (three or more per high power field), the nuclei larger and more hyperchromatic, the cytoplasm scantier and necrosis more pronounced. As indicated, scattered multinucleated giant cells with the appearance of syncytiotrophoblast are often found. These have been shown to contain chorionic gonadotropin, and patients with these tumors may have serum elevation of this hormone. The presence of these cells (seen in 11% to 14% of all seminomas) is not justification to label the tumor as a choriocarcinoma, but it has been our experience that many of the seminomas containing these elements were of the anaplastic variety. We have recently reviewed a series of seminomas of the testis associated with serum elevation of chorionic gonadotropin; most of the tumors were of the anaplastic variety and/or contained scattered syncytiotrophoblastic cells. The natural history of anaplastic seminoma is not well known because the morphologic criteria for its identification have been defined only recently; however, it seems that patients with this tumor do worse, stage for stage, than those with classical seminoma. The most important differential diagnosis of anaplastic seminoma is with embryonal carcinoma; the latter shows more nuclear variability in size and shape, prominent overlapping of nuclei and focal clumping of cells in a carcinomatoid fashion.

This case also illustrates well the importance that immunocytochemical techniques (particularly immunoperoxidase) have acquired in the diagnosis and classification of human tumors.
REFERENCES


Case 8 - SKIN - Masson's hemangioma

The section shows a marked proliferation of large blood vessels, many of which exhibit partial or total obliteration of the lumen by a complex -- sometimes papillary -- proliferation of endothelial cells supported by thin fibrous septa. Anastomosing channels are thus formed. In some of the sections, thrombi in various stages of evolution are present. We interpret this lesion as a benign large vessel hemangioma in which thrombosis and exuberant recanalization has occurred. This change was originally described by Masson in hemorrhoids and is sometimes confused with angiosarcoma.

In 1976, we collected 17 cases occurring in the skin and soft tissues. They presented either in a pure form with a clinical appearance reminiscent of an ordinary hemangioma, or more commonly, as a focal change in pyogenic granulomas or hemangiomas.

Of the 14 cases with available follow-up information, there was no instance of local recurrence, with the possible exception of an unusual case of pyogenic granuloma recurring with multiple satellites around the excision site, a phenomenon previously described.

The microscopic differential diagnosis of Masson's hemangioma includes several types of benign and malignant vascular proliferation.

Angiolymphoïd hyperplasia with eosinophilia, also known as pseudo- or atypical pyogenic granuloma, shares with Masson's hemangioma a predilection for the head and neck region, the reddish or blue color, the nodular appearance, and, at a microscopic level, the marked proliferation of endothelial cells. However, it usually shows a prominent inflammatory component, in the form of lymphoid follicles and/or massive eosinophilic infiltrate, that is lacking in Masson's hemangioma. The endothelial proliferation is haphazard and rather solid, and it does not result in the typical anastomosing channels of the latter lesion. Finally, the process has ill-defined margins, whether located in the dermis or subcutaneous tissue, and is never fully contained within a vascular wall, as it is always the case with Masson's hemangioma.

Cutaneous angiosarcomas also commonly affect the head and neck regions and they can exhibit papillary growth patterns on microscopic examination. However, they often form anastomosing vascular channels lined by anaplastic endothelial cells with invasive growth and frequent mitoses. These papillary fronds usually consist of piled-up cells in clumps, in contrast to the single layer of endothelial cells without nuclear anaplasia seen in Masson's hemangioma. Occasionally, the villi in Masson's lesion appear to be covered by multiple layers of endothelial cells, but they never exhibit frank anaplasia or necrosis. In addition, cutaneous angiosarcomas present as dermal infiltrative neoplasms rather than intravascular growths.
The differentiation from Kaposi's sarcoma should pose no difficulty. The latter lesion has a quite different clinical presentation and is characterized microscopically by vascular slits, spindle cells, and extravasated red blood cells, with no papillary fronds or anastomosing channels. Intravascular growth is not prominent.

In some cases located in the fingers, the possibility of confusion with pigmented villonodular synovitis also arises.

The histogenesis of Masson's hemangioma is still debated. Its form of presentation, association with other lesions, and pattern of growth suggest that it is not a true neoplasm but rather a lesion of reactive nature. The question remains as to whether the endothelial proliferation is a primary event and the thrombosis secondary, as postulated by Masson or whether it simply reflects the exuberant growth phase of an organizing thrombus, as preferred by most authors at the present time.

Salyer et al. compared the changes seen in this entity, which they refer to as intravascular angiomatosis, with those of angiosarcoma and with a large number of arterial thrombo-emboli and venous thrombi obtained at autopsy. Their conclusion was that all the features of Masson's hemangioma could be seen in organizing thrombo-emboli and, therefore, regarded the former as a peculiar morphologic feature of thrombus undergoing organization.

The importance of Masson's hemangioma resides in its capacity to simulate the growth pattern of a malignant vascular tumor. It should be recognized by the pathologist on the basis of its characteristic appearance and location. It should also be identified as a perfectly benign condition, as clearly evidenced by the follow-up of our cases and those of similar nature reported by other investigators under the designation of intravascular papillary endothelial hyperplasia.
REFERENCES


The sections show a cystic formation in the subcutaneous fat lined by a fibrous wall containing inflammatory cells, including multinucleated giant cells. The distinctive feature is the presence within the cavity of large "bags", each containing a variable but usually large number of pale eosinophilic spherules suggestive of fungal spores or some other organism. This is a good example of the condition recently described as myospherulosis. This was first reported in Kenya and Uganda as subcutaneous nodules, and later in St. Louis, USA, presenting in the paranasal sinuses, nose or middle ear in individuals who had had previous operations in the region. It was concluded that the disorder was related to the use of hemostatic packing containing petrolatum-based ointments and gauze.

In a recent case seen at our Institution, we performed a series of studies in order to ascertain the nature of these mysterious "organisms".

The morphologic features of these formations and their positivity with stains for hemoglobin, peroxidase, and lipofuscin strongly suggested that they represent nothing more than collections of erythrocytes altered by a foreign substance. This interpretation was confirmed by experimental production of these structures by the action of tetracycline ointment on a pure preparation of human erythrocytes. Wheeler and McGavran further confirmed this by producing myospherules in vitro using either lanolin or petrolatum, the two components of the vehicle of Achromycin. Most interestingly, they also showed that human fat was capable of producing myospherules in vitro.

Beurlet et al reached independently similar conclusions on the nature of the spherules on the basis of histometric comparison with normal red blood cells.
REFERENCES


The section shows replacement of the splenic parenchyma by a cellular tumor composed of dilated lymphatic vessels. The lumina are large and occupied by lymph. The most distinctive feature of the neoplasm is the appearance of the neoplastic endothelial cells. They are plump and resemble either epithelial cells or histiocytes. Their nucleus is prominent and vesicular, occasionally deeply indented. The cytoplasm is abundant, eosinophilic, sometimes vacuolated.

This tumor probably represents the lymph vessel counterpart of the blood vessel lesion that we have proposed to designate as histiocytoid hemangioma. The premise of this proposal is that a number of previously described entities of skin, soft tissue, large vessels, bone and heart actually constitute different manifestations of the same basic process, characterized by the proliferation of a highly distinctive cell type descriptively identified as a "histiocytoid endothelial cell". The entities in question are angiolymphoid hyperplasia with eosinophilia and related cutaneous, subcutaneous and mucosal disorders; atypical vascular proliferation of large vessels (including aorta); hemangioendothelioma of bone; hemangioendothelioma of spleen; and endocardial benign angioectaticuloma of the heart. The main cell that proliferates in all of these conditions has the basic features of an endothelial cell but also exhibits histochemical and ultrastructural characteristics that are more akin to those of a histiocyte.

The studies of Eady et al. on a series of 4 cutaneous cases of this condition showed that these cells exhibit marked histochemical and ultrastructural differences with normal endothelial cells. Instead of the high alkaline phosphatase activity and low level of non-specific esterase, acid phosphatase and respiratory enzymes characteristic of the endothelium of normal capillaries, these "extraordinary" cells showed a negative alkaline phosphatase reaction (both by the Gomori lead phosphate and the azo-dye method) and a very intense positivity for nonspecific esterase, acid phosphatase, dehydrogenase, glucose-6-phosphate dehydrogenase, cytochrome oxidase and NADH diaphorase. Ultrastructurally, the cells were separated by extensive gaps, alternating with areas of interdigitation and intercellular tight junctions. Their cytoplasm contained prominent 100 to 150 Å cytofilaments and bundles of finer filaments associated with dense bodies; occasional microbodies were also observed. A notable feature of the cytoplasm was the presence of large membrane-bound vacuoles, either single or multiple. Weibel-Palade bodies (a characteristic albeit not pathognomonic cytoplasmic marker of endothelial cells) were sparse, particularly in the larger cells. A basal lumina was present on the side opposite to the lumen; it was thin, fragmented and sometimes multilayered.
These unusual features could be the expression of a morphologic abnormality or represent an overgrowth of a specific and as yet undefined sub-population of endothelial cells, such as Majno's "contractile endothelial cell". Whether this group of proliferative diseases is of a reactive or neoplastic nature is not immediately apparent, although the latter is favored. However, it is clear that the behavior of these lesions, as a group, is quite indolent and even self-limited, in contrast to the aggressive behavior and often fatal outcome of the true angiosarcomas that they so closely resemble on microscopic grounds.
# TABLE I

DISEASES INCLUDED IN THE SPECTRUM OF HISTIOCYTOID HEMANGIOMAS

<table>
<thead>
<tr>
<th>Skin, oral cavity, anditory canal and penis</th>
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<tbody>
<tr>
<td>Angiolymphoid hyperplasia with eosinophilia</td>
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<tr>
<td>Subcutaneous angioblastic lymphoid hyperplasia with eosinophilia</td>
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<tr>
<td>Pseudo or atypical pyogenic granuloma</td>
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<tr>
<td>Papular angioplasia</td>
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<td>Inflammatory arteriovenous hemangioma</td>
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<td>Inflammatory angiomatoses</td>
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<tr>
<td>Atypical vascular proliferation with inflammation</td>
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<tr>
<td>Some reported cases of cutaneous angiosarcoma and Kaposi's sarcoma</td>
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<th>Large vessels</th>
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<tr>
<td>Intravenous atypical vascular proliferation</td>
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<td>? Some reported cases of angiosarcomas of vessels</td>
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<tr>
<th>Soft tissue</th>
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<tr>
<td>&quot;Epithelioid&quot; hemangioma</td>
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<tr>
<td>Some reported cases of hemangioendothelioma and angiosarcoma</td>
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<thead>
<tr>
<th>Spleen</th>
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<tr>
<td>Some reported cases of hemangioendothelioma</td>
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<thead>
<tr>
<th>Bone and periosteum</th>
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<tr>
<td>Many (? most) reported cases of angioendothelioma, hemangioendothelioma and low grade angiosarcoma</td>
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<th>Heart</th>
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<td>Endocardial benign angioreticuloma</td>
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## TABLE II

**DISEASES NOT INCLUDED IN THE SPECTRUM OF HISTIOCYTOID HEMANGIOMAS**

- Kimura's disease of the Orient
- Masson's "vegetant intravascular hemangioendothelioma"
- Intravascular papillary endothelial hyperplasia
- Pyogenic granuloma with recurrent satellites
- Intravenous pyogenic granuloma
- Proliferating angioendotheliomatosis
- True angiosarcoma of skin, soft tissue, large vessels, bone and other organs
- Malignant endovascular papillary angioendothelioma
REFERENCES


