ARTHUR PURDY STOUT SOCIETY
OF
SURGICAL PATHOLOGISTS

ANNUAL SLIDE SEMINAR

TUMORS OF "SMALL" CELLS

1978

Grand Ballroom East, Atlanta Hilton Hotel
Atlanta, Georgia
Slide Seminar - 8:30 A.M. - 12:30 P.M.
Business Meeting - 12:30 - 1:30 P.M.

Monday, March 6, 1978

(please bring to meeting)

The Annual Banquet will be held Sunday, March 5, from 6:30 - 8:30 P.M. in the Crystal Ballroom E & F of the Atlanta Hilton Hotel.

I plan to attend the Annual Banquet on Sunday, March 5.
Yes_____ No_____

I will be accompanied by guest(s).
Yes_____ No_____

No._____

_____

Name (please print)

Please return to Dr. William Hartmann, Vanderbilt University, Nashville, TN 37232 by March 1, 1978.

HISTORIES

Case #1 - Dr. William H. Hartmann, Vanderbilt University

This 24-year-old man presented with a homonymous hemianopsia. C.T. scan demonstrated a left occipital lobe tumor. Slides are from the resected brain mass.

metastatic Ewing's sarcoma (primary = rib) –

Case #2 - Dr. Saul Kay, Medical College of Virginia

This is a 6-month-old female child who presented with hepatosplenomegaly and flaccid paraplegia which was rapidly progressive. A myelogram showed a large paraspinal extradural tumor in the region of T8 to L2 causing a partial block. A decompression laminectomy with partial excision of a tumor was performed. A. died a few weeks later - at autopsy, there was necrotic residual tumor, but not distant metastases –

The surgical specimen consisted of skeletal muscle and fragments of bone and cartilage. The muscle tissues were from the right and left paraspinal muscles, and the largest piece measured 6 x 4 cm.

Kay's Dx = embryonal rhabdomyosarcoma –

Case #3 - Drs. Antonio L. Cubilla and James M. Woodruff, Memorial Sloan-Kettering Cancer Center

This firm, tan mass showing central stellate sclerosis and measuring 2 cm in greatest dimension presented in the left breast of a 33-year-old woman. Two years ago she underwent a right radical mastectomy for infiltrating lobular carcinoma.

carcinoid tumor. It metastasized to liver & ovaries –

Case #4 - Dr. Sharon Thomsen, University of Miami

43-year-old female complained of pain occurring in the coccygeal region beginning in August, 1975. One and a half months later, a 4 x 1 cm. tender fixed mass was palpable adjacent to the coccyx on rectal examination. A hard, tender, slightly raised ulcer was present in the anterior lateral anus at the pectinate line and was continuous with a fixed tumor mass extending into the lateral pelvis. This ulcer was biopsied. The remainder of physical examination and laboratory examination was within normal limits. After the diagnosis was established, the patient received 3,000 rads to the pelvis and adjacent lymph node areas over a twelve day period. During the treatment, bilateral inguinal lymphadenopathy developed. A 1 cm. firm mobile nodule was palpable in the right breast but over the ensuing twenty days, she developed bilateral breast masses which were biopsied. A representative section of one of these masses is submitted for study. The histologic pattern is essentially identical to that seen in the biopsies of the anal tumor mass.

carcinoma of anus (? undiff. carcinoid) metastatic to breast – looks like the small cell basaloid carcinoma and she thinks it is a carcinoid, equivalent to that seen in anus and bladder –

Case #5 - Drs. Louis Dehner and Juan Rosai, University of Minnesota

The patient was originally admitted to the University of Wisconsin Hospitals in July of 1975 because of opacification of the right lung. He had been well until two months previously when he developed severe febrile episodes and shortness of breath. He was treated with antibiotics with regression of the fever but he acutely presented with marked respiratory difficulties. A work-up disclosed an elevated VMA and a needle biopsy was performed with the diagnosis of a malignant small cell tumor. Following the biopsy, a thoracotomy was performed and a large lobulated tumor attached to the chest wall and compressing a normal appearing right lung was identified. Excision of the tumor was performed. The patient was then treated with multidrug chemotherapy and he received irradiation. Although we do not have figures available, apparently the VMA returned to normal limits. A thorough work-up of this child failed to disclose any other site for a primary tumor, including the adrenals and the head and neck region. The patient was initially seen in our hospital in December of 1976. At this time, small peripheral nodules were identified in the opposite lung. The slide submitted is from the metastatic tumor. The patient has subsequently had recurrences of tumor in the right chest wall and right upper lobe of the lung in August of 1977.

Malignant small round cell tumor of chest wall—

DIAGNOSES

	My Diagnosis	Contributor's Diagnosis
#1		
#2		
#3		
#4		
#5		

Dr. Rosai

UNIVERSITY OF MINNESOTA
TWIN CITIES

Department of Laboratory Medicine and Pathology
Medical School
Box 609 Mayo Memorial Building
420 Delaware Street S.E.
Minneapolis, Minnesota 55455

January 26, 1978

Azorides R. Morales, M.D.
Professor of Pathology
Jackson Memorial Hospital
1700 North West Tenth Avenue
Miami, Florida 33136

Dear Dr. Morales:

This letter is written in response to a call for cases for the future Arthur Purdy Stout Society Slide Seminar. I know that you have talked to Juan about this particular case. The tumor represents a small round cell neoplasm of thoracopulmonary origin which we have presented previously at the Pediatric Pathology Club in 1976. A copy of the abstract is submitted. Since that report of 13 cases, we have now expanded the series to 20 cases and the manuscript is nearly completed and will be submitted to Cancer. This particular case is number 18 in the series. The history is as follows:

The patient was originally admitted to the University of Wisconsin Hospitals in July of 1975 because of opacification of the right lung. He had been well until two months previously when he developed severe febrile episodes and shortness of breath. He was treated with antibiotics with regression of the fever but he acutely presented with marked respiratory difficulties. A work-up disclosed an elevated VMA and a needle biopsy was performed with the diagnosis of a malignant small cell tumor. Following the biopsy, a thoracotomy was performed and a large lobulated tumor attached to the chest wall and compressing a normal appearing right lung was identified. Excision of the tumor was performed. The patient was then treated with multidrug chemotherapy and he received irradiation. Although we do not have figures available, apparently the VMA returned to normal limits. A thorough work-up of this child failed to disclose any other site for a primary tumor, including the adrenals and the head and neck region. The patient was initially seen in our hospital in December of 1976. At this time, small peripheral nodules were identified in the opposite lung. The slide submitted is from the metastatic tumor. The patient has subsequently had recurrences of tumor in the right chest wall and right upper lobe of the lung in August of 1977. We have done electron microscopy and have found microfilaments and a few microtubules. Membrane-bound dense bodies were present in the cytoplasm, also. The patient is doing well at the present.

We felt that this tumor is representative of a unique clinicopathologic entity and this case supports our current hypothesis that we are dealing with a soft tissue tumor of peripheral neuroectodermal derivation. We do not have electron microscopy on all of our cases, but the hypothesis is supported in some of the cases by electron microscopy. These neoplasms are PAS negative and in only a few cases is there osseous involvement. We feel that the behavior is not that of an Ewing's tumor, malignant lymphoma or embryonal rhabdomyosarcoma. We have sufficient material to provide the number of slides that are required for distribution.

Sincerely,

Louis P. Dehner, M.D.
Professor of Laboratory Medicine
and Pathology

kmh

cc: Dr. J. Rosai

UNIVERSITY OF MIAMI
MIAMI, FLORIDA 33152

Mailing Address:
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SCHOOL OF MEDICINE
P.O. BOX 520875, BISCAYNE ANNEX

Location:
SOUTH WING
JACKSON MEMORIAL HOSPITAL
1700 N. W. 10TH AVENUE

February 7, 1978

William H. Hartmann, M. D.
Professor and Chairman
Department of Pathology
Vanderbilt University
School of Medicine
Nashville, Tennessee 37232

Dear Bill:

I hasn't been easy, but we have finally been able to round up the cases for the forthcoming program of the Stout Society of Surgical Pathologists. The contributors have already been contacted and instructed to submit directly to you, 125 slides, along with the summary of the history, for distribution to the members of the Society. The list of cases is as follows:

CASE NUMBER	CONTRIBUTOR	DIAGNOSIS
1	Hartmann	Brain-metastatic Ewing's
2	Kay	Paraspinal mass-Rhabdomyosarcoma
3	Woodruff	Breast-infiltrating lobular carcinoma vs. carcinoid tumor
4	Thomsen	Cloacogenic oat cell carcinoma
5	Dehner/Rosai	Neuro-ectodermal small cell tumor

Discussion of these cases will be preceded by a fifty minute lecture on electron microscopic differentiation of small cell tumors, to be given by Ron Alexander. The three hour program will be completed with a presentation by

Bill Meissner of a follow-up of an interesting tumor of the thyroid gland, discussed at one of our previous seminars and a brief discussion of small cell tumors of the thyroid gland.

The experience of the last two years seems to underline the necessity to review the Society's format in selecting contributors for our program. By copy of this letter, I am requesting the members of the Membership Committee to meet with me in Atlanta in order to formulate plans for future programs.

Best personal regards.

Sincerely yours,

Azofides R. Morales, M. D.
Professor and Chairman,
Department of Pathology

ARM:cb

cc: Contributors
William Meissner, M. D.
Gerald Fine, M. D.
Members, Program Committee
Ron Alexander, M. D.

ARTHUR PURDY STOUT SOCIETY
OF
SURGICAL PATHOLOGISTS

ANNUAL SLIDE SEMINAR
1978

SMALL CELL TUMORS

DIAGNOSES AND REFERENCES

DIAGNOSES

Case 1 - Metastatic Ewings Tumor

Case 2 - Embryonal Rhabdomyosarcoma

Case 3 - Carcinoid Tumor of the Breast

Case 4 - Cloacogenic Carcinoma - Basaloid Small Cell Type

Case 5 - Soft Tissue Tumor of Peripheral Neuroectodermal Derivation

CASE 1

D.S., a 24 year old white male, presented to Vanderbilt University Hospital in November of 1977 suffering from headaches and visual field defects. A CT scan showed the presence of a left occipital lobe mass, which was resected.

The tumor had a rather uniform microscopic appearance, and was composed of densely packed small cells with round nuclei and scanty, lightly staining cytoplasm.

A periodic acid-Shiff's stain on an air-dried touch preparation taken from the freshly resected tumor showed considerable PAS positivity which was sensitive to diastase digestion. Electron microscopy showed uniform, rather polygonal small cells with abundant cytoplasmic particulate glycogen and occasional junctional complexes. Microfilaments and microtubules were not present in tumor cells.

Past History

This patient was first seen at a private Nashville hospital five years prior to this admission with a right posterior rib fracture and extrapleural mass. This was resected and is similar histologically to the current material. Since that time the patient has suffered two local recurrences in 1975 and 1977 (treated with chemotherapy and local radiation) and metastases to the right upper and right lower lung lobes in 1974 and 1976. The metastases were resected and showed similar histologic appearance to the present material.

Since the last admission the patient has continued to receive systemic chemotherapy for his recurrent chest wall mass, with partial regression. He also received a post-operative course of cranial radiation. There is presently no further evidence of metastatic tumor.

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Hou-Jensen, K., E. Priori, and L. Dmochowski, 1972. Studies on Ultrastructure of Ewing's Sarcoma of Bone. Cancer 29: 280-286.

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CASE 2

There are bundles of striated muscle infiltrated by a small cell tumor. The neoplastic elements are distinctly anaplastic with hyperchromatic pleomorphic nuclei filling most of the cells. Actually, there is only a narrow rim of cytoplasm, and no clue as to the origin of these cells was furnished with special stains. Since it was thought that the tumor cells were probably embryonal rhabdomyoblasts, it was hoped to gain additional information by electron microscopy. Again, the completely undifferentiated status of the tumor cells was borne out in the ultrastructural observations. Neither actin or myosin fibers were identified, though conceivably this may have been a problem of sampling. A diagnosis of embryonal rhabdomyosarcoma was rendered on the basis of exclusion.

References:

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SUMMARY OF CASE #3
Arthur Purdy Stout Society Meeting
Atlanta, Georgia, March, 1978

The third case concerned an approximately 2 cm. mass removed from the left breast of a 33 year-old-woman. She had a right mastectomy two years earlier because of an infiltrating lobular carcinoma.

Slides from the left breast (present material) showed a fairly well-defined tumor composed of confluent strands of neoplastic cells separated by thin fibrous bands. The pattern at this low power suggested a medullary or confluent lobular carcinoma.[1] Inspection at higher magnification revealed the tumor cells to be small and monotonously uniform in size. The nuclei were centrally or eccentrically placed and occupied about half of the cell volume. Some cells had a plasmacytoid look and pleomorphism when noted was mild. Special stains revealed cytoplasmic argyrophilia but no argentaffin granules or mucin.

Slides from the right breast tumor were reviewed and found to be histologically identical to the left breast lesion. Its cells also contained pin-point argyrophil granules when stained using a modified Grimelius reaction.[2] Although tumor cells in both cases showed indian filing, no in-situ lobular carcinoma was identified.

Electron microscopic study of tumor from the left breast revealed cytoplasmic dense core neurosecretory type granules. They were uniformly round and averaged about 250 mn. in diameter. With the thought that we were dealing with bilateral mammary carcinoids we interviewed the patient but failed to obtain any history of flushing, wheezing, dyspnea or diarrhea.

Seven months later the patient was readmitted with epigastric distress and heaptomegaly. At laparotomy she was found to have tumor nodules in the liver and both ovaries. Only the left ovarian masses (2 and 5 cm) and liver nodules were examined microscopically. These showed a small cell tumor which in the ovary had the features of an insular carcinoid. Extensive sampling of the ovarian masses failed to reveal evidence of a teratoma. Neurosecretory type granules were demonstrated by electron microscopy in tumor from both sites.

This case presents obvious problems in interpretation. It is unlikely that it represents an example of primary ovarian carcinoid metastatic to both breasts and the liver, for the work of Robboy et al.[3] indicates that primary insular type ovarian carcinoids: 1) are almost always unilateral, 2) usually arise in teratomas, 3) usually are argentaffin positive, 4) on electron microscopy contain pleomorphic, not round granules, and 5) are rarely malignant. Examination of the intestines during laparotomy and chest roentgenograms failed to reveal a tumor mass, so a primary in these sites also is unlikely.

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2. Lack, E. and Mercer, L. A modified Grimelius argyrophil technique for neurosecretory granules. Am J Surg Pathol 1:275-277, 1977.

3. Robboy, S.J., Norris, H.J., and Scully, R.E. Insular carcinoid primary in the ovary. Cancer 36:404-418, 1975.

4. Cubilla, A.L. and Woodruff, J.M. Primary carcinoid tumor of the breast. A report of eight patients. Am J Surg Pathol 1:283, 1977.

5. Rosai, J. and Higa, E. Mediastinal endocrine neoplasm of probably thymic origin, related to carcinoid tumor. Clinicopathologic study of 8 cases. Cancer 29:1061-1074, 1972.

6. Albores-Saavedra, J., Larraza, O., Poucell, S. and Rodriguez Martinez, H.A. Carcinoid of the uterine cervix. Cancer 38:2328-2342, 1976.

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CASE 4

Clinical Summary

This 43 year-old female complained of pain occurring in the coccygeal region beginning in August, 1975. One and a half months later, a 4 x 1 centimeter tender fixed mass was papable adjacent to the coccyx on rectal examination. A hard, tender slightly raised ulcer was present in the anterior lateral anus at the pectinate line and was continuous with a fixed tumor mass extending into the lateral pelvis. This ulcer was biopsied. The remainder of physical examination and laboratory examination was within normal limits. After the diagnosis was established, the patient received 3,000 rads to the pelvis and adjacent lymph node areas over a twelve day period. During the treatment, bilateral inguinal lymphadenopathy developed. A 1 centimeter firm mobile nodule was palpable in the right breast but over the ensuing twenty days, she developed bilateral breast masses which were biopsied. A representative section of one of these masses was submitted for study.

The histologic pattern of the biopsies from both breasts was essentially identical to that seen in the biopsies in the anal tumor mass. After the pathologic confirmation of bilateral metastatic lesions in both breasts, the patient was begun on multiple drug chemotherapy given in 2 courses with a 6 week interval between each. No clinical response to this therapy was obtained. Twenty months after the initial onset of her symptoms, she died secondary to bowel obstruction by recurrent tumor. Just prior to death, she also had clinical manifestations of metastasis throughout the peritoneal cavity, omentum, liver and lungs. Permission for autopsy was not granted.

The pathologic diagnosis of the ulcerated anal tumor was cloacogenic carcinoma, basaloid small cell type, as first described by Whittoesch, et al, in 1957. The metastatic carcinoma to the breasts was histologically similar to that found in the anus. The tumors are composed of irregular cords and sheets of small pleo-morphic cells. Their granular, eosinophilic cytoplasm is scanty. Mitoses are frequent. No foci of "in situ" carcinoma were seen on the mucosal surfaces included in the anal biopsies. Extensive lymphatic permeation and invasion by the tumor cells into the lobules with replacement of breast tissue was prominent in the biopsies from both breasts. Electron microscopic examination of tissue from the anal lesion revealed the cells to have a large abundance of membrane-bound granules containing electron dense cores, so-called "neurosecretory granules." These granules measured 50 to 300 mm.

The light microscopic and electron microscopic features of this patient's tumor are quite similar to the variant of cloacogenic carcinoma first designated by Wittoesch and his colleagues (1) as the basaloid small cell type. They and other observers (2) noted that this type of tumor was highly lethal. Most patients did not live more than one to two years after diagnosis. The patient presented is no exception to this pattern.

Electron microscopic study of the basaloid type of cloacogenic carcinoma have been of lesions which at the light microscopic level had histologic features resembling the cutaneous basal cell carcinomas. (3) This case shows histologic and cytologic features at the light and electron microscopic levels reminiscent of the "oat cell" variant of the small cell undifferentiated carcinoma of the uterine cervix and lung. (4, 5). These tumors tend to share with certain tumors, the "apudomas", of the gastrointestinal tract, pancreas, and ovaries, histochemical, morphological and immunological common features which suggests that they are derived from a similar type of cell. The embryologic origen of this cell is unclear. Some studies have suggested that the cell is a direct descendant from cells of the neurocrest (6, 7, and 8), but other studies have suggested that the actual tumor cells are derived from endodermal epithelial cells which may be influenced by or otherwise related to neurocrest and neural elements in the adjacent tissue. (9-10)

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CASE 5

The patient was originally admitted to the University of Wisconsin Hospitals in July of 1975 because of opacification of the right lung. He had been well until two months previously when he developed severe febrile episodes and shortness of breath. He was treated with antibiotics with regression of the fever but he acutely presented with marked respiratory difficulties. A workup disclosed an elevated VMA and a needle biopsy was performed with the diagnosis of a malignant small cell tumor. Following the biopsy, a thoracotomy was performed and a large lobulated tumor attached to the chest wall and compressing a normal appearing right lung was identified. Excision of the tumor was performed. The patient was then treated with multidrug chemotherapy and he received irradiation. Although we do not have figures available, apparently the VMA returned to normal limits. A thorough workup of this child failed to disclose any other site for a primary tumor, including the adrenals and the head and neck region. The patient was initially seen in our hospital in December of 1976. At this time, small peripheral nodules were identified in the opposite lung. The slide submitted is from the metastatic tumor. The patient has subsequently had recurrances of tumor in the right chest wall and right upper lobe of the lung in August of 1977. We have done electron microscopy and have found microfilaments and a few microtubules. Membrane-bound dense bodies were present in the cytoplasm also. The patient is doing well at the present.

We felt that this tumor is representative of a unique clinicopathologic entity and this case supports our current hypothesis that we are dealing with a soft tissue tumor of peripheral neuroectodermal derivation. We do not have electron microscopy on all of our cases, but the hypothesis is supported in some of the cases by electron microscopy. These neoplasms are PAS negative and in only a few cases is there osseous involvement. We feel that the behavior is not that of a Ewing's tumor, malignant lymphoma or embryonal rhabdomyosarcoma.

References

1. Abella, M.R., Art, W.R. and Olsen, J.R.: Tumors of the Peripheral Nervous System, Human Pathology 1: 503-551, 1970.

2. Angervall, L., and Enzinger, F.M.: Extraskeletal Neoplasm Resembling Ewing's Sarcoma, Cancer 36: 240-251, 1975.

3. Nesbitt, K.A. and Vidone, R.A.: Primitive Neuroectodermal Tumor (Neuroblastoma) Arising in Sciatic Nerve of a Child, Cancer 37: 1562-1570, 1976.

4. Seemayer, T.A., Thelmo, W.L. Bolande, R.P. and Wiglesworth, S.W.: Peripheral Neuroectodermal Tumors, Persp. Ped. Path. 2: 151-172, 1975.

5. Wigger, H.J., Salazaf, G.H. and Blanc, W.A.: Extraskeletal Ewing's Sarcoma: An Ultrastructural Study, Arch. Path. Lab. Med. 101: 446-449, 1977.

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We believe that the present case probably represents a primary carcinoid tumor (s) of the breast which metastasized widely. In support of this interpretation is our discovery of 16 other mammary tumors which have a histologic pattern consistent with carcinoid and show cytoplasmic argyrophilia. Those tumors studied ultrastructurally contained dense core neurosecretory type granules. Ten of these cases have already been published.[4] The use of the term "carcinoid" for these lesions may be questioned on the basis of the lack of proof that they are hormone secreting or that the cytoplasmic granules contain seratonin or 5-hydroxytryptophan. However, carcinoids of the rectum may be non-functioning and argyrophil negative but histologically indistinguishable from functioning carcinoids. Rightfully or wrongfully the carcinoid concept has been broadened to include tumors originating in non-intestinal sites. The term is used for histologically, histochemically, and ultrastructurally similar tumors arising in the thymus,[5] breast and cervix,[6] and until it is demonstrated that these tumors elaborate a substance different from other carcinoids we feel there is no need to give them special identities.

Of interest is the close resemblance of this tumor to some reported cases of confluent lobular carcinoma of the breast, suggesting that a carcinoid (primary or metastatic) should be ruled out before making such a diagnosis.