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. . . an entirely new life began for Nekhlyudov, not so much because he had entered into a new condition of life, but because everything that happened to him from that time on was endowed with an entirely different meaning . . .

- L. Tolstoy

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INTRODUCTION

Extramedullary solid tumors composed of partially differentiated hematopoietic precursors have been variously described in the literature, with some 500 case reports since 1824 employing such terms as chloroma, chloroleukemia, and myeloblastoma. Early case reports (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11) took particular note of the green color of many of the lesions, hence the term chloroma, and the dramatic orbital involvement in children, sometimes producing frog-like facies. Frequently however, these lesions lack distinctive coloration so that Rappaport has suggested the more general term, granulocytic sarcoma (12). Presently, this term is used to characterize invasive and destructive tumor masses composed of immature cells of the myelomonocytic series.

Although for many years the lesions were associated with leukemia of various cell types, presently they are understood to be an uncommon variant of acute myelogenous leukemia, sometimes presenting before systemic involvement is detectable. In these cases, a retrospective review of the pathologic interpretation(s) reveals a wide spectrum of diagnoses, the most common misdiagnosis being histiocytic lymphoma. Thus, although extramedullary tumors of myeloid origin are thought to be fairly rare, they present a difficult diagnostic challenge, particularly in those cases in which definitive diagnosis may be of some therapeutic value. An elevated index of suspicion would therefore be of value in certain clinical settings, for example, the evaluation of proptosis in African children, where granulocytic sarcoma ranks second to Burkitts lymphoma in incidence of orbital neoplasms. Perhaps a full hematologic evaluation should also be performed in persons with "lymphomatous" skin nodules of questionable nature, after consultation with an experienced hematopathologist. Indeed, a component of the presumed rarity of granulocytic sarcoma may correspond to a low degree of surveillance, a situation which would merit correction, particularly as the possibilities for "prophylaxis"

or early treatment of acute myelocytic leukemia become less debilitating and the outcome more favorable.

The present study considers such diagnostic problems associated with granulocytic sarcoma in the context of eight cases presenting to Yale-New Haven Hospital and its affiliated hospitals during the years 1976-1979.

PATIENTS AND METHODS

The hematopathology files of Yale-New Haven Hospital were reviewed for cases known to the Pathology Service during the past two years 1978-1979. These clinical charts were reviewed, and follow-up information was obtained from the patient's clinic chart and/or from the patient's physician directly. The Yale-New Haven Hospital Tumor Registry was examined for coded cases of chloroma, chlorosarcoma, leukosarcoma, lymphochloroma, and malignant neoplasms of the spleen and lymph glands, with subsequent review of the charts of these suspected cases. The Tumor Registry was also examined for coded cases of reticulum cell sarcoma (histiocytic lymphoma), lymphosarcoma, giant follicular lymphoma, malignant reticulosis, and reticuloendotheliosis associated with, or terminating in, acute myelocytic leukemia. These charts were reviewed in an effort to detect cases of granulocytic sarcoma which had been misdiagnosed. Similarly, the Tumor Registry of Danbury Hospital was personally examined for coded cases of chloroma, chlorosarcoma, leukosarcoma, lymphochloroma and malignant neoplasms of the spleen and lymph glands until 1975, and for all cases of granulocytic sarcoma after 1975, with review of the charts of all suspected cases. A collation of all such coded cases after 1975 on file at the Connecticut State Tumor Registry was also performed. In addition, cases referred to Yale-New Haven Hospital from Greenwich Hospital and Uncas-on-Thames Hospital for pathologic consultation were fully reviewed, including interviews with the patients and gross and microscopic examination of their lesions.

In each of the seven cases accepted for this study, a tumor was evident clinically as well as pathologically. Each case also satisfied at least two of the following criteria: 1) the histopathologic picture was considered diagnostic by an academic pathologist experienced in hematologic pathology, with convincing evidence of granulocytic differentiation; 2) cytochemical stains for naphthol AS-D

chloracetate esterase done on formalin-fixed, paraffin-embedded tissue sections according to the procedure of Leder (13) revealed positive reactions in the cytoplasm of undifferentiated or poorly differentiated neoplastic cells; 3) there was hematologic evidence of granulocytic leukemia.

In three cases both hematologic confirmation and positive staining for esterase activity supported the diagnosis; in two cases there were abnormal hematologic data possibly indicative of, but notdiagnostic for evolving leukemia in addition to positive esterase activity. Biopsies from lesions in three of the patients were positive for esterase activity in the absence of hematologic indication of malignancy. One of these patients has expired, but for the remaining two patients, efforts have been made to include current follow-up information in this report. A final case is noted of a patient with acute myelocytic leukemia and multiple green nodules over his trunk and lower extremities, although lack of histopathologic evidence of granulocytic sarcoma precludes inclusion of this case within the series.

CASE REPORTS

Case Report: A. A.

A. A., a 65-year-old white female, was admitted on 5/21/79 with an eight-month history of melena and constipation, and a six-week history of constant epigastric abdominal pain associated with bloating and nausea. Physical exam revealed an abdominal mass 18 cm in diameter, extending from the epigastrium to below the umbilicus. In addition, two 2 cm by 2 cm nontender, soft, mobile nodes were present in the right posterior cervical chain, and a 1 cm by 1 cm soft node was present in the right axilla. A spleen tip was 7 cm below the left costal margin and the liver edge 12 cm from the right costal margin. Complete blood count revealed Hct. 35.9 vol. %, Hgb 12.2 gm/dl, WBC 6,200 cells/mm^3 with 50% segs/17% bands/17% lymphs/ 11% monos/1% eo/4% blasts. The LDH was elevated to 4730 IU/dl. Upper GI barium study demonstrated the stomach to be compressed by a large retroperitoneal mass. Anterior elevation of the pancreas and superior mesenteric vein was evident by ultra sound. The liver-spleen scan showed splenomegaly and a patchy hepatic uptake. Bone marrow aspirate revealed 80% blasts consistent with acute myelocytic leukemia. Special staining showed 20% of the marrow cells to be peroxidase positive, most blasts with a few granules positive to acid phosphatase, but negative to PAS, and 20% of the immature forms positive to Sudan B. Alpha-naphthol esterase stain was positive. The right cervical lymph node biopsy revealed a diffuse infiltrate of immature cell forms consistent with involvement by acute leukemia, myelomonocytic type. IgM Ab with mixed κ and λ light chains were present on the surface of the neoplastic cells. On the 18th hospital day the patient became febrile, hypotensive and died of acute posterior wall myocardial infarction.

Post-mortem examination revealed tumor infiltration of the cervical, para-aortic, and inguinal lymph nodes, pancreas, and kidneys bilaterally, in addition to the large midline retroperitoneal mass lesion.

Comment: A. A.

In this patient, abdominal symptomatology resulting from extensive extra-myelogenous involvement of the retroperitoneum preceded by 8 months the diagnosis of acute myelomonocytic leukemia. It is significant that biopsy of a soft, mobile posterior cervical node revealed infiltration by primitive hematopoietic cells. In light of the prognosis of untreated AMML, it is likely that this patient's tumor masses preceded bone marrow evidence of leukemia by a number of months. The patient died approximately 3 weeks after diagnosis, approximately 9 months after the onset of symptoms referable to granulocytic sarcoma.

Case Report: L. M.

L. M., is a 72 year-old white female who for the preceding year had experienced pain in the lower back and in the right anterior femoral area. On 2/20/79 she had low-grade fever, and was found to have several immature granulocytic cells on peripheral blood smear. Her last blood count was in 4/78. Physical examination was remarkable only for obesity and slight induration of the right thigh. Complete blood count showed Hct. 39.2 vol. %, Hgb. 13.2 gm/dl, WBC 12,500 cells/mm^3 with 19% segs, 27% bands, 19% lymphs, 18% monos, 3% myelos, 3% metas, 5% atyp lymphs and 6% blasts. The bone marrow biopsy was consistent with a hematopoietic neoplasm manifesting predominantly erythroid differentiation. The blasts cells were negative for four stains. Intermediate forms were positive to sudan B, peroxidase, and alph-naphthol esterase. Aspirate suggested acute myelocytic leukemia, with 53% blasts.

By 3/15/79, physical examination revealed an ill-defined soft tissue mass in the mid-portion of the right thigh. The left calf was also tender with an ill-defined mass, the circumference being 6 cm greater than the right side. In addition, multiple 1 cm nontender subcutaneous lesions were noted on the anterior abdominal wall of the left upper quadrant. Increased gallium uptake in the soft tissues of the right thigh, left calf, and also the left lateral thigh was present. Biopsy of the left calf demonstrated involvement by acute non-lymphoid leukemia; results of esterase staining are presently unavailable.

The patient subsequently received 1800 Rads to the right thigh, and 1800 Rads to the left calf, which resulted in total regression of the lesions. Peripheral smear at that time however, showed 21% blasts. In accordance with her wishes, aggressive systemic chemotherapy was not initiated. She expired on 5/9/79 and a post-mortem examination was not permitted.

Comment: L. M.

In this patient, symptomatology possibly referable to extramyelogenous involvement by primitive hematopoietic cells preceded apparent systemic involvement by approximately two years. As the offending lesions were not as well-defined as in other cases, gallium scan served well in localizing them, supporting its general use in the detection of tumor masses in leukemic patients (14). This patient expired almost 10 weeks after definitive diagnosis, approximately 27 months after the onset of symptoms possibly referable to granulocytic sarcoma.

Case Report: I. B.

I. B., a 77 year-old white male, noted an enlarging right cervical mass over a six month period, with associated weight loss. On admission in 12/78, physical exam revealed a firm, nonmobile right cervical mass measuring 15 by 9 by 15 cm. Histology was initially interpreted as poorly differentiated carcinoma and further workup, including brain scan, liver-spleen scan, intravenous pyelogram, bone scan, lung tomography, barium enema, sinus films, and C-spine films were normal. Complete blood count was within normal limits, and a bone marrow examination was not performed. The patient was treated with 5,600 Rads to the neck mass, with an excellent result.

On further evaluation of the patient's surgical specimen, the diagnosis of granulocytic sarcoma was established, and he was re-admitted on 3/6/79. Physical examination was significant for two masses in the right posterior triangle, one measuring 1 by 1 cm, the other being 2½ by 2½ cm. Biopsy was consistent with granulocytic sarcoma, with positive staining to Giemsa and alpha-naphthol esterase. Complete blood count showed Hct 36.2 Vol. %, WBC 5,100 cells/mm^3 with 73% segs, 9% bands, 2% lymphs, 13% monos, and 3% eos. Bone marrow biopsy revealed an abnormal hypercellular marrow with sideroblastic hematopoiesis and marked relative increase in immature granulocytes, suspicious for evolving leukemia.

Although no significant adenopathy had been noted on 3/6/79, by 3/20 the patient had developed firm, 3 by 3 cm, non-tender, bilateral axillary masses. By 3/23 the masses had evolved markedly, and now included a submental mass measuring 5 by 5 cm. Extensive mediastinal adenopathy, partially compressing the trachea was seen on chest x-ray. Emergency radiotherapy was initiated, with a final total dosage of 2,000 Rads to the submental region,

1400 Rads to the mediastinum and lung parenchyma. The patient also received a ten-day course of Hydroxyurea. The masses continued to enlarge, and by 3/31/79 the tumor masses appeared to be completely refractory to therapy, resulting in the patient's death on 4/8/79.

Post-mortem examination revealed a firm, nonmobile right anterior neck mass 10 by 6 cm, bilateral axillary masses 8 by 6 cm and 4 by 3 cm, infiltrating lesions of the omentum and peritoneal surface, and involvement of the liver, small intestins (5 cm diameter transmural mass), as well as the hilar, esophageal, peripancreatic, and para-aortic lymph nodes.

Comment: I. B.

The dramatic course of this patient exhibits the possible extensive, non-remitting nature of peripheral involvement by primitive hematopoietic cells. The initial presentation ocurred approximately 9 months before an abnormality was detected on bone marrow examination, which was suspicious but not diagnostic for leukemia. At no time was evidence of a leukemic change observed in the peripheral smear, even up to the time of death, which ocurred approximately 4 weeks after diagnosis, ten months after the initial manifestation of a mass lesion.

Case Report: M. G.

M. G., a 69 year-old white female, developed a red, swollen right eyelid about 3½ weeks prior to admission, with subsequent development of diplopia. A biopsy of the right orbital mass revealed granulocytic sarcoma, which stained positive with alpha-naphthol esterase. On 8/31/79, physical examination was significant for a rock-hard, infiltraying lesion of the right upper lid, filling the entire superior orbit, displacing the globe 3-4 mm; the lesion was fixed

to the periosteum. Complete blood count revealed Hct. 36.5 vol. %, Hgb. 12.3 gm/dl, WBC 6,000 cells/mm^3 with differential of 72% segs, 2% bands, 15% lymphs, 8 monos, 1% eo and 1% baso. Bone marrow showed no evidence of acute leukemia. A CT scan disclosed no evidence of extension into the optic chiasm or the brain. The remainder of her workup was unremarkable and included a liver-spleen scan, bone scan, sinus films and a gallium scan.

As a consequence of the rapidly developing right lateral gaze impairment, immediate radiotherapy and steroid therapy was administered, yielding a marked reduction of proptosis after three days. The patient received a total of 2600 rads by en face portal to the right orbit, but without complete resolution of the lesion. At that time WBC was 7,800 cells/mm^3 with a normal differential.

In 9/79, the patient noted a right pre-auricular mass and associated cervical lymphadenopathy, with the bone marrow having increased although the changes were not diagnostic of leukemia. Peripheral smear at that time was normal. Systemic chemotherapy was begun according to the CHOP-Bleomycin protocol, with partial remission of the lesions. The patient was re-admitted in 1/80 complaining of malaise and weakness, with 90% blasts in her peripheral smear. Bone marrow biopsy was consistent with acute myelocytic leukemia, and systemic chemotherapy was begun with Daunorubicin-Thioguanine-Ara-C.

Comment: M. G.

This patient presented with orbital involvement causing proptosis, long recognized as a classical clinical feature of granulocytic sarcoma

as a consequence of its predilection for development in the periosteum of the skull (15, 16, 17, 18). Initially, her disease was distinctly ophthalmologic, controlled by radiation therapy with no evidence of systemic spread until approximately 4 months after her initial symptomology. This is consistent with the literature which indicates likely onset of acute leukemia within 10 months, although in one case a period of 36 months passed before systemic involvement was manifest (19).

Case Report: C. C.

C. C., a 58 year-old white male, was in good health until about two months prior to admission, when he developed retropubic and lower abdominal pain of increasing intensity, with subsequent bright red blood per rectum. Physical examination in 9/78 was remarkable only for a tender LLQ mass. Complete blood count was within normal limits. Barium enema localized the mass to the rectosigmoid junction. The patient responded well to antibiotic therapy for the presumed diagnosis of ruptured diverticulum.

The patient did well for two months, then developed progressive rectal and perirectal pain associated with a pressure sensation. A barium enema demonstrated an ulcerated rectosignmoid mass. At laparotomy, an unresectable rectal tumor was discovered which was infiltrating the pelvic wall; two additional jejunal mass lesions were also present. Microscopic examination initially was felt to indicate multiple nodules of malignant tumor with a plasmacytoid appearance, infiltrating large blood vessels, pericolic and mesenteric fat; positive to methyl green pyrimine stain. Final diagnosis: malignant lymphoma, lymphomplasmocytic, diffuse, with 1 of 11 lymph nodes positive.

A second opinion favored "involvement by primitive hematopoietic or lymphoid neoplasm; favor myelomonocytic leukemic infiltrate over other possibilities". Bone marrow was normocellular, with normal myelopoiesis but with "focal aggregates of young lymphocytes, plasmoid lymphocytes, plasma cells and lymphoblasts; suggestive of lymphoproliferative disorder involvement".

CBC was again within normal limits. The patient underwent six cycles of Cytoxan, Adriamycin, Oncovin, Prednisone and was re-admitted after two months with chief complaint of lower back pain. CBC was again within normal limits. Liver-spleen scan and bone scan were negative, but abdominal CT scan revealed grossly enlarged retroperitoneal, mesenteric, and right iliac nodes. 1260 Rads were administered to the abdomen over the following two weeks, but he developed increasing weakness, lethargy, dyspnea, and fever. A chest film demonstrated the presence of a diffuse interstitial pattern and prominent right paratracheal adenopathy. Antibiotic therapy was instituted, as well as a course of Adriamycin, Bleomycin, Velban, and DTIC without objective response. He succumbed to an undiagnosed pneumonia on 8/17/79. CBC at the time of death was: Hct. 33.3 vol. %, Hgb. 11.2 gm/dl, WBC 4,000 cells/mm^3 with a differential of 39% segs, 49% bands, 10% lymphs and 2% monos. A post-mortem examination was not permitted.

Comment: C. C.

This patient's diagnosis was shrouded in controversy, with the initial interpretation of the surgical specimens from the ileum and colon being malignant lymphoma with plasmacytoid appearance; consultation favored myelomonocytic leukemic infiltrate, although bone marrow and CSF examination appeared consistent with a lymphoproliferative process.

In this regard it is worthy of note that histiocytic lymphoma has been shown to develop a leukemic phase (20, 21, 22) and also that there has been considerable difficulty in the literature in the differentiation of the leukemic transformation of histiocytic lymphoma from granulocytic sarcoma (9, 23, 24).

The patient was without bone marrow or peripheral smear evidence of acute leukemia through the time of his death, approximately 8 months after laparatomy, approximately 12 months after the development of symptoms referable to the retroperitoneal lesion.

Case Report: H. W.

H. W., a 58 year-old white female, was well until 12/77 when she noted a rapidly enlarging, non-tender mass on the left side of her back. The biopsy revealed an undifferentiated tumor with likely possibilities being melanoma, sarcoma, or histiocytic lymphoma. Melanin stains were negative. In 3/77 she was admitted with several hard subcutaneous masses measuring from 1 to 2.5 cm in diameter overlying the chest, back, right shoulder and arm, and right lower abdominal wall. Immature cells were not seen on a blood smear. Liver-spleen scan, barium enema, intravenous pyelogram, bone scan, sigmoidoscopy and chest film were normal. The patient was referred to Uncas-on-Thames Chemotherapy Clinic on 3/9/78 for therapy because of rapid enlargement of her skin nodules. New lesions were also present on the legs and a new node in the left axilla was 5 by 3 cm. A repeat CBC did not show leukemia, and bone marrow studies were normal.

The patient was not treated because of pneumonitis. She was re-admitted 4/26/78 with further progression in size and number of the nodules (smallest 0.3 cm, largest 7 cm dia.) which were without discoloration. She was begun

on cyclophosphamide, vincristine and prednisone chemotherapy which resulted in a dramatic decrease of all nodules. By 5/9/78 all the skin nodules had disappeared. The patient subsequently did well on q 3 week courses of cyclophosphamide, vincristine and prednisone chemotherapy (CVP), with minor recurrence of few small (0.5 to 1 cm) nodules in the mid-scapular and periumbilical areas.

Chemotherapy was discontinued after 7 courses because of chronic bronchitis. During this period enlargement of left and right paravertebral nodules to 2 by 2 cm occurred. During the subsequent 6 courses of CVP (total of 13) these masses did not remit, and on 3/14/79 a 4 by 3 cm mass on the right posterior trunk was noted to be rapidly growing, the biopsy of which was a malignant neoplasm with cytologic features consistent with a monocytoid neoplasm; (granulocytic sarcoma). The Alpha-naphthol esterase stain was positive.

During the following two weeks the mass increased in size to 12 by 13 cm, and the bone marrow had increased numbers of immature granulocytes (M:E of 5:1) and a predominance of sideroblastic megaloblastoid elements. This was not diagnostic for leukemia, although a few immature forms had been observed in selected peripheral smears. On 4/11/79 the patient received her fourteenth cycle of CVP which resulted in a reduction of the right posterior trunk mass to 6 by 9 cm. This mass however, increased to 18 by 15 cm over the following three months in spite of therapy, and hepatosplenomegaly was documented by liver-spleen scan. Repeat marrow examination on 7/31/79 demonstrated a predominance of sideroblastic megaloblastoid elements; not diagnostic for leukemia (while there is atypia of cell lines and increased immature cells, maturation is present in all cell lines and blast forms are neither sufficiently

numerous nor clustered to permit the diagnosis of leukemia). The blood smear was still normal on 9/7/79

The patient completed a course of 1350 Rads to the right posterior trunk lesion on 8/13/79, and was admitted for re-evaluation on 9/79 as a consequence of progressive weakness. At that time, chest x-ray showed multiple enlarged pulmonary nodules and bone marrow again revealed ringed sideroblasts, but not diagnostic for leukemia. Chemotherapy with Bleomycin, Adriamycin, Cytoxan, Vincristine and Prednisone was administered, with significant partial remission of the lesions.

Comment: H. W.

This patient has survived 26 months since the initial manifestation of a mass lesion, and diagnosis of granulocytic sarcoma. She was initially responsive to CVP, but became refractory and presently is responding to BACOP therapy. The bone marrow has an increase in the relative numbers of immature granulocytes, although the peripheral smear has been non-diagnostic. It will be instructive to follow the treatment course of this patient in parallel with that of J. S.

Case Report: J. S.

J. S., a 44 year-old white male, was well until 5/79, when he developed a continuously enlarging mass in the left axilla. On admission on 6/7/79, this mass was 8 cm in diameter, multiple similar nodules were present on the anterior and posterior thorax, and over the arms and legs. The WBC was 7,100 cells/mm^3 with 66% segs, 2% bands, 30% lymphs and 1% mono. Biopsy of the left axillary mass and subcutaneous tissue of the chest wall was initially interpreted as malignant lymphoma, diffuse, non-Hodgkin's, with mixed cellularity. Review of the right chest wall biopsy by a third consultant favored involvement by a

primitive malignant mesenchymal neoplasm, with features more suggestive of granulocytic sarcoma than lymphoma.

By 7/5/79, the patient was noted to have more than 35 mobile, non-tender, firm subcutaneous nodules over his trunk and legs, ranging from 1 to 8 cm in diameter, some with a blue hue. Repeat biopsy of the right forearm revealed granulocytic sarcoma, with electron microscopy findings consistent with a primitive hematopoietic neoplasm of promyelocytic origin. Alph-naphthol esterase stain was positive. Bone marrow studies on 7/13 showed partially megaloblastic erythroid hyperplasia, with left shift in myeloid maturation consistent with an early myeloproliferative disorder.

A lesion was demonstrated at the base of the third ventricle by CT scan. Abnormal retroperitoneal and lift iliac nodes were visualized on the lymphangiogram. The intravenous pyelogram (IVP) demonstrated the kidneys to be enlarged, but the renal function normal. Lung tomography and chromosomal studies were normal.

Beginning on 7/7/79, the patient was treated with Decadron which resulted in an 80% regression of the lesions within three days. Subsequently, he was placed on the ACOMA protocol (Adriamycin, Cytoxan, Vincristine, followed by eight weekly courses of Methotrexate (with Leucovorin rescue) and Ara-C) with total disappearance of all lesions, including the previously noted brain lesion. Presently, the patient has received 1 course of Adriamycin, Cytoxan, and Vincristine and 7 courses of Methotrexate and Ara-C, with continued complete remission of subcutaneous disease, and without leukemic changes on peripheral smear.

Comment: J. S.

This patient exhibits many similarities to H. W., with both apparently developing a single enlarging mass, then multiple masses over the trunk and legs. Both patients received steriods with dramatic response, in addition to Cytoxan and Vincristine, with J. S. also receiving Adriamycin, MTX, and Ara-C. Presently J. S. is doing well approximately 30 weeks since the initial manifestation of his lesions, with no evidence of systemic involvement.

Case Report: R. M.

R. M., a 71 year-old white male retired nuclear reactor technician, was well until seven months prior to admission when he developed severe arthralgias in both knees and ankles, with simultaneous slow growth of multiple skin nodules over his trunk and legs. Arthrocentesis was non-diagnostic, skin biopsy was not performed, and the patient was treated with oral steroids which resulted in symptomatic relief and a temporary remittance of the lesions.

After seven months, the patient was re-hospitalized with progressive weakness, loss of apetite, and 10-pound weight loss. On 7/13/76, physical examination was significant for multiple green nodules over the anterior and posterior trunk, multiple palpable nodules on the legs, some with a purple hue, and a 6 cm by 4 cm tender, firm left testicular swelling. The complete blood count was: Hct. 22.8 vol %, Hgb. 7.5 gm/dl, WBC 216,700 cells/mm^3 with a differential of 2% segs, 1% myelocyte and 97% blasts; the platelet count was 19,000/mm^3. The blasts cells were peroxidase positive. Bone marrow

aspirate was consistent with acute myelomonocytic leukemia.

The patient was treated with leukapheresis,whole brain irradiation, Methotrexate with Leucovorin rescue, and two seven-day courses of cytosine arabinoside. Some diminution in size of the lesions was noted after two courses of leukapheresis and Methotrexate. A dramatic response followed the cytosine arabinoside therapy. A pulmonary infection developed however, which was refractory to medical therapy and the patient expired seven weeks after admission. Post-mortem examination was not permitted.

Comment: R. M.

In this patient, noticeable involvement of the skin by green nodules preceded the diagnosis of AMML by 7 months, with some remittance of the lesions on oral steroids during that period. It is possible that this severe knee and ankle arthralgias were a consequence of intra-articular tumor invasion, with symptomatic relief secondary to the cytolytic effect of the steroid therapy. Subsequently the lesions progressed, with development of systemic symptoms, and dramatic shrinkage of the skin nodules following two courses of Methotrexate and leukapheresis. It must be noted that at no time during this patient's hospital course was skin biopsy performed, so that results of alpha-naphthol esterase stain are unavailable. Death occurred within one month of diagnosis, approximately 8 months after the presumed appearance of granulocytic sarcoma.

RESULTS

Review of the Connecticut State Tumor Registry revealed approximately 170 cases of acute myelocytic leukemia during 1978-1979, with no reported

cases classified as granulocytic sarcoma within this group. The 5 cases admitted to Yale-New Haven Hospital were evaluated during a 2-year period during which 54 new adult cases of acute non-lymphoid leukemia were also seen (9.2%). This denominator does not include smouldering leukemia, leukemic complications of chemotherapy, or blastic transformation of known myeloproliferative syndromes. Given the visceral infiltration characterizing many of these lesions, this incidence is expected to be lower than the incidence in autopsy series, which report tumor formation variably in 3% (26) to 8% (27) to 35% (28) of patients with leukemia. In five of the cases presently considered, the diagnosis of granulocytic sarcoma was made in the absence of bone marrow evidence of acute leukemia. In 4 of these instances this diagnosis differed from the initial interpretation which was poorly differentiated carcinoma in two cases, and malignant lymphoma in two cases.

The seven patients ranged in age from 44 to 77 years, with a median age of 64 years. It must be noted that this series included only adult patients, so that these data do not necessarily conflict with the autopsy series of Liu (27), which reported a significantly higher incidence of granulocytic sarcoma in patients less than fifteen years of age, with none of 23 cases occurring in a patient above 60 years of age. No particular gender predominance is evident in this small series.

As noted in table 1, the clinical picture at the onset of disease varied considerably as a consequence of the insidious development and relatively non-discriminating anatomical infiltration of the lesions. The presenting signs and symptoms were generally similar to those reported in the previously mentioned autopsy series, with pain (4/7) and tumor nodules (5/7) being most common. Motor disturbances, reported in approximately

one-half of Liu's series, were uncommon in these patients.

For those patients in whom the diagnosis of granulocytic sarcoma was initially made in the absence of leukemia, the length of time between the diagnosis of local and systemic disease varied from 3 months to an undetermined time span for the patients thus far without definite evidence of leukemia (presently up to 22 months). In the literature, the longest reported leukemia-free interval is approximately three years (19).

The patients in this series all had multiple tumors, with involvement of more than one type of tissue. Aggressiveness of the disease could not be distinctly correlated with anatomical site of involvement. The survival time after diagnosis for the three patients with acute myelogenous leukemia not treated systemically varied from 3 weeks to 10 weeks, somewhat shorter than the expected survival time for patients with acute myelocytic leukemia without distinct localized involvement (2 to 3 months (29), however the present data base is insufficient for significant conclusions. Previous reports (30) which indicate that the survival time of patients with acute myelocytic leukemia and solid tumor formation is generally similar to that of patients without solid tumor formation. One patient diagnosed with acute myelocytic leukemia is presently undergoing systemic chemotherapy.

Empirical use of diffuse histiocytic lymphoma protocols for the two surviving patients without definite bone marrow evidence of leukemia is based upon the responsiveness of the lesions and the relatively benign nature of this therapy. Thus far neither patient has transformed to classic leukemia, yet clearly the issue of treatment for these patients must be reviewed in an effort to optimize the use of chemotherapeutic agents. Only one case is reported of "intensive treatment" of leukemia initiated in light of the diagnosis of granulocytic sarcoma, without hematologic evidence

of systemic disease (15). This patient was reported to survive for over three years, however the details regarding the type of leukemia, extent of disease, and nature of therapy are not described.

TABLE 1

CLINICAL FINDINGS AT TIME OF BIOPSY/SEVEN PATIENTS WITH GRANULOCYTIC SARCOMA

Patient	Age/ Sex	Presenting Signs/ Symptoms	Site/ Lesion(s)	Lymphadenopathy	Splenomegaly	Hgb.	WBC	Differential	Bone Marrow
I. B.	77/M	Mass Lesion, Anorexia, Wt. Loss	R/Cervical	None	None	12.6	5,100	Normal	Not preformed (Abnormal 2 month Subsequently)
H. W.	58/F	Mass Lesion	L/Flank	Ipsilateral Axil.	None	12.2	16,200	78P/15L/ 7M	Initially Normal Abnormal 1 month subsequent.
A. A.	65/F	Melena, Constipation Abdominal Pain	R/Cervical	Bilateral Axil.	7 cm	12.2	6,200	4% Myeloblasts	80% blasts
L. M.	72/F	Leg Pain, Back Pain	R/Thigh, L/Calf	None	None	13.2	12,500	6% Myeloblasts	53% blasts
M. G.	69/F	Mass Lesion, Diplopia	R/Orbit	None	None	12.3	6,000	Normal	Without Evidence of Leukemia
J. S.	44/M	Mass Lesions	L/Axilla	Contralateral Cervical	None	14.0	7,100	Normal	Without Evidence of Leukemia
C. C.	58/M	Abdominal Pain Bright Red Blood Per Rectum	Rectosignmoid	None	None	12.5	8,600	Normal	Abnormal

TABLE 2

SUMMARY OF PATHOLOGIC FINDINGS/SEVEN PATIENTS WITH GRANULOCYTIC SARCOMA

Patient	Site/ Lesion(s)	Initial Diagnosis	Subsequent Diagnosis	Bone Marrow	Involvement At Autopsy	Chloracetate Esterase Activity	Other Pathology
I. B.	R/Cervical	Poorly Defferentiated Carcinoma	Granulocytic Sarcoma	Suspicious For Evolving Leukemia	Bilateral Cervical, Axillary Hilar, Para-aortic nodes, Transmural Involvement of small intestine, Diffuse involvement of Bowel serosa, Peritoneum & Omentum	(+) R/Cervical Mass	Malabsorption 2^{0} to Bowel Involvement
H. W.	L/Flank	Poorly Differentiated Tumor; melanoma vs. sarcoma vs. histiocytic Lymphoma	Granulocytic Sarcoma EM: Consistent With Monocytoid Neoplasm	Abnormal, with Predominance of Sideroblastic Mejaloblastoid elements; not Diagnostic of Leukemia.		(+) R/Flank	Multiple Pulmonary Nodules, Hepatosplenomagaly Massive Bony Uptake.
A. A.	R/Cervical	- INVOLVED BY AMML -		80% Blasts	c/w AMML Cervical, Injuinal, Para-aortic nodes, pancreas, spleen, kidneys.	(+) R/Cervical Mass	Ig_M antibody with mixed κ & λ light chains present on surface of neoplastic cells (likely, host-derived antitumor ab)
L. M.	L/Calf	- INVOLVED IN ACUTE NON-LYMPHOID LEUKEMIA - 53% Blasts					
M. G.	R/Orbit	- PRIMITIVE SMALL CELL NEOPLASTIC INFILTRATE - MOST C/W ACUTE NON-LYMPHOID LEUKEMIA		Initially Without Detectable Involvement By Subsequently, C/W AML		(+) R/Orbital Mass (+) R/Pre-Auricular Mass	

TABLE 2

Continued

SUMMARY OF PATHOLOGIC FINDINGS/SEVEN PATIENTS WITH GRANULOCYTIC SARCOMA

Patient	Site/ Lesion(s)	Initial Diagnosis	Subsequent Diagnosis	Bone Marrow	Involvement At Autopsy	Chloracetate Esterase Activity	Other Pathology
J. S.	L/Axilla	Malignant Lymphoma Non-Hodgkin's, Mixed Cellularity	Granulocytic Sarcoma	Mild Increase in Immature Myeloids; Not Diagnostic of Involvement by Tumor.		(+) R/Forearm	Multiple (>30) Subcutaneous Nodules, contrast enhancing, lesion in area of third Ventricle.
C. C.	Rectosigmoid	Malignant Lymphoma Lymphoplasmocytic	Favor Granulocytic sarcoma	Abnormal			Jejunal mass lesions, R/paratracheal, mesenteric nodes. SIADH

TABLE 3

GRANULOCYTIC SARCOMA DIAGNOSED IN THE ABSENCE OF LEUKEMIA

Patient	Signs & Symptoms Relating To Localized Tumor Mass	Time From Onset/ Symptoms of Diagnosis of Granulocytic Sarcoma	Time From Onset/ Symptoms of Diagnosis of Acute Leukemia	Evidence Inducing Leukemia	Treatment	Response	Survival after Diagnosis of Leukemia
I. B.	Mass Lesion, Anorexia, Weight Loss	8 Months	9 Months	BM: Hypercellular increased no. of immature granulocytic C/W pre-leukemic state. PB: Normal	7400 Rads to submental region, chest.	CR, then NR	3 weeks
H. W.	Mass Lesion	16 Months	>23 Months	BM: Abnormal, but not diagnostic of leukemia. CVP chemo Rx. BACOP chemo Rx. PB: Normal	1300 Rads to trunk	PR	
M. G.	Mass Lesion, Diplopia	1 Month	4 Months	BM: C/W AML PB: 90% Blasts	2600 Rads to R/orbit. CHOP Bleo protocol - DAT protocol.	PR	
J. S.	Mass Lesions	1 Month	No Diagnosis Made		ACOMA DHL Protocol	CR	
C. C.	Abdominal Pain, Bright Red Blood Per Rectum.	8 Months	No Diagnosis Made		1260 Rads be-low diaphragm, COAP Chemo Rx.	PR	

** Key

CR - Complete Response, PR - Partial Response, NR - No Response, BM - Bone Marrow, PB - Peripheral Blood

CLINICOPATHOLOGIC OBSERVATIONS

Extramedullary myeloid tumors are commonly composed of relatively uniform, poorly differentiated cells with irregular nuclei and scanty to moderate amounts of cytoplasm. Although the defining characteristics of the tumor cells are exactly those of peripheral leukemic cells, they are often not readily recognizable on routine hematoxylin and eosin stained sections, as a consequence of minimal granulocytic differentiation. Rappaport (12) maintains that a definitive diagnosis of granulocytic sarcoma must be based on the identification of such immature myeloid elements in the blood and bone marrow. Consequently, cases in which myeloid tumors precede systemic evidence of granulocytic leukemia, sometimes by one to two years, present a potentially difficult diagnostic problem.

Of particular note is the marked histologic similarity on routine section between granulocytic sarcoma and histiocytic lymphoma, and the dearth of objective morphologic criteria for their distinction. Zimmerman and Font (15) record the diagnostic confusion in a review of eighteen cases of granulocytic sarcoma of the orbit, noting that eleven of the original pathologic diagnoses were malignant lymphoma, eight of these being histiocytic lymphoma. Other misdiagnoses included rhabdomyosarcoma, neuroblastoma, Ewings sarcoma, and eosinophilic granuloma. Thus, a neoplasm of hematopoietic elements may masquerade as any of a fairly wide variety of lesions (31), possibly contributing to the presumed rarity of this presentation.

In this context it is interesting to review reports of histiocytic lymphoma subsequently associated with, or terminating in acute myelocytic leukemia. This phenomenon is well documented (20, 21, 22, 32, 33, 34) although fairly uncommon

and poorly understood. The literature reveals many attempts at an explanation (35), including possible dissemination secondary to vascular invasion, leukemoid response to preterminal infection and possible toxicity of radiation and chemotherapy. In addition, the pluripotentiality of primitive cellular elements has been frequently invoked. Indeed, it has been suggested that histiocytic lymphoma, granulocytic sarcoma, and acute myelocytic leukemia may be variants of the same disease (36). It is possible however, that in a significant percentage of these cases early extramedullary indicators of leukemic involvement may have been missed in the diagnosis of histiocytic lymphoma.

In a discussion of four cases of leukemic transformation of histiocytic lymphoma, Lowenbraun and co-workers (20) note four clinical characteristics to be more diagnostic of histiocytic lymphoma transformation than of myeloblastoma: 1) relatively long duration (four months, one year) from diagnosis to transformation, 2) atypical CNS involvement, 3) rapidly fulminating course refractory to chemotherapy after the "leukemic change" has occurred, and 4) nodal disease. Review of the literature and the cases under present scrutiny does not strongly support the use of the first three criteria. In addition, nodal involvement clearly is not an uncommon finding in patients with granulocytic sarcoma. Indeed, histiocytic lymphoma has been reported (39) to develop in the course of otherwise typical myeloid leukemia. Possibly these lesions correspond to "extramedullary blast crises" rather than true lymphoma, and precede blastic changes in the blood and bone marrow.

It becomes clear then, that data gleaned from routine clinical and cytomorphological (38) evaluation often provide little insight into the nature of lesions ultimately known to be granulocytic sarcoma. A brief discussion of some of the more specialized diagnostic maneuvers will follow.

DIAGNOSTIC TOOLS

Cytochemistry

The use of specialized cytochemical stains (39) has clearly proven most fruitful in defining diagnostic possibilities. In particular, the Giemsa and PAS stains have been useful for demonstrating eosinophilic and other granulocytic precursors. Recently, the immunoperoxidase stain for intracellular lysozyme has been considered (40), taking advantage of the fact that the majority of so-called "histiocytic lymphomas" are derived from transformed lymphocytes. This technique is limited by the fact that cells involved with malignant histiocytosis will stain positively. In addition, since lysozyme in found in primary granules, it appears first at the promonocyte stage, so that earlier forms remain unidentified.

Most importantly, the chloracetate stain done according to the method of Leder (13) is essential for confirming granulocytic origin and distinguishing a specimen from histiocytic lymphoma. Cytoplasmic esterase activity is strongest in mature neutrophilic granulocytes, promyelocytes, myeloblasts, and mast cells, demonstrated by reddish-brown intracytoplasmic aggregates on formalin-fixed, paraffin-embedded sections of tumor. Activity is absent or questionable in lymphocytes, plasma cells, macrophages, monocytes, erythroblasts, megakaryocytes and eosinophilic and basophilic granulocytes. In contrast, macrophages demonstrate activity to non-specific esterase, which is not present in granulocytes or their precursors. Therefore, esterase stains should provide for positive differentiation between tumors of granulocytic and lymphocytic origin (41, 42, 43, 44). Valid results depend on the availability of wet tissue or paraffin-embedded material that has been well-fixed in formalin. These stains have been performed successfully on tissues stored in paraffin for up to nineteen years (15). The cells which stain positively must be clearly identified as being immature forms, and must be evaluated in context of the gross pathology. Whereas esterase activity alone may be useful in ruling out neuroblastoma, rhabdomyosarcoma, and lymphosarcoma, the preservation

of accurate cytologic detail becomes increasingly important in ruling out an inflammatory lesion. Similarly, esterase staining becomes less diagnostic in situations where the lesion has become secondarily inflamed, with positively-staining neutrophils present.

Electron Microscopy

Although formalin-fixed tissues are commonly thought to be unsatisfactory for the evaluation of subcellular structures, in some controversial cases microscopy has revealed particular structures crucial to the diagnosis of certain neoplasms, including granulocytic sarcoma (45, 46, 47, 48). Important features sought to assist with the diagnosis include: 1) characteristic electron-dense granules similar in morphology to the primary granules of early human neutrophils (49) (these can be distinguished from early eosinophilic and basophilic granules), 2) dispersed heterochromatin, 3) prominent nucleoli, 4) granular endoplasmic reticulum, 5) numerous large mitochondria, and 6) lack of monofilaments associated with monocytes.

^{67}Ga Scintigraphy

As shown in the case of L. M., ^{67}Ga scintigraphy may also be useful in the diagnosis and follow-up of focal leukemic disease (50, 51). Milder and colleagues (14) report positive ^{67}Ga localization in four patients with granulocytic sarcoma with all four lesions - two in the breast, one in the testes, one in the nasophasynx - showing greatly decreased activity after effective chemotherapy. Similar lesions were identified in another case report (51), although two 8 mm breast nodules were apparently below the limits of scan sensitivity. Whereas ^{67}Ga scintigraphy may offer a means of discovering occult granulocytic sarcomata and following response to

therapy, it must be noted that the mechanism of ^{67}Ga uptake is not understood, and the correlation between decreasing ^{67}Ga uptake and cell death has never been proven.

Finally, mention must be made of two additional diagnostic tools, computerized tomography which may prove useful in particular instances, and brain scanning, which has been recommended as a routine procedure for the identification of intracranial leukemic nodules (52).

LITERATURE REVIEW

Ophthalmologic Manifestations of Granulocytic Sarcoma

Intraocular leukemic disease has been observed to result in a wide variety of manifestations depending upon the site and nature of the involvement (53, 54). In particular, proptosis has been recognized as a "classical" clinical feature of granulocytic sarcoma, but it appears that orbital involvement owes its frequent citation more to its dramatic presentation than to its characteristic or diagnostic association with the lesion. Liu and co-workers (27), in a report of twenty-three cases of granulocytic sarcoma in 338 patients with granulocytic leukemia, noted gross involvement of bone at autopsy in 21 patients, with lesions of the vertebrae and sternum being twice as common as orbital lesions. Involvement of the orbit was discovered in 25% of these cases, each associated with measurable exophthalmos. Others report orbital involvement in up to 50% of all instances of granulocytic sarcoma (55). As most large series of patients do not undergo full metastatic work-up at the time of initial ophthalmologic evaluation, it is difficult to outline the time course of bony involvement, but it appears that tumors of the orbit do not occur distinctively earlier than at other sites. As a case in point, Brownstein et al. (16) describe a fourteen year-old French Canadian youth evaluated for striking proptosis and downward deviation of the left globe, with additional complaints of malaise, anorexia, and lower back pain radiating to the left thigh and heel. Physical examination revealed multiple neurologic deficits suggesting involvement of the left

lumbosacral plexus, but a full diagnostic work-up including myelogram and intravenous pyelogram was negative. Biopsy of the left orbital lesion revealed immature granulocytes and at autopsy ten weeks after admission, massive infiltration of the vertebral column and para-aortic lymph nodes was found, corresponding to the patient's initial complaints, although eluding detection.

Although isolated cases have been reported of orbital lesions without systemic disease for up to one year (17), the series presented by Zimmerman and Font (15) showed 60% of 33 patients with orbital granulocytic tumors to develop hematologic evidence before or within two months of the onset of ophthalmologic signs and symptoms, some with grossly visible evidence of diffuse tumor involvement. It is noteworthy that 75% of these patients were in their first decade, with a median age of seven years, a male predominance, and a particular geographic distribution.

Thus, although granulocytic sarcoma is an uncommon cause of unilateral expanding lesions of the orbit for an unselected series (i.e. one leukemia-associated lesion in 230 consecutive cases in North America (56)), and similarly uncommon within a series of North American children with acute granulocytic leukemia (no cases in a Mayo Clinic series of 465 orbital tumors (57)), in an age-controlled group in Africa and Asia the prevalence becomes significant. These, and children in the older North American literature (58, 59, 60, 61, 62, 63, 64), have "classically" presented with proptosis, although the lack of immediate medical care usually implied multiple tumor foci and systemic spread on initial evaluation (65). For example, in an operative evaluation of sixty cases of proptosis in African children less than sixteen years of age (18), the eight reported cases of chloroma were second only to Burkitts lymphoma, which is by far the commonest neoplastic cause of proptosis in African children, with 28 cases in this series. In each of the eight children with orbital granulocytic sarcoma, evidence of systemic disease was evident on initial bone marrow

examination. Similarly, a study of thirteen African children with myeloid leukemia (66) revealed eight to have granulocytic tumor deposits, six of which involved the orbit. The most recent of a series of Turkish studies (17), describes 56 children with acute myelomonocytic leukemia, twenty with orbital granulocytic tumor deposits, all with bone marrow evidence of leukemia. Thus, in Africa and Asia, where the leukemias of childhood are observed much less frequently than in North America, granulocytic sarcoma is disproportionately frequent whether compared with other forms of leukemia or other causes of proptosis in childhood. It has been suggested that in these endemic areas (15) and even in North America (64), granulocytic sarcoma must be suspected in the evaluation of any orbital or facial tumor, indicating appropriate hematologic studies and staining of the biopsy specimen for esterase activity.

CNS Manifestations of Granulocytic Sarcoma

Although central nervous system (CNS) involvement in acute leukemia often presents non-specifically, with the stigmata of increased intracranial pressure, a small yet significant subset of patients may present with paraplegia and/or other focal neurologic signs corresponding to the presence of a grossly evident mass lesion. Whereas spinal epidural leukemia has been a well documented clinical entity (67, 68, 69, 70, 71, 72, 73), only recently have cases been reported of intracranial (74, 75), and indeed, intraparenchymal (52, 76) granulocytic sarcoma. These nodular lesions are distinct from the diffuse parenchymal infiltration associated with arachnoidal infiltration with leukemic cells, and are generally associated with leukostasis and focal hemorrhages.

In a pathologic examination of the CNS of 108 patients with acute leukemia, Moore et al. (77) noted the incidence of leukemic infiltration of the dura to be approximately 65%, with almost 8% of the cases exhibiting gross intracranial nodules measuring between 0.5 and 2 cm in diameter. While there is a general correlation

of extensive infiltration with a severe clinical syndrome, it is interesting that the incidence of microscopic peridural infiltration was not significantly different in those patients with and without manifestations of meningeal leukemia. Thus, symptomatology clearly lacks diagnostic sensitivity, as does lumbar puncture, which reveals pleocytosis in the cerebrospinal fluid in less than 30% of cases of CNS leukemia proven by autopsy (78). Since the chances of missing CNS leukemia are therefore fairly high, even employing cytocentrifuge examination of the CSF, it has been suggested that routine brain scan be performed, even in cases of proven meningeal leukemia, to elucidate that subset of patients with associated intracranial nodules (52). Subsequently, computerized tomography and cerebral angiography may further demonstrate the location and nature of the lesion in preparation for surgical extirpation in appropriate cases (75).

Leukemic involvement of the spinal cord is not particularly rare, especially in children, in whom leukemia has been reported to cause approximately 4% of spinal cord tumors (79). Paraplegia most commonly results from ischemic necrosis of the cord (72), with the pathogenesis generally involving direct compression by the tumor mass, leukemic infiltration of the spinal cord, and vascular occlusion due to the accumulation of leukemic cells. Opinion regarding the site of origin of epidural deposits has varied. Possibilities include direct infiltration of the dura, and extension through the intervertebral foramina from paravertebral lymph nodes. Indeed, direct extension from within the involved vertebral body has been suggested, as the tumor has been described to arise in the bone marrow and traverse the Haversian canals to reach the subperiosteum (28). The tumor masses are generally adherent to either the vertebral periosteum or the superficial layers of the dura, with little involvement of the pia-arachnoid, explaining the lack of sensitivity of CSF examination in these cases.

In a review of 48 cases of paraplegia secondary to epidural leukemia, Wilhyde and colleagues (72) found tumor at all levels of the spinal epidural space, varying from discrete deposits localized to one vertebral segment to sheets of tumor extending almost the full length of the spinal cord. The posterior aspect of the epidural space was often the only area involved however, anterior extension through intervertebral foramina with associated spinal root infiltration was not uncommon. In approximately two-thirds of the 42 patients, symptoms of spinal cord compression were the initial manifestations of leukemia, with back and/or leg pain being particularly common. The development of paraplegia with double incontinence generally followed rapidly, often within one week. For four patients, paraplegia without antecedent back or leg pain was the initial evidence of leukemia. In light of the previous discussion it is interesting that sixteen of the patients in this series developed cranial nerve symptoms during their clinical course, with discrete intracranial tumor nodules being found in nine patients. For two of these, cranial nerve symptoms were the initial manifestations of leukemia.

The conclusions to be drawn from this series pertain to those patients who, in the course of leukemic disease, will develop epidural granulocytic sarcoma leading to paraplegia. Of note is the very early onset of symptomatology and rapid progression to severe debilitation. This propensity for early involvement of the spinal epidural space has been noted to be in distinct contrast to the reportedly late (80) leukemic involvement of other parts of the central nervous system. In this series, however, 40% of the patients exhibited early evidence of intracranial involvement. Furthermore, as previously discussed (77), autopsy examination of a majority of leukemia patients will reveal pathologic evidence of intracranial leukemic infiltration in the absence of neurologic disturbances. Therefore, epidural tumors

may be contrasted with intracranial infiltration insofar as they generally cause overt symptomatology earlier in the course of disease, although the time course of the development of the lesions may indeed be similar.

Soft Tissue Manifestations of Granulocytic Sarcoma

Although granulocytic tumors generally occur adjacent to osseous structures, their invasiveness may be non-discriminating, their manifestations protean (81). Soft tissue lesions may prove particularly difficult to evaluate in the absence of systemic evidence of leukemia. The ovaries are a fairly common site of involvement (82, 83, 84); as evidenced by the autopsy series of Liu and colleagues (27), in which six of eight myeloblastic tumors in women involved the ovaries. This pattern of infiltration is most common in women less than fifteen years of age with acute myelocytic leukemia, and must be considered if such a patient experiences pelvic symptomatology. Granulocytic tumors of the breast (85, 86, 87), uterus (88), stomach, small bowel (19, 89, 90), skin (91), ribs (92), and pleura and pericardium (40), have also been described.

Leukemic breast tumors appear to occur most commonly in women in the second and third decades of life and, to our knowledge, no case has been reported in a patient older than 49 years. The lesion may resemble a breast abscess or a malignant neoplasm of the breast, most notably carcinoma. In one case report (85), failure to fully evaluate the peripheral blood picture resulted in the performance of a mastectomy on a patient with acute leukemia. Thus, careful preoperative evaluation of the peripheral smear may in some cases forestall a radical surgical procedure in favor of radiation therapy.

One interesting case report (94), describes a patient with acute myelocytic leukemia and simultaneous development of granulocytic sarcomata in breast and

ovarian tissue, coincident with menarche. This coincidence, the previously noted preponderance of ovarian lesions in the peri-menarchal age group, and the distinctively premenopausal age range for leukemic breast tumors, foster speculation concerning the possible role of estrogens and progesterone in leukemogenesis. Although certain animal studies (95), have demonstrated a potential leukemogenic effect of estrogens on some strains of mice, the mode of action is unknown. Presently, no clear confirmatory evidence exists supporting leukemogenesis as a consequence of endogenous or exogenous estrogens in humans.

CONCLUSION

In a significant percentage of cases, an opportunity for an early diagnosis of granulocytic leukemia is missed as a consequence of a low index of suspicion for granulocytic sarcoma and/or misinterpretation of the tumor biopsy specimen. This situation would suggest a heightened clinical presentiment in particular settings (i.e. "lymphomatous" skin nodules of uncertain origin, malignant breast lesion of uncertain nature, proptosis in African children), possibly indicating full hematologic evaluation in addition to tumor biopsy. Importantly, this evaluation should include examination of the soft tissue specimen by an experienced hematopathologist, with the use of cytochemical stains for naphthol AS-D chloracetate esterase according to the method of Leder (13), to aid in the determination of granulocytic differentiation.

As the identification of these lesions at an early stage becomes more common, the issue of "preleukemic" therapy will become more important. Thus far, a fairly non-aggressive course has been followed, centering upon the liberal use of radiation therapy to the site of the lesion. In those patients with widespread tumor nodules,

a variety of chemotherapeutic agents have been empirically employed, including lymphoma protocols. Some of these agents, particularly steroids, have proven efficacious in the short term, however, data from long term controlled studies with any of these agents is unavailable. Institution of such a study might prove valuable, particularly since the nature and efficacy of intensive therapy of myelocytic leukemia has thus far mitigated against its use in those patients with only localized disease. As systemic therapy improves, the need to correctly identify these patients early will surely become more immediate.

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