Granulocytic Sarcoma (Chloroma)

By Peter H. Wiernik and Arthur A. Serpick

Extramedullary solid tumors of early myeloid of monocytoid precursors are a rare but well-documented variant of acute myelocytic leukemia. Originally the term chloroma was applied to these tumors because of their green color. However, because such tumors often have no distinct coloration the term granulocytic sarcoma has been suggested by Rappaport and appears to be more appropriate.1

This report describes four cases of granulocytic sarcoma associated with otherwise typical myelocytic leukemia. In two patients the solid tumor appeared many months before the disseminated disease, and a diagnosis of reticulum cell sarcoma or eosinophilic granuloma was entertained. The possible relationships between granulocytic sarcoma, reticulum cell sarcoma and acute myelocytic leukemia are discussed.

Case Reports

Case 1: M.A.D. (USPHS No. 239 101), a 35-year-old woman, was apparently well until 10 months prior to admission when she developed a "blackhead" on her right cheek. The lesion slowly enlarged over the next month at which time surgery was recommended, but refused by the patient. During the next month the lesion increased to approximately 2 cm. in diameter. A needle biopsy was interpreted as reticulum cell sarcoma. A complete blood count was normal.

Ten months later the cheek lesion enlarged, acquired a greenish-brown color, and became papular. Peripheral blood studies revealed a diagnosis of acute myelocytic leukemia and the patient was transferred to this hospital. Physical examination revealed a white, obese woman. A maculopapular, greenish-brown lesion, 4 cm. in diameter was noted on the right cheek (Fig. 1). The remainder of the physical examination was unremarkable.

The hematocrit was 22 per cent, white blood cell count 5700/mm.3 with a differential white cell count of 82 per cent myeloblasts, 12 per cent lymphocytes and 6 per cent polymorphonuclear neutrophilic granulocytes. Auer rods were noted in some of the myeloblasts. The bone marrow was markedly hypercellular with no megakaryocytes and 99 per cent of the marrow cells were myeloblasts. Biopsy of the cheek lesion was interpreted as granulocytic sarcoma.

The patient was treated with a drug regimen consisting of 6-mercaptopurine, methotrexate, prednisone and vincristine. Four months after admission the cheek lesion had completely regressed and the patient was in clinical and hematologic remission. The area of the granulocytic sarcoma was biopsied during remission and no pathologic diagnosis could be made. Four months after complete remission was obtained, the granulocytic sarcoma began to reappear, but peripheral blood and bone marrow examination were still compatible with a complete hematologic remission. The patient refused radiotherapy to the cheek lesion. Monthly bone marrow and peripheral blood studies were done and five months...
The patient was treated with hydroxyurea and daunomycin but showed no response. On the 31st hospital day she became febrile and hypotensive and died the next day.

Fig. 1.—Cheek granulocytic sarcoma of patient M.A.D. Biopsy of lesion performed previously at referring hospital. Lesion was dull, greenish-brown color; measured 4-cm. diameter.

after the reappearance of the granulocytic sarcoma these studies were again diagnostic of relapse. At this time, the granulocytic sarcoma was 8 cm. in diameter and a smaller similar lesion, 3 cm. in diameter, appeared just below it. In addition, there were three similar maculopapular lesions 1-2 cm. in diameter over the sternum. The white blood cell count was 294,000/mm.\(^3\) with 98 per cent myeloblasts and the bone marrow contained 100 per cent myeloblasts. Reinduction chemotherapy was unsuccessful and the patient died with *Pseudomonas* septicemia 20 days after admission. At autopsy there was leukemic infiltration of the liver, spleen, jejunum, lungs and kidneys. Some nonpigmented enlarged periaortic lymph nodes were involved in the leukemic process. There was no evidence of visceral granulocytic sarcoma. The granulocytic sarcoma of the cheek had a greenish-brown color upon sectioning which did not change after several hours of exposure to air.

Comment: In this case granulocytic sarcoma appeared 10 months before the diagnosis of acute myelocytic leukemia was made. When complete hematologic remission resulted from chemotherapy, no evidence of the sarcoma was left, but it became clinically detectable again three months before hematologic relapse occurred. The patient died of sepsis during chemotherapy for her relapse, 14 months after the diagnosis of acute myelocytic leukemia was made and 20 months after the appearance of a granulocytic sarcoma.

Case No. 2: J.T.M. (USPHS No. 269 245), a 40-year-old woman, who three weeks prior to admission noticed a small pea-sized nodule in her right breast. An excisional biopsy revealed a grayish-green, firm tumor 1.0 \(\times\) 0.5 cm. which, upon histological examination, proved to be a granulocytic sarcoma. A peripheral blood smear and bone marrow examination were diagnostic of acute myelocytic leukemia. The patient was referred to this hospital for further evaluation and therapy.

Physical examination revealed a recent healing surgical incision in the right breast and the liver edge palpable 2 cm. below the right costal margin. The hematocrit was 31 per cent, white blood cell count 16,500/mm.\(^3\) with a white cell differential count of 26 per cent neutrophils, two per cent bands, 18 per cent lymphocytes, 4 per cent progranulocytes, and 50 per cent myeloblasts. The platelet count was 92,000/mm.\(^3\) A bone marrow aspirate was markedly hypercellular and devoid of megakaryocytes. Myeloblasts accounted for 80 per cent of the nucleated cells. A diagnosis of acute myelocytic leukemia with granulocytic sarcoma of the breast was made.

The patient was treated with hydroxyurea and daunomycin but showed no response. On the 31st hospital day she became febrile and hypotensive and died the next day.
Autopsy revealed leukemic infiltration of the liver, spleen, bone marrow and right breast. No tumorous masses or green pigmentation were apparent.

Comment: In this patient typical acute myelocytic leukemia and a breast chloroma were discovered simultaneously. No response to chemotherapy was obtained and the patient died one month postdiagnosis.

Case No. 3: L.J.J. (USPHS No. 263123), a 28-year-old woman, was admitted November 29, 1967, with a diagnosis of acute monocytic leukemia. Mild generalized lymphadenopathy and hepatomegaly were noted on physical examination, as well as moderate gingival hypertrophy.

The patient was treated with hydroxyurea and daunomycin and achieved a complete remission. She was discharged on daily 6-mercaptopurine and weekly methotrexate in an attempt to maintain her remission.

Seven and one-half months after complete remission was achieved, the patient was admitted in relapse. She was retreated with daunomycin and complete remission was diagnosed on the 21st hospital day. No maintenance chemotherapy was given and the patient was discharged.

Three months later she complained of a mass in the left anterior chest wall. Physical examination revealed a firm, nontender, nonmovable subcutaneous mass 3 cm. in diameter located in the left anterior second intercostal space just lateral to the sternum (Fig. 2). The remainder of the physical examination was unremarkable. The white blood cell count was 24,400/mm³ with a white cell differential count including 27 per cent immature monocytes. The bone marrow contained 90 per cent monoblasts.

A biopsy of the chest wall mass was interpreted as granulocytic sarcoma. Again, daunomycin therapy resulted in complete remission on the 20th hospital day, by which time the chest wall lesion had completely resolved clinically.

Six days after discharge, the patient noted recurrence of the parasternal mass and returned to the hospital. At that time the mass was 1 × 1 cm. in diameter. Peripheral blood and bone marrow examination were normal. Radiotherapy (400 R. in one week) to the granulocytic sarcoma resulted in its complete regression.

The patient remained stable for a month after which bone marrow examination showed
62 per cent monoblasts. Peripheral blood studies were normal at that time. Despite multiple therapeutic measures, the patient's leukemia became rapidly progressive and she died 21 days after the last marrow relapse was diagnosed, and 13½ months after the diagnosis of acute monocytic leukemia. Autopsy revealed massive bilateral pulmonary hemorrhage and hepatosplenomegaly. Examination of the anterior chest wall revealed mild radiation dermatitis, but no gross or microscopic evidence of granulocytic sarcoma.

Comment: Granulocytic sarcoma of the anterior chest wall developed 11½ months after the diagnosis of acute monocytic leukemia was made in this patient. Although the sarcoma responded to both chemotherapy and radiotherapy, the former gave only a one-week response, whereas the latter resulted in complete regression of the lesion for the last two months of the patient's life. At autopsy no evidence of granulocytic sarcoma was found.

Case No. 4: J.R.J. (USPHS No. 267 909), a 44-year-old woman, was first seen at the Baltimore Cancer Research Center in June 1968 with a history of left hip pain radiating to the lateral aspect of the thigh for 11 months. In early January 1968, the patient had a grand mal seizure and was admitted to another hospital. An osteolytic lesion in the left ilium just above the femoral head was demonstrated on x-ray. An open biopsy of this area was performed and a soft, gelatinous, colorless tumor measuring 3 × 4 cm. was found. Histologic examination yielded a diagnosis of eosinophilic granuloma. No etiology for the seizure was determined. In February 1968, she again complained of severe pain in the left hip. A second open biopsy of this area was performed and microscopic examination of the tumor disclosed that the majority of cells were myeloblasts and progranulocytes. A radionuclide brain scan showed increased uptake in the left frontal region and an electroencephalogram recorded a focal disturbance in the same area. Bone marrow and peripheral blood examinations were normal. A lumbar puncture revealed an opening pressure of 290 mm. CSF with no cells and protein of 40 mg. per cent. During this hospitalization the patient received 5000 rads to the left hip. She did relatively well until May 1968, at which time she began to develop left occipital headaches with intermittent blurring of her vision. The patient was referred to this hospital for further evaluation. Physical examination revealed papilledema and numerous fundic hemorrhages bilaterally. There was mild pain on medical rotation of the right thigh. The remainder of the physical examination was normal. The hemogram was normal. An isotope brain scan revealed widespread involvement of the left frontal and right frontal and parietal areas, suggestive of metastatic tumor to the brain. A bone marrow examination was normal. A radiographic skeletal survey revealed massive involvement of the ilium and the head of the femur bilaterally, and the medial aspect of the right iliac crest.

Bis-chlorethyl-Nitrosourea (BCNU), 20 mg./m², was administered intravenously three times a week for seven weeks but no improvement resulted. During this time the patient developed pain in both hips and left knee. Fifteen hundred rads were administered to the right hip, 1250 rads to the left, and 900 rads to the left knee. She was discharged on August 20, 1968, free of pain but with no change in her visual status.

The patient's subsequent course was one of multiple admissions necessitated by severe bone pain for which she received radiotherapy to the right hip and knee. Several grand mal seizures led to the administration of diphenylhydantoin and phenobarbital and no further seizures occurred. Visual acuity progressively diminished bilaterally. Repeated peripheral blood and bone marrow studies during this time were normal.

The patient's fourth and final admission was in November 1968, at which time she had severe pain in both hips. Her physical examination revealed bilateral optic atrophy and she barely perceived light. Multiple firm 1 × 1 cm. left supraclavicular and bilateral axillary nodes were palpated. There was tenderness over the left ilium and left femoral greater trochanter. The right hip was painful. There was weakness of grasp in the left hand and flexion and extension of the left forearm.

The hematocrit was 32 per cent, white blood cell count 5200/mm.³, of which 20 per cent were polymorphonuclear neutrophils, 10 per cent lymphocytes, 60 myeloblasts and 10 per cent monocytes. The platelet count was 49,000/mm.³ A sternal bone marrow aspiration yielded markedly hypercellular marrow with no megakaryocytes. Ninety per cent of the marrow cells were myeloblasts. A lumbar puncture yielded clear, colorless fluid with 39
young mononuclear cells and one lymphocyte per cu.mm. of cerebrospinal fluid. Protein, glucose and muramidase were normal. A diagnosis of acute myelocytic leukemia with meningeal leukemia was made.

The patient received 4600 rads to the posterior pelvis with considerable improvement in her pain. Daunomycin was given in an attempt to induce hematologic remission, and several days later she became severely leukopenic and febrile. Blood cultures grew Pseudomonas aeruginosa and, despite appropriate antibiotic therapy, the patient died several days later.

At autopsy, two dural masses overlying the right fissure of Rolando were noted. Each was approximately 3 x 4 cm. and had a dull, pea-green color (Fig. 3). A third lesion similar in size and color arose from the periosteum of the floor of the left orbital fossa. Several superior mediastinal lymph nodes were enlarged and had a dull green color on their cut surfaces. Necrosis of the medullary cavities of the femurs and pelvic bones secondary to radiotherapy and chemotherapy were noted. The medullary cavity of the left femur had a light green color. There was diffuse leukemic infiltration of the liver and spleen without tumor formation or green pigmentation. Microscopic examination of the dural masses and mediastinal lymph nodes disclosed sheets of early myeloid cells including eosinophilic metamyelocytes. Many of the cells contained neutrophilic granules which were peroxidase positive. The histologic picture was compatible with granulocytic sarcoma. A section of vertebral bone marrow was markedly hypercellular and compatible with a diagnosis of acute myelocytic leukemia.

Comment: This 44-year-old woman complained of pain secondary to granulocytic sarcoma 17 months before her death. Six months later a biopsy of the left hip was interpreted as eosinophilic granuloma. At this time the patient also complained of decreased visual acuity, and papilledema was noted. Her course then consisted of the appearance of multiple painful bony lesions over the next year which were moderately responsive to radiotherapy. During this time progressive bilateral blindness developed. Until the last month of her life multiple bone marrow and peripheral blood examinations were entirely normal, but terminally a diagnosis of acute myelocytic leukemia was made. There was no response to chemotherapy, and the patient died of gram negative sepsis one month after the diagnosis of acute myelocytic leukemia, and 17 months after the first clinical evidence of granulocytic sarcoma of bone. Autopsy revealed two dural and one orbital chloromas and acute myelocytic leukemia. The medullary cavities of most of the involved bones were fibrotic secondary to extensive radiotherapy.

DISCUSSION

The details of the patients reported in the present series are summarized in Table 1.
Table 1.—Granulocytic Sarcoma and AML. *

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age and Sex</th>
<th>Location</th>
<th>Granulocytic Sarcoma Color</th>
<th>Sarcoma Response</th>
<th>Radiotherapy</th>
<th>Onset of AML</th>
<th>AML Response to Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.A.D.</td>
<td>35 F</td>
<td>Cheek</td>
<td>Green</td>
<td>Complete</td>
<td>—</td>
<td>10 mo. after</td>
<td>CR†</td>
</tr>
<tr>
<td>J.T.N.</td>
<td>40 F</td>
<td>Breast</td>
<td>Green</td>
<td>—</td>
<td>—</td>
<td>Simultaneously</td>
<td>NR</td>
</tr>
<tr>
<td>L.J.J.</td>
<td>28 F</td>
<td>Chest</td>
<td>Grey-Brown</td>
<td>Complete but Brief</td>
<td>Complete</td>
<td>11-½ mo. before</td>
<td>CR</td>
</tr>
<tr>
<td>J.R.J.</td>
<td>44 F</td>
<td>Multiple Bones, Lymph Nodes, Orbit, Dura</td>
<td>Green</td>
<td>—</td>
<td>—</td>
<td>Sarcoma</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Acute myelogenous leukemia
†Complete remission; NR = no response
The first reported case of chloroma was probably that of Burns, who in 1823 described a patient with proptosis and green retroorbital tumors. King was the first to use the term chloroma in describing a similar patient thirty years later. Dock established the relationship of chloroma to acute leukemia; however, he thought the predominant cell of the tumor was of lymphoid origin. Turk disagreed and reported the first case of myelocytic leukemia associated with chloroma and suggested that the tumor cells were the same as the leukemia cells. Virtually all cases of chloroma reported since then have been shown to be associated with myelocytic or monocytic leukemia.

The most common presentation of chloroma is that of a green orbital tumor with resultant proptosis in association with acute myelocytic or occasionally acute monocytic leukemia. The tumor is more common in children and young adults and has been reported in the newborn. The vast majority of chloromas occur in the subperiosteal region of the bone, with skull, sternum, ribs and proximal portions of long bones being common sites of involvement. It is thought that the tumor arises from the bone marrow and traverses the Haversian canal to reach the subperiosteum. Chloromas unrelated to bone are less common but have been found in ovary, breast, lymph nodes, and dura, and rarely do thyroid, thymus, lung, stomach, intestine and urinary bladder harbor such lesions. Patches or nodules of chloromatous tissue have been found in liver and spleen. Greenish coloration of the bone marrow in an otherwise typical case of acute myelocytic leukemia may be a more common presentation of chloroma than discrete tumor formation. Often distinctive pigmentation is absent from histologically characteristic chloromas, and for that reason the term granulocytic sarcoma is more appropriate than chloroma.

Usually, acute leukemia and chloroma are diagnosed simultaneously, as in our Case 2. Rarely, chloroma precedes acute leukemia by less than one month to over a year, as in Cases 1 and 4 of the present series. Granulocytic sarcoma occurring late in the course of acute leukemia, such as our Case 3, is apparently very rare.

The survival of patients with granulocytic sarcoma is similar to that of patients with acute myelocytic leukemia without tumor formation. The disease is probably uniformly fatal; only two questionable reports to the contrary have appeared. Tumor response to localized external irradiation has been well documented and occurred in our Cases 3 and 4. The tumors of Cases 1 and 3 responded completely, but only temporarily to chemotherapy. Drug-induced regression of granulocytic sarcoma has not been previously reported.

Granulocytic sarcomas usually appear green in white light, and often fluoresce red with ultraviolet light. The green color usually fades upon exposure to air, but occasionally the color is intensified by such exposure. The faded green color can be temporarily restored in formalin fixed tissue by treatment with hydrogen peroxide and may be preserved temporarily in fresh tissue by storing the tissue in glycerin.

The cause of the green color and red fluorescence has been the subject of much study. Agner isolated crude myeloperoxidase from leukocytes and found it to be green in color and suggested that this enzyme was responsible for the color of the tumor. Amano suggested that porphyrins were responsible...
for the tumor's red fluorescence. Zeldenrust, et al. proposed that the green color was due to protoporphyrins. The problem appears to be resolved by the work of Schultz and Rosenthal who found that crystalline myeloperoxidase has a green color and a red fluorescence under ultraviolet light. They identified the fluorescent material as porphyrins and postulated that the enzyme myeloperoxidase may be derived from a porphyrin protein complex. This enzyme has a molecular weight of about 160,000 and catalyses the oxidation of amino acids by hydrogen peroxide. The enzymes from normal and neoplastic granulocytes are apparently similar in all aspects studied.

Chloromas are usually composed of relatively uniform, primitive cells that are not readily recognizable in routine hematoxylin and eosin stained sections as belonging to the granulocytic series. The cells may be peroxidase positive or negative. Rappaport maintains that a definite diagnosis must be based on the identification of such cells in the blood and marrow. The diagnostic difficulty encountered when nonpigmented granulocytic sarcoma precedes acute leukemia is apparent. Under such circumstances the pathologist may suggest a diagnosis of reticulum cell sarcoma or eosinophilic granuloma, as in our Cases 1 and 4, depending on the maturity of the tumor cells. It is interesting with these thoughts in mind to review reports of reticulum cell sarcoma terminating in acute myelocytic leukemia or reticulum cell sarcoma developing in the course of otherwise typical myeloid leukemia. It has been said that the most common lymphosarcoma of the orbit is reticulum cell sarcoma, and two cases of orbital reticulum cell sarcoma associated with acute monocytic leukemia have been reported. It is possible that many reticulum cell sarcomas associated with acute leukemia are in fact nonpigmented granulocytic sarcomas and that reticulum cell sarcoma, granulocytic sarcoma, and acute myelocytic leukemia are variants of the same disease. One form of the disease, reticulum cell sarcoma, occurs primarily as a single or multiple solid tumors. Another more malignant form of the disease, acute myelocytic or monocytic leukemia, commonly occurs as a widespread infiltrative malignancy without discrete tumor formation. Intermediate between these two extremes may be granulocytic sarcoma, a phase of the spectrum where solid tumors and widespread diffuse infiltration generally coexist.

SUMMARY

Four patients with granulocytic sarcoma are described. Granulocytic sarcoma of the cheek occurred in one patient 10 months before the diagnosis of acute myelocytic leukemia could be made. Another patient had multiple bone and dural granulocytic sarcomas 17 months before she developed acute myelocytic leukemia. One patient had a breast granulocytic sarcoma and acute myelocytic leukemia diagnosis simultaneously, and a fourth patient developed a chest wall granulocytic sarcoma 11½ months after the diagnosis of acute monocytic leukemia. The cheek and chest wall granulocytic sarcomas responded completely to antileukemic chemotherapy but subsequently recurred. Radiotherapy effected a permanent complete remission of the chest wall sarcoma, and partial regression of the bone granulocytic sarcomas in another case.

The possibility that acute myelocytic leukemia, granulocytic sarcoma and
reticulum cell sarcoma are variations of the same disease is suggested and discussed.

REFERENCES

Granulocytic Sarcoma (Chloroma)

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