Chloroma and Other Myeloblastic Tumors

By Hyman B. Muss and William C. Moloney

Fifteen cases (3.1%) of localized myeloblastic tumors occurring among 478 patients with acute granulocytic leukemia (AGL) and chronic granulocytic leukemia (CGL) are described. The majority of tumors were discovered at autopsy. Numerous cases of chloroma associated with AGL have been reported; however, in this series, the incidence of myeloblastic tumors in CGL was twice as high. The importance of employing histochemical methods for myeloperoxidase activity to identify myeloblastic tumors is pointed out. Experience in this group of cases confirm the frequent involvement of the ovary and the common localization of myeloblastic tumors to perineural and epidural structures. With CNS involvement by myeloblastic tumors, pain and compression symptoms may be effectively relieved by laminectomy and local x-ray therapy. After the appearance of a myelogenous tumor in CGL, the course of the disease is rapidly progressive.

Localized myelogenous cell tumors have been described for many years in the medical literature. While these tumors frequently involve periosteal and perineural structures, they may occur anywhere in the body and give rise to a variety of signs and symptoms. Often, however, they are clinically silent and are discovered unexpectedly at postmortem examination. Tumors of myelogenous origin are considered to be of rare occurrence; however, 15 cases have been encountered among our leukemia patients. The clinical, pathological, and other features of these tumors are described in this report.

MATERIALS AND METHODS

From July 1, 1954 to December 1, 1972, among a series of 869 leukemias in adults, there were 478 patients with myelogenous leukemia; of these, 155 were chronic (CML) and 323 acute (AML). Classification by cell type was established by morphological studies on Wright-Giemsa stained peripheral blood and bone marrow smears. Histochemical methods were employed when indicated and included peroxidase, special esterase, leukocyte alkaline phosphatase and PAS stains. Cytogenetic studies were carried out during the past 10 yr and, more recently, serum and urine lysozyme levels were performed routinely. Postmortem examinations were carried out on 52% of the myelogenous leukemia cases in this series.

RESULTS

Terminology

Tumors of myelogenous origin can be divided into chloromas which have a characteristic green color and nonpigmented myeloblastomas. Both consist of neoplastic myelogenous cells, i.e., myeloblasts and promyelocytes. The green color is indicative of specific enzymatic and biochemical properties and does
not denote a difference in cell line. Because the masses are not always green in color, they have been termed myeloblastomas and, more recently, granulocytic sarcomas. Rarely, a green tinge may be present in organs and bone marrow diffusely infiltrated with leukemic cells. Several instances of this phenomenon were noted in this series of myelogenous leukemia, but were not included in this presentation.

**Incidence**

Myeloblastic tumors are considered to be of rare occurrence; however, in this series, 15 of 478 patients with myelogenous leukemia developed tumor masses (3.1%). It is generally believed that myelogenous tumors occur only in AML; actually, in this series, the incidence in CML patients was 4.5%, while in AML, it was 2.5%. Moreover, it should be emphasized that the great majority of tumors were discovered at autopsy and, in this series, only 52% of the patients with myelogenous leukemia had a postmortem examination. In this small series of tumor cases, there was no significant age or sex difference (Tables 1 and 2).

**CLINICAL FEATURES**

Myelogenous tumors may be found in any location in the body, but in this series, as in the majority of reported cases, the tumor masses were most frequently located in close proximity to bone. Tumors were often present in perineural and epidural structures. Of the seven chloromas and myeloblastomas among the CML cases, four were identified pathologically at laminectomy and two by biopsy of extradural masses. Five of the seven patients had cord compression and demonstrated classical findings of numbness, weakness, progressive paralysis, and urinary retention. Three of five patients had significant objective and subjective improvement with laminectomy followed by radiation therapy, and two had significant relief of pain. Another patient developed severe pain over the sciatic nerve distribution with progressive weakness of the leg. Biopsy revealed a myeloblastic tumor involving the sciatic nerve. This patient responded well to local radiation therapy. Among four of the seven CML patients that were autopsied, two were found to have unsuspected chloromas involving the dura. It was noteworthy that, in six of seven cases, the peripheral blood picture and clinical course were compatible with CML in remission when the myeloblastic tumors were discovered. However, as noted in Table 1, in all CML cases the course was rapidly downhill with an average survival of less than 2 mo.

In comparison to CML, the localization and clinical features of myeloblastic tumors in AML patients were somewhat different (Table 2). Among CML cases, two of seven tumors were green, while seven of eight myeloblastic tumors in AML patients were chloromas. Two patients had severe lower back and sacral pain with nerve root distribution. Following x-ray therapy, both patients experienced marked relief from pain. The lesions in these two patients were considered to be epidural in location. At autopsy, in one of these cases, chloromatous masses were present in the pre- and paravertebral regions. A noteworthy finding was the replacement of the ovary by myeloblastic tumors in
<table>
<thead>
<tr>
<th>Case/Innals</th>
<th>Age/Sex</th>
<th>Blood Picture at Time of Diagnosis</th>
<th>Duration to Tumor (mo)</th>
<th>Therapy: Leukemia</th>
<th>Comment</th>
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<tbody>
<tr>
<td>1/AC</td>
<td>13/M</td>
<td>Hgb 11.5; WBC 16,200; PMN 33.5; EG 17.0; MB 2.5; L 13.4; M 33.5; Platelets normal on smear</td>
<td>11 14</td>
<td>Busulfan</td>
<td>Cord compression</td>
</tr>
<tr>
<td>2/DL</td>
<td>14/F</td>
<td>Hgb 10.0; WBC 3400; PMN 66; EG 2; L 28; M 4; Platelets 75,000; BM early blastic formation</td>
<td>5 7</td>
<td>Busulfan</td>
<td>Cord compression</td>
</tr>
<tr>
<td>3/LB</td>
<td>36/M</td>
<td>Hgb 10.0; WBC 9000; PMN 76; EG 2; BS 1; Pits normal on smear; BM compatible with CML</td>
<td>90 91</td>
<td>Busulfan</td>
<td>Cord compression</td>
</tr>
<tr>
<td>4/MQ</td>
<td>48/F</td>
<td>Hgb 9.4; WBC 2,400; PMN 87; EG 1; L 2; M 10; Platelets 48,500; BM aneuploid line in addition to previously documented Ph' chromosome</td>
<td>37 38</td>
<td>Busulfan</td>
<td>Cord compression</td>
</tr>
<tr>
<td>5/FC</td>
<td>51/M</td>
<td>Hgb 9.7; WBC 78,500; PMN 6; EG 10.0; MB 82.5; BS 0.5; M 1; Platelets 28,000; BM transformation to acute myelogenous leukemia</td>
<td>76 77</td>
<td>Busulfan</td>
<td>Green tumor on dura at autopsy, myeloblasts in meninges and all organs, no symptoms</td>
</tr>
<tr>
<td>6/CL</td>
<td>53/M</td>
<td>Hgb 6.4; WBC 2600; P 86; L 10; M 4; BM compatible with CML Ph' positive</td>
<td>67 68</td>
<td>Cyclophosphamide</td>
<td>Presented with adenopathy; lymph node biopsy showed myeloblasts at autopsy</td>
</tr>
<tr>
<td>7/AR</td>
<td>54/F</td>
<td>Hgb 6.3; WBC 1400; PMN 49; EG 9; BS 35; L 6; M 1; Platelets normal on smear</td>
<td>8 9</td>
<td>Busulfan</td>
<td></td>
</tr>
</tbody>
</table>

Hgb—hemoglobin in gm/100 ml.
WBC—white blood cells/cu mm.
PMN—polymorphonuclear cells.
EG—early granulocytes.
BS—basophiles.
MB—myeloblasts.
L—lymphocytes.
M—monocytes.
Pits—platelets.
BM—bone marrow.
<table>
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<tr>
<th>Case/Initials</th>
<th>Age</th>
<th>Sex</th>
<th>Signs and Symptoms</th>
<th>Onset of Leukemia</th>
<th>Leukemia Therapy</th>
<th>Autopsy Findings</th>
<th>Comment</th>
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<tr>
<td>8/PS</td>
<td>18/39</td>
<td>F</td>
<td>Table 3</td>
<td>11</td>
<td>Prednisone and 6-MP</td>
<td>Light gray-green tumors in breasts, ovaries, and left adrenal composed of myeloblasts</td>
<td>Good initial remission of leukemia on Prednisone and 6-MP therapy</td>
</tr>
<tr>
<td>9/MS</td>
<td>31/F</td>
<td>None</td>
<td>4 days</td>
<td>VAMP</td>
<td>Light green tumor</td>
<td>Died soon after admission</td>
<td></td>
</tr>
<tr>
<td>10/MB</td>
<td>36/F</td>
<td>Tender nodule over left precordium, 2 x 2 cm</td>
<td>VAMP</td>
<td>Both ovaries replaced by light green tumor. Aspiration of chest nodule prior to death revealed a myeloblastoma</td>
<td>Progressive downhill course. Chest nodule regressed after radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/DH</td>
<td>36/M</td>
<td>None</td>
<td>11 VAMP</td>
<td>Anterior mediastinal mass 36 g in size and light green in color</td>
<td>Admitted in terminal stage of disease with gram negative sepsis and pulmonary hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/SA</td>
<td>41/M</td>
<td>None</td>
<td>8 VAMP</td>
<td>Multiple green nodules composed of myeloblasts, found in esophagus, jejunum, and rectum</td>
<td>Masses turned gray on exposure to air but became light green again when bathed with dilute hydrochloric acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13/AS</td>
<td>54/F</td>
<td>None</td>
<td>1 6-MP and Cortisone</td>
<td>Green tumors on dura, retropreural and paravertebral grooves</td>
<td>Rapid downhill course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14/WL</td>
<td>59/F</td>
<td>Table 3</td>
<td>4 6-MP</td>
<td>Retrosternal, paravertebral, right atrial (intramural) and right lobe of prostate involved with &quot;chloromas&quot;</td>
<td>Green color to marrow at autopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15/CR</td>
<td>30/F</td>
<td>None</td>
<td>8 VAMP Ara-C and 6-TG</td>
<td>Gray-white mass composed of myeloblasts, right ovary</td>
<td>Good initial remission. CNS involvement with leukemia prior to death</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All patients had blood and bone marrow findings of acute myelogenous leukemia.

6-MP — 6-Mercaptopurine.
CTX — Cyclophosphamide.
Ara-C — Cytosine Arabinoside.
VAMP — Vincristine, 6-MP, Methotrexate, Prednisone.
6-TG — 6-Thioguanine.
four of five females with AML. Involvement of the ovaries by myelogenous tumors has been previously noted, but the reason for this localization is not known.3,7,13

At autopsy, retrosternal chloromas were found in two patients and various organs were involved in other cases as noted in Table 2.

Pathology

Granulocytic tumors may be either green or whitish in color and are nodular and invasive in character. Cellular composition is mainly myeloblastic, although promyelocytes and myelocytes may be present in some tumors and this was found in this series. Nongreen pigmented tumors may be confused with lymphoreticular malignancies in the routine hematoxylin and eosin stained preparations. Zenker-fixed sections stained with Giemsa and imprint smears from fresh tissues stained with Wright-Giemsa stain along with special esterase, peroxidase, and other histochemical procedures are essential for accurate histological identification.14 As noted in this series, myeloblastomas, while frequently found to be involving periosteal structures, rarely form bone destructive lesions.

DISCUSSION

The first case report of a chloromatous tumor was made by Burns in 1811.1 This patient presented with visual disturbances in his left eye and, soon after, developed exophthalmos, diplopia, and blindness. Later on, he developed similar findings in the right eye and finally died after developing lower limb paralysis and urinary retention. At autopsy, green tumors were found in the sinuses, dura, lacrimal glands, and outer surface of the skull. The author was puzzled as to the etiology, but no mention was made of any hematological association. Subsequently, several other reports appeared in the literature, but it was King who, in 1853, described a similar case in a 6-yr-old girl and called the disease chloroma because of the greenish color present in the tumor nodules found at postmortem examination.2 He believed this to be a fibrous tumor, but noted that granules were seen in the microscopic sections of the nodules. In 1904, the association of chloroma and leukemia was firmly established in an extensive review by Warthin and Dock. In many of these cases, the tumors as well as the marrow were crowded with granulated cells. These authors stated that the disease could be found in lymphatic as well as myelogenous leukemias; most observers believed that the disease was one of lymphoid origin.3

Finally, in 1912, with the use of the peroxidase stain, convincing evidence was presented that the chloroma was a tumor of myelogenous origin.4

It is apparent that myeloblastic tumors are more commonly present in patients with myelogenous leukemia than hitherto supposed. On occasion, these tumors may precede by many months the onset of leukemia; however, this type of presentation appears to be extremely rare.15 While myeloblastic tumors have usually been present in the earliest stages of AML, it is possible that longer survival due to recent advances in chemotherapy may enhance the development of these tumors. There is no evidence in this series, however, of a situation similar to the blood–brain barrier and intracranial “sanctuary” localization of
Table 3. Myeloblastomas Presenting with Cord Compression

<table>
<thead>
<tr>
<th>Case</th>
<th>Symptoms and Signs</th>
<th>Autopsy/Biopsy Findings</th>
<th>Radiation to Tumor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bilateral hip and thigh pain with numbness in feet, progressing to weakness in legs, foot drop, and urinary retention.</td>
<td>Gray-green tumor extending from L-1 to L-3 at laminectomy; two &quot;chloromas&quot; on cranial dura found at autopsy.</td>
<td>2200 R</td>
<td>Able to walk with crutches and return of bladder function after laminectomy and radiation therapy.</td>
</tr>
<tr>
<td>2</td>
<td>Numbness and pain in left leg becoming bilateral and associated with paraplegia and urinary retention</td>
<td>Gray-red tumor extending from T-4 to T-6 at laminectomy; no autopsy</td>
<td>3000 R</td>
<td>Decreased pain and return of bladder function after therapy; Moderate return of motor ability</td>
</tr>
<tr>
<td>3</td>
<td>Localized pain over T-3 vertebra; no other neurological findings</td>
<td>Biopsy from osteolytic mass at level T-3 showed myeloblastoma; no autopsy</td>
<td>Radiation to area of T-3</td>
<td>Relief of pain after radiation therapy</td>
</tr>
<tr>
<td>4</td>
<td>Progressive back pain in T-4 area with numbness and loss of sensation, urinary retention, and paraplegia</td>
<td>Yellow-gray tumor at laminectomy; no tumor at autopsy</td>
<td>2500 R</td>
<td>Return of urinary and motor function after treatment; complete relief of pain</td>
</tr>
<tr>
<td>7</td>
<td>Weakness of the right leg with severe sciatic nerve root pain</td>
<td>Yellowish tumor at laminectomy extending from L-3 to S-1; no autopsy</td>
<td>2000 R</td>
<td>Minimal improvement in motor function after radiation therapy with moderate relief of pain</td>
</tr>
<tr>
<td>8</td>
<td>Severe pain over S-1 nerve root distribution</td>
<td>No tumor in epidural space at autopsy; no laminectomy</td>
<td>Low dose of radiation to lumbo-sacral area</td>
<td>Relief of pain with radiation therapy</td>
</tr>
<tr>
<td>14</td>
<td>Recurrent back pain and numbness in right arm</td>
<td>Retrosternal and paravertebral &quot;chloromas&quot;</td>
<td>Low dose of radiation to lumbosacral area</td>
<td>Relief of pain with radiation therapy</td>
</tr>
</tbody>
</table>
leukemic cells so commonly found in acute leukemia in childhood. The frequency of myeloblastic tumors among patients with CML, some of them while in apparent remission, has not been previously noted. Differences between the type, i.e., green colored versus nonpigmented tumors in AML, compared to CML, as well as the variation in localization are of interest, but in this small series, no conclusions can be drawn. Since at least one-half of myeloblastic tumors are asymptomatic, the true incidence depends on the percentage and extent of the postmortem examinations in patients with myelogenous leukemia.

It is well established that the green color, seen in the chloromatous form of myeloblastic tumors, is due to the enzyme myeloperoxidase. Chloromas have been described in species other than man, and these green tumors occur commonly in rats with myelogenous leukemia. Chloroleukemia in the rat, as first noted by Shay et al., can be readily transplanted. Myeloperoxidase (verdoperoxidase) in rat chloromas is apparently similar in many respects to the human variety and rat chloroma has furnished an opportunity to study enzymes such as verdoperoxidase and lysozyme. Physiochemical studies have been carried out on the interesting green pigment obtained from human and rat chloroma tissue. Although the exact biochemical and physiochemical structure of this green pigment has not been established, it has been shown that the enzyme is composed of a hemeprosthetic group and a peptide moiety: unlike other heme-protein enzymes, the heme group is connected by a covalent bond. The substituent groups of the porphyrin are unusual and do not resemble those found on uro-, copro-, and protoporphyrin. The fact that some myeloblastic tumors possess a green color and others do not is probably related to the amount of enzyme present, as well as the oxidation state of the enzyme.

It is worth considering the concept that dysplastic leukemic cells, arising as they do from a common stem cell which differentiates into myeloblasts, erythroblasts, and megakaryoblasts, may represent a disorder in maturation with retention in the myeloblastic cell of peroxidases and porphyrin destined originally for erythroblast precursors.

From a practical standpoint, it is important to emphasize the frequent epidural and perineural localization of myeloblastic tumors. With localized cord compression, laminectomy should be carried out as an emergency measure and should be followed by local x-ray therapy. In more diffuse involvement and with evidence of other perineural infiltration, local x-ray therapy is the treatment of choice (Table 3). Scanning techniques utilizing gallium may be of value in localizing these masses early in their course and might avoid laminectomy if radiation therapy could be instituted early before motor function is compromised. Unfortunately, the ultimate answer to the treatment of myeloblastic tumors rests with the development of methods to cure or control myelogenous leukemia.

ACKNOWLEDGMENT

We would like to thank Dr. Mark H. Cooley of Harvard Medical School for helping us collect data on patient No. 3.
REFERENCES

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