Ten of 136 consecutive adult patients with previously untreated acute leukemia had morphologically undifferentiated leukemia by light microscopy. Leukemic cells from these patients were characterized by agranular cytoplasm, negative histochemical staining with sudan black (SB) and nonspecific esterase, and absent lymphoid cell surface markers and therefore were not classifiable according to the French-American-British (FAB) system. Electron microscopy with myeloperoxidase (MPO) staining revealed the presence of peroxidase positive cytoplasmic granules and endoplasmic reticulum in eight of the nine patients studied. Cells from the patient who was negative for MPO were also negative for platelet peroxidase. A series of monoclonal antibodies to myeloid antigens also revealed myeloid features with all patients having at least one myeloid differentiation antigen present on the surface of their cells. Common acute lymphoblastic leukemia (ALL) antigen was absent in the nine patients tested. Cytogenetic analysis of blast cells was abnormal in seven patients on whom adequately banded chromosomes were obtained although there were no consistent abnormalities. No patient had a Ph1 chromosome. Only two of the ten patients achieved a complete remission. Morphologically undifferentiated leukemia may have myeloid features when studied by transmission electron microscopy or with monoclonal antibodies for cell surface markers. Such studies should be performed when the leukemia cannot be classified using either light microscopy or lymphoid cell surface markers. Such patients infrequently achieve remission with standard therapy and constitute a distinct entity.

The distinction between acute lymphoblastic leukemia (ALL) and acute nonlymphocytic leukemia (ANLL) can usually be made on the basis of light microscopy, polychrome stains, and cytochemical stains such as myeloperoxidase (MPO), sudan black (SB), and periodic acid Schiff (PAS). This distinction is important because of the differences between ALL and ANLL in the choice of chemotherapeutic agents, length of therapy, and propensity of ALL to involve the CNS. The biological basis for this distinction is the presumed origin of the leukemia from the malignant transformation of a stem cell that has undergone limited differentiation. The French-American-British Cooperative Group (FAB) has published standardized criteria by which ALL can be distinguished from ANLL and then further classified into subtypes.1,2 ALL is defined as a leukemia in which the majority of cells have scant amounts of agranular cytoplasm, predominantly round nuclei, and homogeneous, slightly condensed chromatin without prominent nucleoli (L1 subtype). The leukemic cells can also be large, with abundant vacuolated basophilic cytoplasm, and prominent nucleoli (L3 subtype). Both of these variants can be readily distinguished from ANLL in Romanowsky polychrome stained preparations. A third subtype of ALL is characterized by large cells that exhibit some heterogeneity in size and have irregular nuclear shape with one or more large nucleoli (L2 subtype). Although blasts from patients with ANLL often contain cytoplasmic granules and thus can be easily distinguished from ALL, some have only small numbers of granules. Such patients with ANLL can then be best distinguished from L2 by cytochemical staining. Using arbitrary criteria, the FAB group states that the presence of <3% MPO positive cells suggests the diagnosis of ALL, whereas, if ≥3% of cells are positive, the diagnosis is ANLL.

In this report we present the results of studies of leukemic cells of ten patients with acute leukemia who did not meet these FAB criteria for ANLL. These patients had leukemic cells that were small, with scant agranular cytoplasm and distinct nucleoli. Auer rods were not seen and cytochemical stains (PAS, SB, chloroacetate esterase, α-Naphthyl butyrate esterase) were negative. The leukemic cells from these patients were studied by ultrastructure and for cell surface markers using monoclonal antibodies. Our data suggest that such undifferentiated leukemias frequently exhibit features that suggest a myeloid origin. Furthermore, our results suggest that these patients infrequently achieve remission when treated with conventional therapy for ANLL.

MATERIALS AND METHODS

Leukemic cells obtained from peripheral blood or bone marrow from 136 consecutive patients (Table 1) referred to the University of Maryland Cancer Center with previously untreated acute leukemia were analyzed. Thirteen patients (eight ALL, five ANLL) had inaspirable marrows at the time of diagnosis, and laboratory studies were performed on peripheral blood or cells obtained from a bone marrow biopsy core. Whenever possible, all of the following series of studies were performed.

Light microscopy. Bone marrow smears (or touch preparations from biopsy cores) and peripheral blood smears were stained with Wright-Giemsa for cell morphology and differential, with histochemical stains including SB, PAS, chloroacetate esterase, and alpha-naphthyl butyrate esterase. Terminal deoxynucleotidyl transferase (Tdt) was detected by indirect immunofluorescence (Bethesda Research Laboratory Inc, Gaithersburg, MD) using the method of Bollum.3

Immunologic cell surface marker studies. Cell surface marker studies using a variety of monoclonal antibodies and indirect immunofluorescence microscopy were done using standard methods described elsewhere.4 Monoclonal antibodies were used to identify
MINIMALLY DIFFERENTIATED ANLL

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>de novo ANLL</th>
<th>2nd ANLL</th>
<th>ALL</th>
<th>M-O</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (no. evaluable for response to therapy)</td>
<td>136 (129)</td>
<td>94 (90)</td>
<td>16 (14)</td>
<td>16 (15)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Median age (yr) (range)</td>
<td>60 (15-83)</td>
<td>61 (15-83)</td>
<td>58 (29-77)</td>
<td>52 (20-83)</td>
<td>52 (34-71)</td>
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<tr>
<td>Male</td>
<td>69</td>
<td>48</td>
<td>7</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Female</td>
<td>65</td>
<td>46</td>
<td>7</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Complete response (%) of evaluable patients</td>
<td>53</td>
<td>63</td>
<td>36</td>
<td>53</td>
<td>20</td>
</tr>
</tbody>
</table>

Abbreviations: de novo ANLL, no previous hematologic disorder; 2nd ANLL, chemotherapy, radiotherapy, or another stem cell disorder preceded the diagnosis of leukemia; M-O, minimally differentiated ANLL.

determination antigens of T lymphocytes, B lymphocytes, monocytes and granulocytes, as well as to identify the presence and nature of surface or cytoplasmic immunoglobulins. An antigen was considered present if >20% of cells studied were positive.

Ultrastructural studies. Bone marrow particles were fixed in a phosphate-buffered formaldehyde-glutaraldehyde mixture and further processed for transmission electron microscopy (TEM) in a routine fashion. For the ultrastructural localization of platelet-specific peroxidase, the tissue was first fixed in a tannic acid-aldehyde mixture. Thereafter, the material for peroxidase staining was incubated in 3,3'-diaminobenzidine (DAB) medium, fixed, embedded, and sectioned.

Cytogenetic analyses. Procedures for the cytogenetic analysis of leukemia patients have been described in detail elsewhere. Procedures for the cytogenetic analysis of leukemia patients have been described in detail elsewhere. Procedures for the cytogenetic analysis of leukemia patients have been described in detail elsewhere. Procedures for the cytogenetic analysis of leukemia patients have been described in detail elsewhere. Procedures for the cytogenetic analysis of leukemia patients have been described in detail elsewhere. Procedures for the cytogenetic analysis of leukemia patients have been described in detail elsewhere. Procedures for the cytogenetic analysis of leukemia patients have been described in detail elsewhere. Procedures for the cytogenetic analysis of leukemia patients have been described in detail elsewhere. Procedures for the cytogenetic analysis of leukemia patients have been described in detail elsewhere.

RESULTS

Of the 136 patients analyzed, 110 (81%) had ANLL, 16 (12%) had ALL, and ten patients (7%) had leukemia that was not classifiable by conventional morphologic and cytochemical criteria (Table 1). There were no clinical characteristics, abnormalities on physical examination or initial laboratory parameters that distinguished these ten patients. One of these patients (no. 8) developed leukemia after extensive chemotherapy and radiotherapy for Hodgkin’s Disease. No history of mutagen exposure was noted in any of the other nine patients. A second patient (no. 6) had a low WBC count for 4 to 5 months before developing leukemia but no other patient had a hematologic disease before the diagnosis of acute leukemia. The results of laboratory investigations on these ten patients are summarized in Tables 2 and 3.

Light microscopy. Marrows were hypercellular in all but one patient. Six patients had only occasional cells identifiable that were not leukemic whereas the other four patients had easily identified populations of residual mature myeloid or erythroid cells. In all of these patients, the leukemic cells were small with sparse, agranular, lightly basophilic cytoplasm, round nuclei, immature chromatin and prominent nucleoli (Fig 1). Auer rods were absent. In all

Table 2. Hematologic and Cytogenetic Features

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Peripheral Blood</th>
<th>Bone Marrow</th>
<th>Karyotype</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>WBC*</td>
<td>BL (%)</td>
<td>HCT (%)</td>
</tr>
<tr>
<td>1</td>
<td>3.0</td>
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<td>2</td>
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<td>5</td>
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<td>36</td>
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<td>6</td>
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<td>27</td>
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<td>7</td>
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<td>9</td>
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<td>38</td>
</tr>
<tr>
<td>10</td>
<td>0.6</td>
<td>5</td>
<td>23</td>
</tr>
</tbody>
</table>

Abbreviations: WBC, white blood count; BL, blast percentage; HCT, hematocrit; PLT, platelet count.

* x 10^3/μL.

† Graded as 0-4/4.
patients, <3% of the blasts were positive with cytochemical staining for SB and staining with specific or nonspecific esterases and PAS was uniformly negative. Thus, although the appearance of the leukemic cells did not suggest lymphoid origin, cytochemical criteria for the suspected diagnosis of ANLL were not met.

Leukemic cells were evaluated for the presence of Tdt by indirect immunofluorescence in all ten patients. In one patient (no. 1), 20% of the blasts were positive and in a second (no. 3), 40% were positive. The other eight patients each had <5% of their leukemic cells stain positively.

**Ultrastructural studies.** TEM was performed on leukemic cells of nine of the ten patients. Blast cells in all patients appeared extremely undifferentiated on TEM. The nuclei contained primarily euchromatin with little heterochromatin, and large nucleoli were seen. With MPO staining (Fig 2), eight of the nine patients had leukemic cells containing small numbers of MPO positive granules in the cytoplasm in 6% to 40% of the blasts. Other cells had MPO-positive material in endoplasmic reticulum and nuclear membrane. MPO-positive cytoplasmic granules are not found in megakaryocytes or their precursors, or in cells of lymphoid lineage. Except when cells are fixed with tannic acid, the presence of MPO staining in endoplasmic reticulum and nuclear membrane identifies cells of myeloid lineage. Thus, these patients were thought to have leukemia derived from a very early precursor cell committed to myeloid differentiation. Only patient no. 2 had leukemic cells lacking MPO activity, and megakaryocyte-specific peroxidase was also absent from bone marrow and peripheral blood cells examined after tannic acid fixation. Thus, eight of nine patients studied with TEM had evidence suggesting myeloid origin of their leukemic cells.

**Cell surface markers.** Leukemic cells from all ten patients were evaluated for the presence of cell surface antigens with monoclonal antibodies to normal myeloid differentiation antigens. Myeloid differentiation antigens were present on the leukemic cells of all 10 patients. All but two patients had several such markers identified on their cells (Table 3). No consistent pattern of reactivity was seen although My-10 (seven of eight patients) and My-11 (six of eight) were frequently found.

The common ALL antigen was not detected on the cells in any of the patients. T-cell differentiation antigens were found infrequently. The cells of two patients (no. 4 and 5) had a single such antigen. Leukemic cells from three patients were evaluated for B lymphocyte markers. None of these studies were positive, whereas all specimens tested were positive by HLA-DR (Ia-antigen).

**Chromosomal analyses.** Cytogenetic analyses were per-
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Fig 2. (A) Electron micrograph of a blast cell from patient no. 4 after formaldehyde-glutaraldehyde fixation and MPO staining. The nucleus contains a large nucleolus and little heterochromatin. The nuclear membrane stains positively with MPO (arrowheads). The cytoplasm contains endoplasmic reticulum, which also stains positively for MPO (arrows). (Original magnification x 14,000; current magnification x 11,060.) (B) Electron micrograph of a blast cell from patient no. 6 after formaldehyde-glutaraldehyde fixation and MPO staining. The nucleus contains a large nucleolus and little heterochromatin. The cytoplasm contains mitochondria, endoplasmic reticulum, and MPO positive granules (arrows). (Original magnification x 9,300; current magnification x 7,350.)

formed in all ten patients. No patient had a Ph1 chromosome. Two patients (no. 1 and 9) had poorly banded chromosomes that precluded detailed analysis. Seven of the eight patients who had adequate metaphases examined had an abnormal karyotype. Two patients (no. 3 and 6) had loss of one no. 7 chromosome, and a third (no. 5) had loss of part of the short arm of one no. 7 chromosome. One no. 17 chromosome was missing in one patient (no. 3), and a second patient (no. 4) had a dic(17) that resulted in loss of part of the short arm of the no. 17 chromosome. Two patients (no. 2 and 7) had translocations involving one no. 1 chromosome but with the involvement of different chromosomes. One of the latter patients (no. 7) also had t(8;14). No other chromosome was involved in more than a single patient. Patient no. 10 had a normal karyotype.

Response to therapy. The ten patients with FAB-unclassifiable acute leukemia all received intensive chemotherapy. Eight patients were treated with daunorubicin (DNR) and cytosine arabinoside (Ara-C) according to the protocol therapy described below for ANLL. Two of these patients also were treated with vincristine and prednisone, one (no. 3) because of the presence of Tdt, and the other (no. 2) because of the absence of platelet or MPO staining on electron microscopy. One of these eight patients achieved a complete remission (CR). Two patients (no. 1 and 4) were treated with a regimen developed for ALL consisting of tandem methotrexate and L-asparaginase in combination with vincristine and dexamethasone. One of these two patients, also with a low number of TdT-positive cells, achieved a CR. Of the eight patients in whom CR was not achieved, one (no. 7) died on day 15 with an aplastic bone marrow, while all seven of the remaining patients had refractory leukemia.

Of the 110 patients with ANLL diagnosed by routine criteria, 104 were evaluable for response to chemotherapy. Five patients who were not treated and one who was lost to follow-up were invaluable. Of these 104 patients, 57 of 90 (63%) with de novo ANLL achieved CR (Table 1). Five of 14 (36%) patients with secondary ANLL achieved CR. Treatment of these 104 patients consisted of protocol chemotherapy (99 patients) with DNR 45 mg/m2 daily for three days, and Ara-C by continuous infusion for seven days at a dosage of either 100 mg/m2 before December 1982 or 200 mg/m2 after January 1983. Five patients who received other regimens did not achieve a complete response.

Of the 16 patients with ALL, eight of 15 achieved CR after treatment with either DNR, vincristine, prednisone, and L-asparaginase or with a combination of methotrexate and L-asparaginase given in a tandem fashion with vincristine and dexamethasone. One patient refused treatment.

DISCUSSION

The ten patients described here did not meet the FAB criteria for any of the various subtypes of acute leukemia. The diagnosis of ANLL could be made only by ultrastructural MPO staining or cell surface marker studies. Eight of the patients (no. 1, 3, 4, 5, 6, 7, 9, and 10) had MPO positive cells and, on this basis, had ANLL. The FAB group suggests that the demonstration of MPO positive blast cells by TEM is sufficient to establish myeloid lineage. The number of cells with MPO positive material varied considerably, from 6 to 40%, in different patients. It is likely that this underestimates the frequency of positive cells because the thin sections necessary for TEM may by chance not detect the presence of small granules. With MPO at the light microscopy level, an arbitrary minimum percentage of 3% has been set by the FAB group; no such “definition” exists for ultrastructural MPO. The variation in both the percentage of positive cells and the degree of “positivity” per cell emphasizes the considerable heterogeneity of morphologic differentiation occurring even within the same patient.
In the other two patients, the diagnosis of ANLL depended solely on cell surface marker studies. All ten patients tested positively for myeloid antigens, and in two patients (no. 2 and 8), this was the only evidence of lineage specificity. When MPO or platelet PO activity is absent (patient no. 2) or cannot be established (patient no. 8), the constellation of four different positive "myeloid" monoclonal antibodies as for patient no. 2, and five different positive "myeloid" monoclonal antibodies, as for patient no. 8, is sufficient to indicate myeloid features and to confirm the presence of OKM-1 in both patients no. 2 and 8. A recent review notes that OKM-1 has not been reported in cells from any of 92 patients with lymphoid leukemias.9 Other monoclonals positive on cells from these two patients are less lineage-specific. My-10 and My-11 have been identified on both ALL and ANLL.9 The absence of Tdt and CALLA in these two patients in conjunction with several positive myeloid antigens confirms the presence of a very early cell committed to myeloid differentiation.

There have been a number of descriptions of patients with characteristics suggestive of both ALL and ANLL, examples of so-called "lineage infidelity" or biophenotypic leukemia.20-22 Four of our patients may fit into this category. Two patients (no. 1 and 3) had Tdt detected in a minority of their blasts. Tdt positivity was detected in 19 of the 110 (17%) patients with classifiable ANLL in our study. Some may have been due to nonspecific Fc receptor mediated binding of reagents in that they were less positive after incubation of cells in AB plasma. Others, however, seemed to represent "true" positives. The presence of Tdt in some patients with ANLL has been confirmed by other investigators using a biochemical method21 of identifying Tdt activity, and has recently been identified in as many as 22% of patients with ANLL using an immunoperoxidase method.22 Tdt has also been detected in immature cells in regenerating bone marrow24 and in a recent review by Ben-Bassat and Gale,25 it was stated that Tdt positivity alone in association with myeloid characteristics is insufficient to confirm the suspicion of biophenotypic leukemia.

Similarly, antibodies raised against thymic cells (OKT-6 and OKT-10), were reactive in two MPO positive, TdT negative patients (no. 4 and 5). Reinherz et al26 found that the spectrum of OKT-10 positive cells included up to 20% of cells in normal bone marrow, suggesting that the determinant recognized by this antibody is not restricted to lymphocytes, and represents an "early differentiation antigen." Similarly, OKT-6 has been reported to be reactive with malignant cells from patients with histiocytosis X,27 and with the myeloid cell line HL-60 after stimulation with gamma interferon.28 Neither patient was studied for the presence of T-cell receptor gene rearrangements.

The diagnosis of acute megakaryoblastic leukemia (FAB-M7) was considered and excluded in nine of the ten patients. In immature megakaryocytes, the peroxidase stain is positive only after fixation in tannic acid, and peroxidase-positive material is present in the nuclear membrane and endoplasmic reticulum.7 Two patients with the M7 subtype were identified within the group of 110 with ANLL using this technique. One of the ten patients studied had neither MPO nor megakaryocyte peroxidase positive cells in either peripheral blood or bone marrow. Eight patients had MPO positivity on TEM with standard fixation, a finding not found with M7 leukemia. The FAB-M7 subtype was therefore definitively excluded in these nine patients.

These patients thus had leukemia that lacked features that are currently recognized as diagnostic of ALL or ANLL within the FAB schema. The FAB group recognizes that unclassifiable leukemias occur, but estimates the frequency at 2% in adults.4 They describe this group as a mixture of patients with basophilic leukemia, hypoplastic ANLL, and ANLL requiring ultrastructural peroxidase studies "to confirm their granulocytic nature." In our series, ten of 136 patients (7%) fit this last category. In a series of patients reported by Youness et al,29 22 of 225 patients (10%) were thought to have acute undifferentiated leukemia (AUL), defined by the investigators as patients in whom light microscopy with the usual battery of cytochemical stains was not helpful in classification in the FAB schema. As in our patients, the leukemic cells were described as undifferentiated agranular cells with more cytoplasm than an L1 blast, round nuclei and one to two nucleoli. Of these 22 patients, 14 were classified as ANLL on the basis of TEM and MPO staining. In a third series, four of 56 (7%) ANLL patients were classified as AUL, but were defined only as "unclassifiable."30 A fourth series described nine of 202 (4%) with either AUL or "biphenotypic" leukemia with leukemic cells similar to those described in our patients.31 Despite the lack of uniform definition, all these series identify patients who had undifferentiated leukemia that was nonetheless considered myeloid by varying criteria. This subtype occurs with a frequency similar to that of the M3, M6, or M7 subtypes suggesting that the FAB group has underestimated the frequency of the entity of minimally differentiated acute myeloid leukemia.

Some patients with minimally differentiated ANLL may have been classified as ALL in many centers. A recent report from Cancer and Leukemia Group B (CALGB) of 129 adult patients treated for ALL identified four patients (3%) who lacked both B cell and T cell markers.32 These patients exhibited only myeloid differentiation antigens when studied with monoclonal antibodies. A French group reported 25 adult patients with "ALL" who lacked both B cell and T cell markers.33 Five patients studied by TEM with peroxidase staining demonstrated myeloid blasts.

No consistent cytogenetic abnormality was identified in the group of patients with minimally differentiated ANLL, but the number of patients is small. Seven patients with adequate mitoses for detailed analysis had structural rearrangements. One of these alterations (patient no 7), t(8;14) (q24;q32), is typically found in Burkitt's lymphoma and ALL-L3. Surface immunoglobulin was not evaluated in cells from this patient, although ultrastructural MPO was positive. Many of the other chromosome changes (eg, +7, +8, dic(17), and ring chromosomes) have been reported both in ANLL and ALL. Four of the seven patients had complex karyotypes similar to those in ANLL patients described by Sakurai and Sandberg33 as "major karyotypic abnormali-
ties" (MAKA). Among the remaining three patients, two had ring chromosomes, also a common finding in patients with MAKA. Although one patient (no. 8) with a ring chromosome had a history of prior therapy for Hodgkin's disease and was thought to have a therapy related acute leukemia, the other patients had no history of prior hematologic disease, malignancies, or mutagen exposure. In reviewing the previous mentioned series, only one (Youness et al) examined karyotypes, and the vast majority of cases were examined without the benefit of banding techniques. In the three patients studied with banding, one had a MAKA, a second had two abnormal clones identified, both with different abnormalities of chromosome no. 13, and the third had an abnormality of chromosome no. 21.

Last, the response rate in these ten patients was extremely poor. Treatment in eight patients with standard ANLL chemotherapy produced one brief CR lasting 5 months and six patients had resistant leukemia. The other patient who achieved CR, the eldest of the group, was treated with a regimen active in both ALL and ANLL, and died of complications of further chemotherapy 4 months after achieving CR. These results differ significantly from the 60% CR in the 104 concurrently treated patients with ANLL who were classifiable according to the FAB system (P = .02, Fisher exact test). Youness et al found a CR rate of 68% in the 22 patients reported, but the median survival time was only 26.7 weeks. This is considerably shorter than the median survival for patients with ANLL treated at the same institution. In the four patients described by Foon et al, three achieved complete response but data on survival are not available. Mertlesen et al noted both a decrease in the remission rate and shortened duration of survival and remission in their mixed group classified as AUL although statistical significance is not reached due to small patient numbers. In reviewing their results in patients with minimally differentiated ANLL treated as ALL, Reiffers et al noted that all five patients who were MPO-positive by TEM were among the group of seven patients in whom treatment failed to produce a remission. Lastly, CALGB noted that none of the four patients with what they termed "myeloid" ALL achieved CR when treated with daunorubicin, vincristine, prednisone, and L-asparaginase.

The ten patients described here have leukemia that is nonlymphocytic by morphology, ultrastructure, and cell surface markers. The ability to prospectively identify a group of patients with poor response to chemotherapy suggests that minimally differentiated ANLL is indeed a clinically distinct subtype of acute leukemia. This leukemia is presumably derived from very early committed granulocyte precursors. Our series and those previously cited suggest that an M-O category for ANLL can be created and defined by the presence of MPO detectable only on the ultrastructural level. The absence of lymphoid markers and the presence of myeloid differentiation antigens is confirmatory, and identify patients in whom TEM with MPO should be examined. It would appear that the prognosis for patients with minimally differentiated ANLL is poor using standard therapeutic approaches.

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Minimally differentiated acute nonlymphocytic leukemia: a distinct entity

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