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Case Reports

Immunoblastic Sarcoma with Leukemic Blood Picture in the Terminal Stage of Mycosis Fungoides

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Summary. A 76 year old man with mycosis fungoides developed an immunoblastic sarcoma and a leukemic blood picture in the final tumor stage after 6 years, in which the disease had clinically progressed in a typical manner. The results of histological and cytochemical studies of autopsy material are presented. Based on these findings and evidence of the T cell nature of mycosis fungoides, the immunoblastic sarcoma observed in the terminal stage of this case of mycosis fungoides might be of the rare T cell type.

Key words: Mycosis fungoides — Sézary syndrome — Immunoblastic sarcoma — Cytochemistry, Acid phosphatase — Pathological anatomy.

Mycosis fungoides (m. f.) is a malignant lymphatic neoplasm that affects adults, most frequently those between 40 and 60 years of age (Block *et al.*, 1963; Epstein *et al.*, 1972). It is manifest primarily in the skin, but later involves internal organs (Block *et al.*, 1963; Rappaport and Thomas, 1974). Typical histological lesions do not appear until the infiltrative secondary stage. A leukemic blood picture is seldom observed in classic cases of m. f., even in the terminal stage when tumor formation occurs. In this report we present a special leukemic variant of the terminal tumor stage of m. f.

Case History

At the age of 70, 6 years before his death, the patient G. N. first developed therapeutically reversible skin lesions resembling parapsoriasis lichenoides; histologically, there was an uncharacteristic psoriasiform picture. Erythroderma developed a year later. This suggested Sézary syndrome. However, a skin biopsy and the peripheral blood picture revealed no diagnostic features. Biopsy of an inguinal lymph node showed merely dermatopathic lymphadenitis. Four years after the appearance of the first symptoms, variable sized, firm, red, plateau-like skin infiltrates developed. M. f. could then be confirmed histologically; there were subepidermal infiltrates (Fig. 1a), which were band-like and/or grouped around vessels and cutaneous appendages. These infiltrates were composed mainly of small and medium-sized lymphocyte-like cells (Fig. 2a). There were also larger cells with bizarrely shaped, hyperchromatic nuclei. Progression into the tumor stage the same year could not be arrested.

Four weeks before death, "leukocytosis" of the peripheral blood was observed, with an increase from 17,200 to 57,000 cells/mm^3. There was no clinical evidence of infection. The differential cell count was abnormal, revealing atypical mononuclear cells (Fig. 3), eosinophilia, and relative lymphopenia: 36% polymorphonuclear neutrophils, 4% stab forms, 13% eosinophils, 4% monocytes, 7% lymphocytes, 36% atypical mononuclear cells; $3^0/_{00}$ basophil granulocytes. 62% of the atypical mononuclear cells were approximately 8 μm in diameter and 22% approximately 15 μm; 14% were up to 21 μm in diameter. The small and medium-

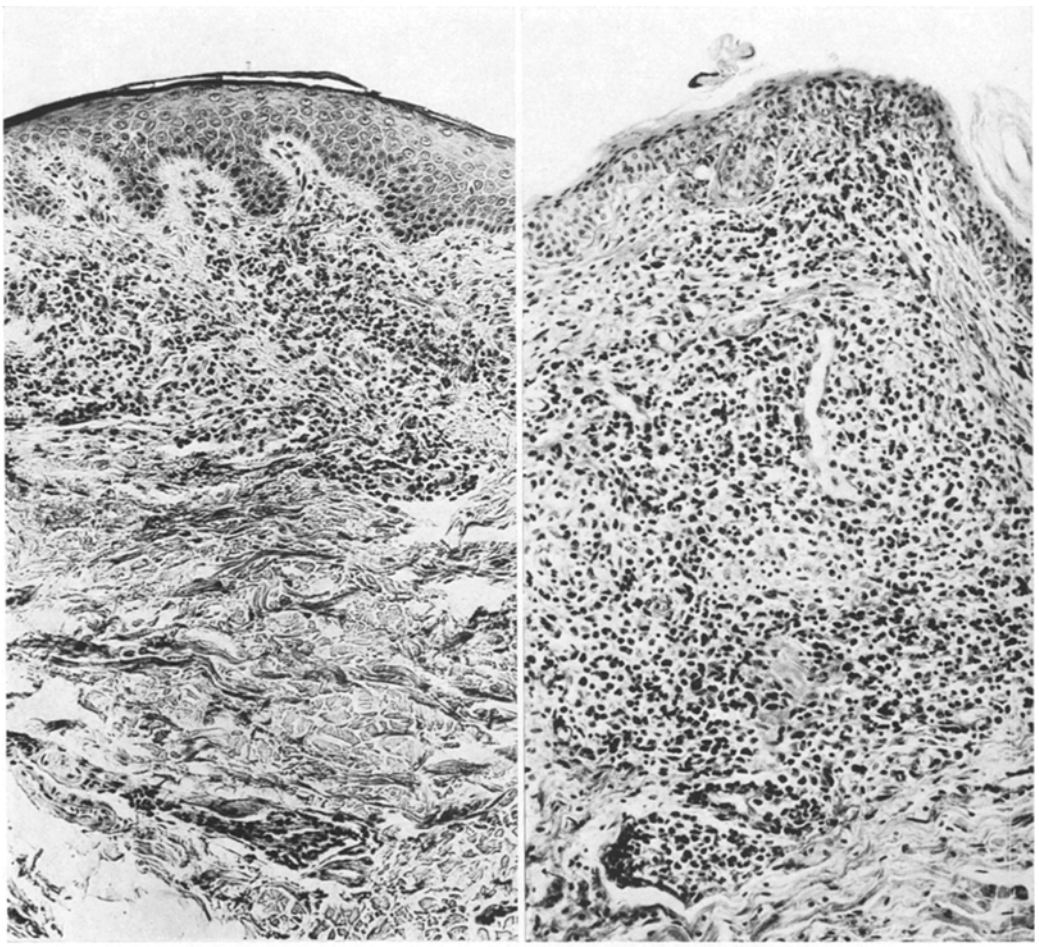

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Fig. 1. (a) Biopsy material obtained a year before death. A band-like cellular infiltrate in the stratum subpapillare. (b) Autopsy material. Tumor infiltration in the whole width of the dermis continuing into the subcutis. H & E. ×140

sized cell variants were of lymphocyte-like appearance. Some of the larger cells were monstrous. All of the cells had a polymorphic nucleus, which was variously folded, indented, or layered serpentinely and had moderately or very dense chromatin. The large basophilic nucleoli were very prominent. The mostly narrow cytoplasmic rim was basophilic or amphophilic and sometimes vacuolated. In 61% of the atypical cells it showed a fine granular and in 6% a coarse granular PAS positivity (Fig. 3; the PAS reaction was carried out on intravital blood smears that had already been stained according to Pappenheim).

Autopsy Findings

There were numerous small and coarse nodular, sometimes ulcerated skin infiltrates, mostly on the patient's face and trunk. Erythroderma and poikiloderma

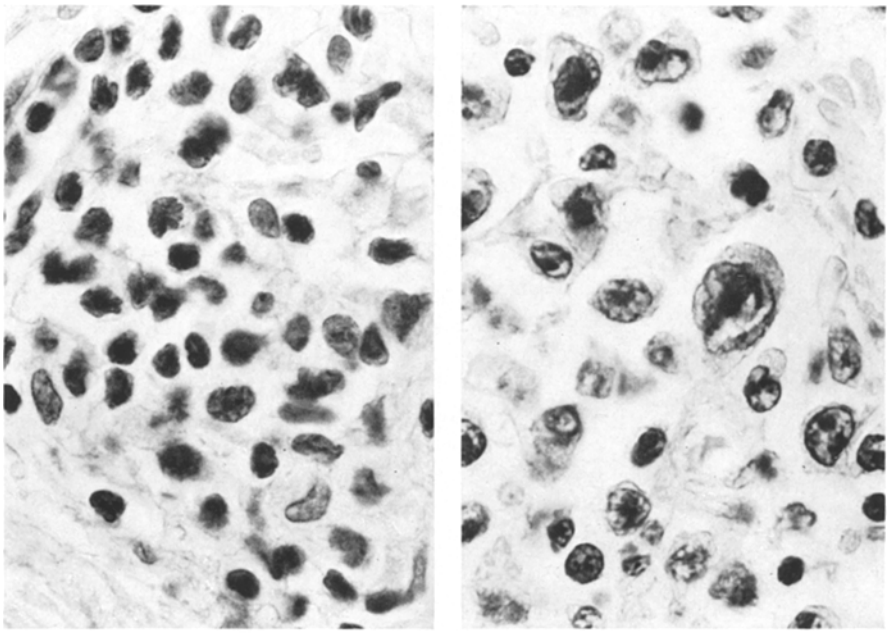

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Fig. 2. (a) Detail of Fig. 1a. Atypical, small and medium-sized lymphocyte-like cells and larger cells with bizarrely shaped nuclei. (b) Detail of Fig. 1b. Medium-sized blast-like cells with light to moderately dense chromatin and prominent nucleoli, and a monstrous cell with irregular nuclear surface. H & E. ×880

were found. There was generalized enlargement of the lymph nodes; their cut surface was grayish white and moist. The spleen was enlarged (810 g); the cut surface was dark violet and soft. There was moderately severe hepatomegaly (2,040 g); macroscopically, m. f. infiltrates could not be recognized. The bone marrow revealed generalized multifocal infiltration. The cause of death was cardiac and circulatory failure.

Histology and Cytology

Skin of the temple (Fig. 1b): In some areas cell-rich infiltrates occupied the whole width of the dermis and continued into the subcutis. There were also smaller, irregularly but sharply defined infiltrates beneath the epidermis and in middle layers of the dermis. They were often found next to vessels or around nerves and cutaneous appendages. Within the infiltrates the collagenous and elastic fiber structure was destroyed and replaced by a fine or moderately coarse network of elastic fibers.

Cytologically, one type of cell predominated in the infiltrates. In sections this cell was $1^1/_2$ to 3 times larger than an erythrocyte. The nucleus was large and vesicular, its edge was creased. One or two, sometimes more, oversized basophilic

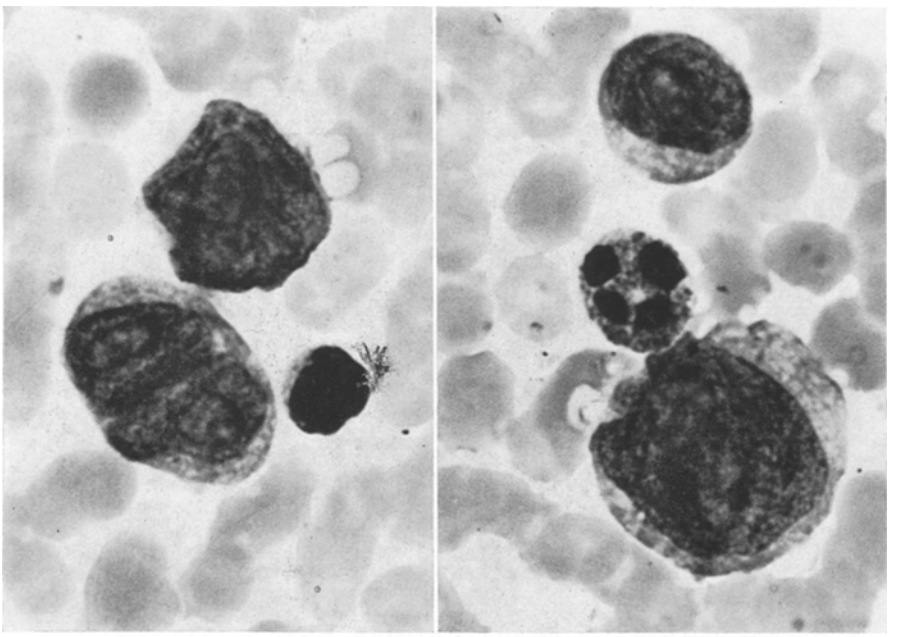

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Fig. 3. Peripheral blood smear obtained shortly before death. Medium-sized and large (monstrous) atypical cells, one lymphocyte in (a), and one eosinphilic granulocyte in (b). Note the irregular, variously folded or serpentinely layered nucleus of the tumor cells (convoluted type), particularly in (a). Pappenheim. ×1,400

nucleoli were in marked contrast to the light chromatin (Fig. 2b). Besides these atypical cells, there were loosely distributed or focally grouped oversized cells, some of which were to three times bigger than the previously described cells. This second type of cell had one or two to three large polymorphic nuclei with dense chromatin and nucleoli which were less prominent than those of the medium-sized tumor cells. The cytoplasm of both types of atypical cell was moderately or strongly basophilic. The tumor cells were PAS negative. In contrast to the mycotic cell forms, an accompanying inflammatory reaction was seen in the background.

Mycotic infiltrates like those in the skin were also found in the enlarged lymph nodes, periportal regions of the liver, the bone marrow, septal and pleural-subpleural regions of the lungs, and mainly paravascular regions of the kidneys. The red and white pulp of the spleen revealed diffuse infiltration. There were also infiltrates in subepicardial soft tissue, the submandibular glands, and the prostate.

In less severely infiltrated lymph nodes, several lymph follicles were intact. However, the adjoining paracortical area was densely infiltrated with myoctic cells. Elsewhere, the lymph node structure was totally destroyed by myoctic infiltrates, which continued into the paranodular soft tissue. The palatine tonsils were not affected. In the bone marrow, disseminated, sometimes large focal infiltrates were found in poorly defined areas, often near the spongiosa. The hematopoietic marrow showed a moderate increase in the number of myelopoietic cells

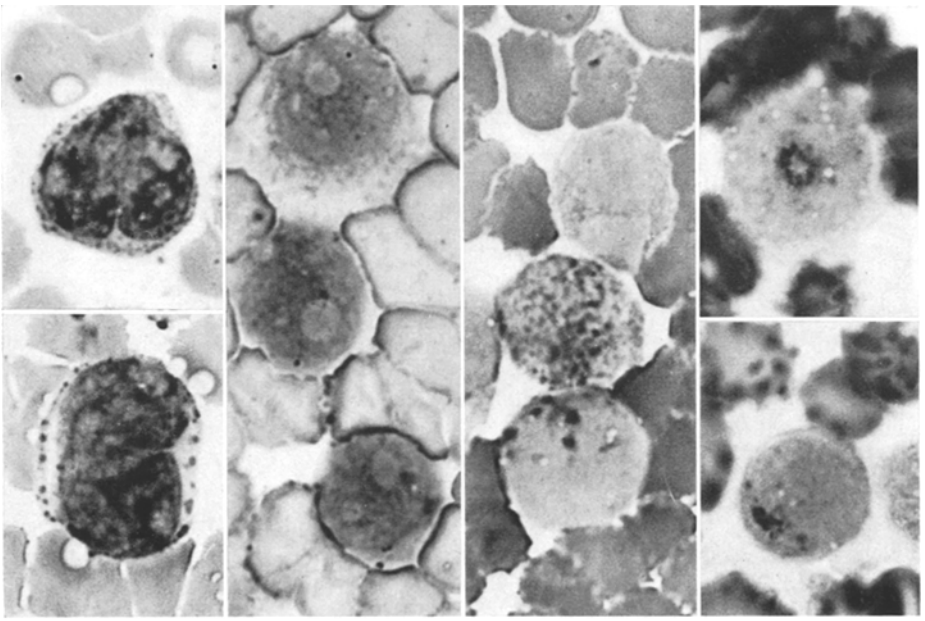

Fig. 4. (a) Peripheral blood smear of Fig. 5. PAS reaction, performed after Pappenheim staining. Fine (above) and coarse granules at the margin of the cytoplasm im tumor cells. (b—d) Cadaveric blood smears. (b) Nonspecific esterase (alpha-naphthyl-acetate-esterase, diazonium salt pararosaniline). Weak positivity in the form of small granules, some of them projected on the nucleus. (c) Acid phosphatase, diazonium salt pararosaniline. Coarse granules in the cytoplasm of a tumor cell (bottom) and disseminated fine and medium-sized granules in a monocyte (middle). (d) Staining as in (c). Two tumor cells. Ring-shaped precipitation in the one above, patchy reaction in the one below. (a—d) ×1,400

with eosinophilia. The number of erythropoietic cells was reduced. There was slight plasmacytosis.

Compared to the preterminal, clinical differential blood picture, the cadaveric blood smear contained almost twice as many atypical cells (67.6%) per 1,000 differentiated cells; the medium-sized forms with a diameter of approximately 15 μm were predominant. Cytochemically, nonspecific esterase (alpha-naphthyl-acetate-esterase, pararosaniline) and acid phosphatase (Fig. 4) could be demonstrated with about equal frequency in the atypical cells. 70% of the cells showed a weakly positive nonspecific esterase reaction with a mostly delicate, partly coarse granular precipitation of the stain. The monocytes were set off by a diffuse intense staining of the cytoplasm. 80% of the atypical cells were acid phosphatase positive with a mostly fine granular staining of the cytoplasm. A coarse granular or patchy precipitation of the stain was found in a paranuclear area in 12% of the atypical cells in cadaveric blood smears and in 31% of the atypical mononuclear cells in lymph node imprints. The peroxidase and naphthol-AS-D-chloracetate-esterase reactions were negative in the tumor cells (cytochemical enzyme reactions performed according to the methods of Leder, 1967).

Discussion

The current view is that mycosis fungoides is a malignant lymphatic neoplasm. It is distinguished from most other malignant lymphomas by the early, typical intracutaneous manifestation in the upper dermal layers. In the terminal stage, when tumor formation occurs, other malignant lymphomas may be simulated: lymphogranulomatosis, lymphosarcoma, and the reticulosarcoma of the old nomenclature (Lund, 1957; Cyr *et al.*, 1966; Lever, 1967; Flaxman *et al.*, 1971; Oota and Yamaguchi, 1973; Rappaport and Thomas, 1974).

In the terminal stage of our case, medium-sized and larger cells with a pale nucleus and folded nuclear edge dominated the cytology of the intracutaneous and organic infiltrates. With their large prominent nucleoli, these cells resembled Hodgkin cells or transformed lymphocytes (cf. Biberfeld, 1971), which Dameshek (1963) also called immunoblasts. When the cells had two or more nuclei they were reminiscent of Sternberg cells (Rosas-Uribe *et al.*, 1974) or polynuclear stimulated lymphocytes, which Lukes *et al.* (1969) observed in organic infiltrates in cases of infectious mononucleosis. Morphologically related to these immunoblast-like, smaller cell forms, there was a type of cell with an oversized, polymorphic, hyperchromatic nucleus and indistinct nucleoli. Such cells were first described by Lutzner and Jordan (1968) as "cerebriform cells", which they found in cases of Sézary syndrome.

Earlier, on the basis of the histological and cytological findings presented above, this case would have been diagnosed as large cell reticulosarcoma, or—due to the leukemic blood picture—large cell basophilic reticulosis (Lennert, 1964). As Stein *et al.* (1974) showed, most cases of reticulosarcoma of the old nomenclature are derived from transformed lymphocytes, which may be called immunoblasts. So tumors of these cells can be called immunoblastic sarcoma (Lennert, 1967; Lennert *et al.*, 1975; Lukes and Collins, 1975). According to the results of exhaustive comparative cytomorphological, immunological, and immunochemical studies by these authors, the vast majority of the cases of immunoblastic sarcoma can probably be ascribed to lymphocytes of the B cell system. In our case we found no indirect morphological indication that the tumor cells were of B cell nature, such as intranuclear or intracytoplasmic globular inclusions signifying immunoglobulin production. On the other hand, the pattern of infiltration of the lymph nodes and the cytology of the tumor cells could be indications of the T cell nature of this tumor. The less severely infiltrated (paratracheal) lymph nodes showed a densely infiltrated paracortical area (T cell region) and intact follicles. Many of the tumor cells were similar to those of T cell lymphoma of the convoluted cell type (Lukes and Collins, 1974, 1975). However, it is impossible to make a distinction between the very rare immunoblastic sarcomas of the T cell system (Lennert *et al.*, 1974, 1975) and those of the B cell system using routine morphological criteria alone (Lukes and Collins, 1975).

There is some evidence that m. f. is a T cell lymphoma. Through immunological and cytochemical studies of Sézary cells, numerous researches have demonstrated the T cell character of Sézary syndrome (cf. Edelson *et al.*, 1974a; Zucker-Franklin *et al.*, 1974; Ding *et al.*, 1975), which is a special, erythrodermic and leukemic variant of m. f. (Lutzner *et al.*, 1971; Rosas-Uribe *et al.*, 1974; Zucker-Franklin, 1974; Lennert, 1975). Sandbank and Ben-Bassat (1971) have shown that Sézary cells are morphologically identical to m. f. cells. The findings of Edelson *et al.*

(1974 b) on the cells of tumor infiltrates in cases of m. f. correspond to those recently reported by Rabinowitz *et al.* (1975). The latter authors demonstrated that at least 72% of the tumor cells formed spontaneous rosettes with sheep erythrocytes, which is a characteristic of T cells.

Our cytochemical findings on the tumor cells found in the peripheral blood of this patient are analogous with the observations of other authors on cases of Sézary syndrome (Löffler, 1973; Löffler *et al.*, 1974; Flandrin and Brouet, 1975). Further, in lymph node imprints, 31% of the tumor cells of this case and 51% of those of another case of m. f. with tumor formation in our autopsy material showed a coarse granular or patchy acid phosphatase reaction in a paranuclear area. This pattern is not specific. However, it is a typical cytochemical characteristic of a T cell lymphoma (Catovsky *et al.*, 1974; Catovsky, 1975).

Taking the findings of other authors on m. f. and Sézary syndrome into consideration, some of our findings suggest that the immunoblastic sarcoma which developed in this case of m. f. could also be of T cell nature.

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