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Malignant Histiocytosis with Chronic Course

Ultrastructural and Ultrastructural Cytochemical Studies

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Summary. Four cases of malignant histiocytosis with leukemic manifestations and chronic course were reported. Light microscopic, ultrastructural and ultrastructural cytochemical details of these atypical cells were demonstrated. Ultrastructurally these cells resembled hairy cells most closely among the known varieties of leukemic cells. However, ribosome-lamella complexes were not found and some atypical cells had a few short cytoplasmic projections. In addition, tartrate-resistant acid phosphatase was absent from these cells. We speculate that this leukemic reticuloendotheliosis with a chronic course seen in Japan seems to be analogous to malignant histiocytosis with massive splenomegaly reported by Vardiman et al.

Key words: Chronic malignant histiocytosis – Hairy cell leukemia – Tartrate-resistant acid phosphatase – Ultrastructural cytochemistry – Ribosome-lamella complex.

Introduction

The term "leukemic reticuloendotheliosis (LRE)" has been used in the literature to describe variable disease conditions throughout the world. It is mainly applied in America and Europe to a disease with a chronic course, presenting with massive splenomegaly, anemia, little or no lymph node involvement and neoplastic cells of characteristic morphology in the peripheral blood and bone marrow. These ard found under phase contrast microscopy to have numerous filamentous cytoplasmic projections. "Hairy cell leukemia" is therefore often used

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as a synonym for this condition (Catovsky et al., 1974; Haak et al., 1974; Golomb et al., 1975; Schmalzl et al., 1975; Burke et al., 1976; Scheinberg et al., 1976; Katayama and Schneider, 1977). In Japan however, the term LRE is still used in a somewhat wider sense and the disease is divided into acute and chronic types (Iijima, 1973). Acute LRE also appears to be heterogeneous. Acute monocytic leukemia of Schilling type, malignant histiocytosis, and even cases of undifferentiated (stem cell) leukemia may be occasionally classified into this category. A more or less chronic form of LRE is not very rare in Japan, but the chronic LRE which seems to roughly correspond to hairy cell leukemia is extremely rare. That form of LRE with a relatively prolonged course which is less rare than hairy cell leukemia in Japan seems to correspond roughly to "malignant histiocytosis with massive splenomegaly in asymptomatic patients" reported by Vardiman et al. (1975).

Ultrastructurally, hairy cells are characterized by many slender cytoplasmic projections and are often found to have cellular inclusions described as ribosome-lamella complexes (Katayama et al., 1972a, b; Catovsky et al., 1974; Daniel and Flandrin, 1974; Fabre and Delsol, 1974; Haegert et al., 1974; Schnitzer and Kass, 1974; Debusscher et al., 1975; King et al., 1975; Burke et al., 1976; Rozenszajn et al., 1976; Diebold et al., 1977; Katayama and Schneider, 1977; Utsinger et al., 1977). However, the latter structures have been also observed in the neoplastic cells of patients with other types of hematopoietic malignancy, namely chronic lymphatic leukemia, lymphosarcoma cell leukemia, macroglobulinemia, monoblastic leukemia (Zucker-Franklin, 1963; Anday et al., 1973; Bockman et al., 1974; Djaldetti et al., 1974; Brunning and Parkin, 1975; Cawley et al., 1975; Henry, 1975; Woessner and Rozman, 1976; Katayama and Schneider, 1977), and in adenoma cells of the human adrenal cortex (Hoshino, 1969), and also in human paraganglioma (Nabarra et al., 1977).

A tartrate-resistant isoenzyme of acid phosphatase found in Golgi saccules and the cytoplasmic vesicles of hairy cells has also been shown to be specific and is now used as a cytoplasmic marker for the diagnosis of this disease (Katayama et al., 1972; Yam et al., 1972).

In the present paper, four cases of malignant histiocytosis with leukemic manifestations and a relatively prolonged clinical course are presented, with special emphasis on the ultrastructural and ultrastructural cytochemical differences between hairy cells and the atypical cells of chronic LRE.

Case Reports

Case 1. A 29-year-old man was admitted with the principle complaints of nasal bleeding, general malaise and high fever. A huge spleen, pancytopenia and hypercellular bone marrow with maturation arest were the most striking findings in physical and laboratory examinations on admission. Four months later, splenectomy (2,500 g) and liver biopsy were performed, when 10% of atypical lymphoid cells was seen in the peripheral blood and 9.2% in the bone marrow. Six months after the splenectomy, he was readmitted because of progressive hepatomegaly and a leukemic blood picture with more than 90% of atypical lymphoid cells in both the peripheral blood and bone marrow. Complete remission was obtained four months later, and lasted for 6 months. However, there was marked hepatomegaly and progressive increase in atypical cells, and he failed to obtain complete remission

in spite of chemotherapy. He died of alimentary hemorrhage 2 years and 4 months after the onset.

Case 2. A 16-year-old female student complained of fullness in the abdomen. She was found to have splenomegaly, anemia, leukopenia and thrombocytopenia. A splenectomy and a liver biopsy were performed; the spleen weighted 2,300 g. After splenectomy, her peripheral blood counts returned towards normal. Six months after splenectomy, she developed hepatomegaly and a peripheral smear revealed the lymphoid cells. In spite of combination chemotherapy, she developed leukocytosis (leukocyte count was 109,000/mm^3 with 68% lymphocytic-reticulum cells) jaundice and hemorrhage after 1 year. She died 1 year and 9 months after the onset.

Case 3. A 28-year-old female was admitted because of splenomegaly and pancytopenia. After a splenectomy (2,900 g) and a liver biopsy, she had had no symptoms for 1 year and 6 months. She was readmitted because of swelling of the left cervical lymph nodes, anemia and 31% atypical cells in the bone marrow. Lymph node biopsy was performed and she was treated with VEMP. She was discharged after complete remission was obtained and felt well for 1 year, after which fever, anemia and 81% atypical cells, but atypical cells in the bone marrow appeared. Combination therapy (BOMP) was started and atypical cells decreased. She died, however, from cerebral hemorrhage 3 years and 8 months after the onset.

Case 4. A 23-year-old man complained of fullness in the left lower part of the abdomen. Physical examination revealed a huge spleen filling the entire left side of the abdomen. A bone marrow aspirate contained some atypical cells could not be found in the peripheral blood. Two months later, atypical cells also appeared in the peripheral blood, and splenectomy (2,000 g) and liver biopsy were performed. Combination chemotherapy (VEMP) was also carried out for two months. He was discharged and is asymptomatic at present without special therapy for 1 year and 2 months, although atypical cells are now found in the bone marrow, but not in the peripheral blood.

Materials and Methods

All peripheral blood specimens and bone marrow aspirations were stained with May-Giemsa. The peroxidase reaction was performed as a diagnostic test. Bone marrow aspirations and/or peripheral blood samples of cases 1 and 4, lymph nodes of case 3, and spleen and liver of case 4 were used for electron microscopy. These samples were fixed in cold 2.5% glutaraldehyde and 2.0% paraformaldehyde buffered at pH 7.2 with 0.05 M phosphate buffer and/or cacodylate buffer. Samples were then washed with phosphate and/or cacodylate buffer. Peroxidase reaction was applied to two blood samples (cases 1 and 4) and spleen of case 4. They were incubated first for 30 min in Karnovsky's solution without hydrogen peroxide, then in complete Karnovsky's solution containing 5 mg of diaminobezidine in 10 ml of Tris-HCl buffer, with 0.01% hydrogen peroxide, at room temperature, also for 30 min. Cytochemical demonstration of acid phosphatase activity and the tartrate-resistant acid phosphatase isoenzyme, were performed according to the methods of Gomori (1952) and Katayama et al. (1972b). Two blood samples (cases 1 and 4) and the spleen of case 4 were used for the former activity and case 4 (blood and spleen) was used for the latter activity. For the latter, naphthol AS-BI phosphoric acid was used as substrate for Na-β-glycerophosphate of Gomori's medium and samples were incubated in each medium with and without lead tartrate, as described by Katayama et al. All ultrastructural samples were then postfixed for 2 h in cold 1% osmium tetroxide buffered with phosphate and/or cacodylate. After dehydration in graded series of ethanol solutions, the samples were embedded in Epon. Ultrathin sections were cut on an LKB Ultratome and a Porter-Blum ultramicrotome, and unstained thin sections and thin sections stained with uranyl acetate and lead compounds were then examined with Hitachi 12 and 12A electron microscopes. For light microscopy, paraffin blocks of the biopsies of spleens and livers of four cases, biopsy lymph nodes of case 3, and autopsy specimens of three cases (cases 1, 2 and 3) were obtained. In addition, blood samples of one patient (case 4) were also examined with phase contrast microscopy.

Results

Peripheral Blood and Bone Marrow. The atypical cells were large and had gray-blue cytoplasm. The nuclei were irregular in outline and very often folded, and had less condensed and finer chromatin than the lymphocytes. Some nucleoli were conspicuous, but others were indistinct. The cytoplasm often contained azurophilic granules (Fig. 1). The peroxidase reaction was negative in all cases. By phase contrast microscopy some cells were seen to have numerous cytoplasmic projections but others had only a few. These projections were usually short and varied in width. Their nuclear membranes were thick, and small mitochondria were moderate in number (case 4).

Spleen. Macroscopically, the spleens had tense and smooth capsules. The cut surface was dark red in color. None contained circumscribed tumor nodules. Light microscopically, the white pulp was atrophic with diminished germinal centers in all cases. The typical cells diffusely infiltrated the red pulp, especially in the splenic cords which were somewhat fibrous in areas. The infiltrating cells were larger than lymphocytes and their nuclei had thick nuclear membrane and prominent nucleoli. Plasma cells, mature lymphocytes and few or moderate numbers of eosinophils were seen in all cases. Mitoses were only occasionally encountered in all four cases (Fig. 2). Erythrophagocytosis was rare in all cases. Some giant cells were present in case 1.

Liver. There was infiltration within the sinusoids by the atypical lymphoid cells, and focal aggregates of these cells were seen within the portal areas in three cases but not in case 2. The mode of infiltration of the atypical cells was that of a leukemia (Fig. 3). The liver of case 2 showed only mild infiltration of lymphocytes within the portal areas.

Lymph Nodes (Case 2). The architecture of these lymph nodes had been diffusely replaced by atypical cells. These atypical cells were large and had clear cytoplasm. They were similar to the proliferating cells of reticulum cell sarcoma with frequent indentations of the nuclei. Mitoses were quite often seen (Fig. 4).

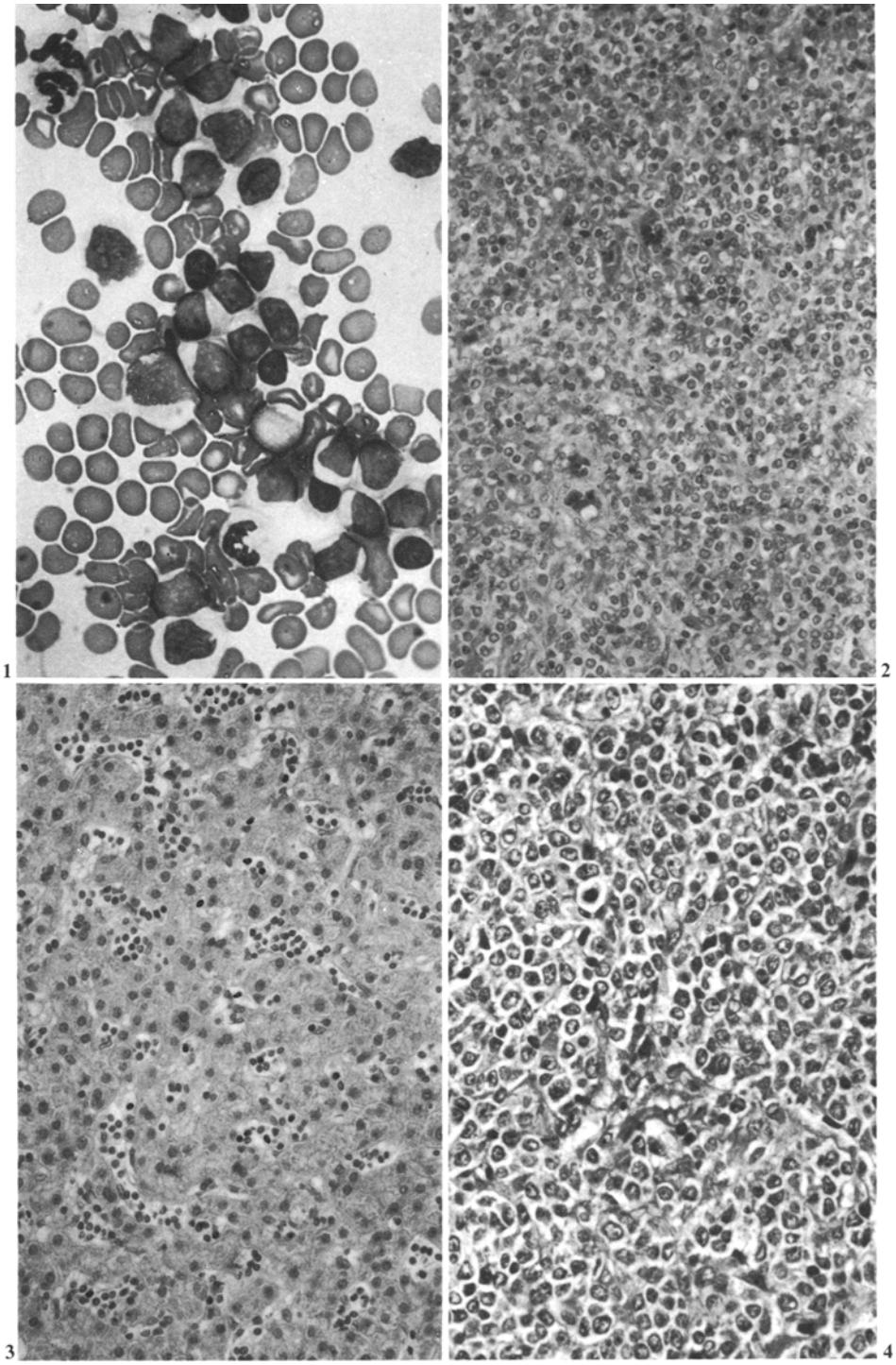
Autopsy Results. Postmortem examination was performed in three cases (cases 1, 2 and 3). Infiltration of atypical cells was scarce due to the effects of chemotherapy, and the patients appearently died of overwhelming infections of various organs.

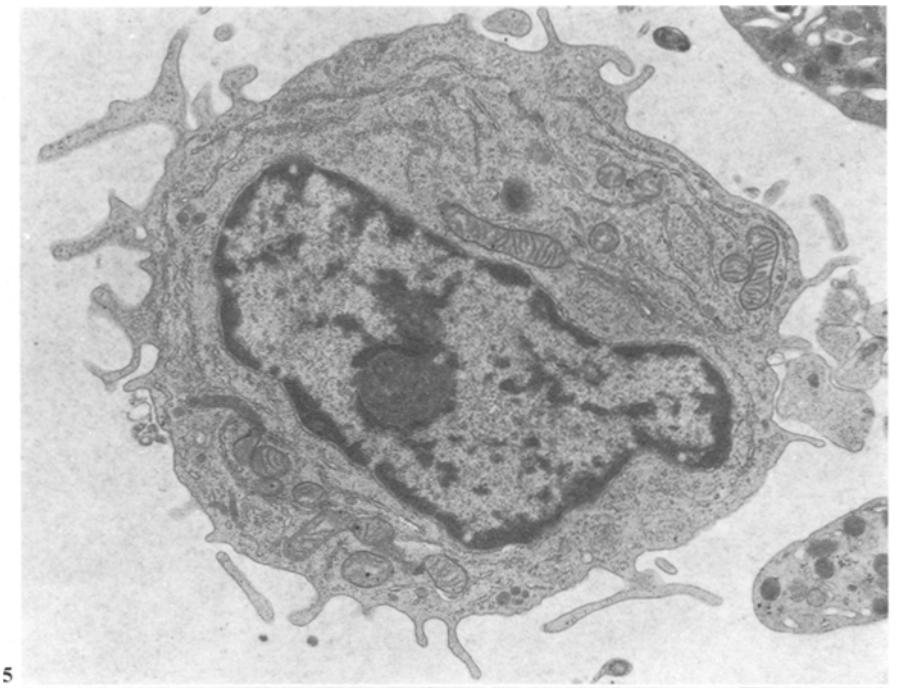
Fig. 1. Peripheral blood of case 2. Large atypical cells are seen. May-Giemsa. × 560

Fig. 2. Spleen of case 3. Many atypical cells infiltrate diffusely. Hematoxylin-eosin. × 260

Fig. 3. Liver of case 3. The pattern of infiltration of the atypical cells is intrasinusoidal and is identical to that of a leukemia. Hematoxylin-eosin. × 220

Fig. 4. Lymph node of case 3. The lymph node is filled with atypical cells. Hematoxylin-eosin. × 330





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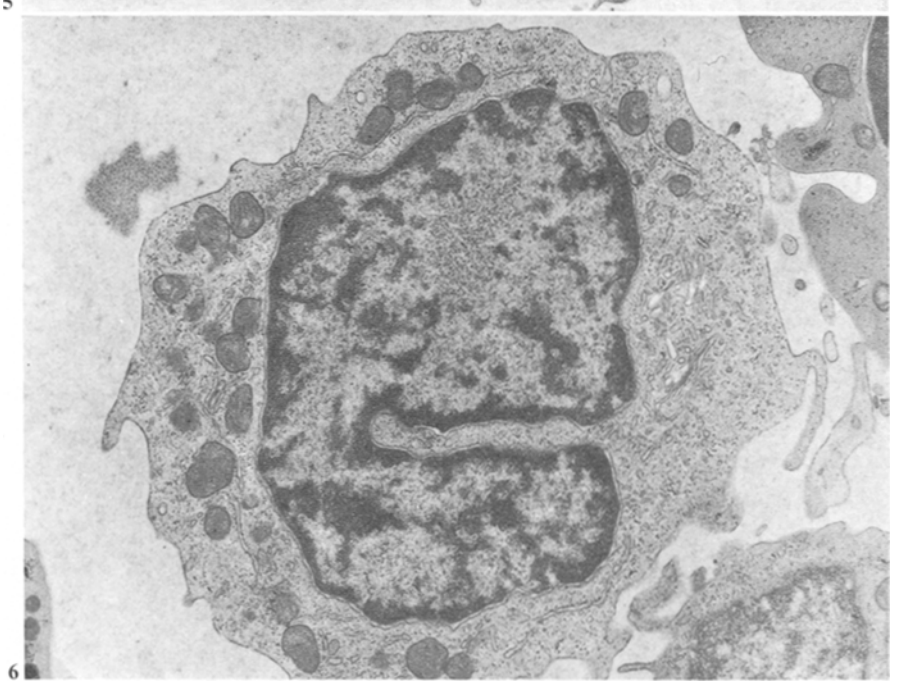

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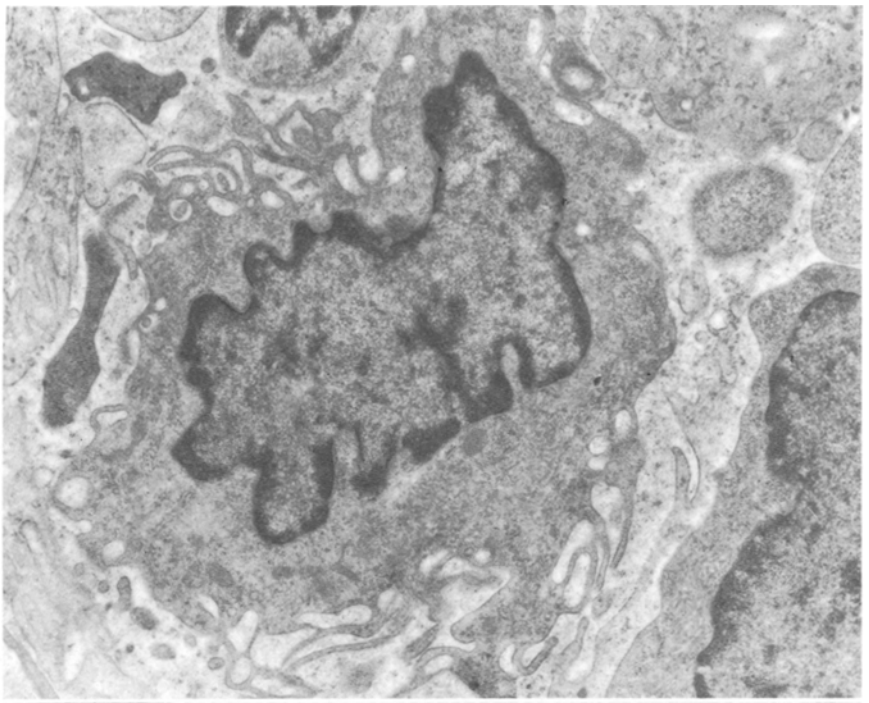
Fig. 5. Case 1. An atypical cell in the bone marrow with long and slender cytoplasmic projections. ×11,000

Fig. 6. Case 1. An atypical cell in the bone marrow with a few cytoplasmic projections. ×12,000



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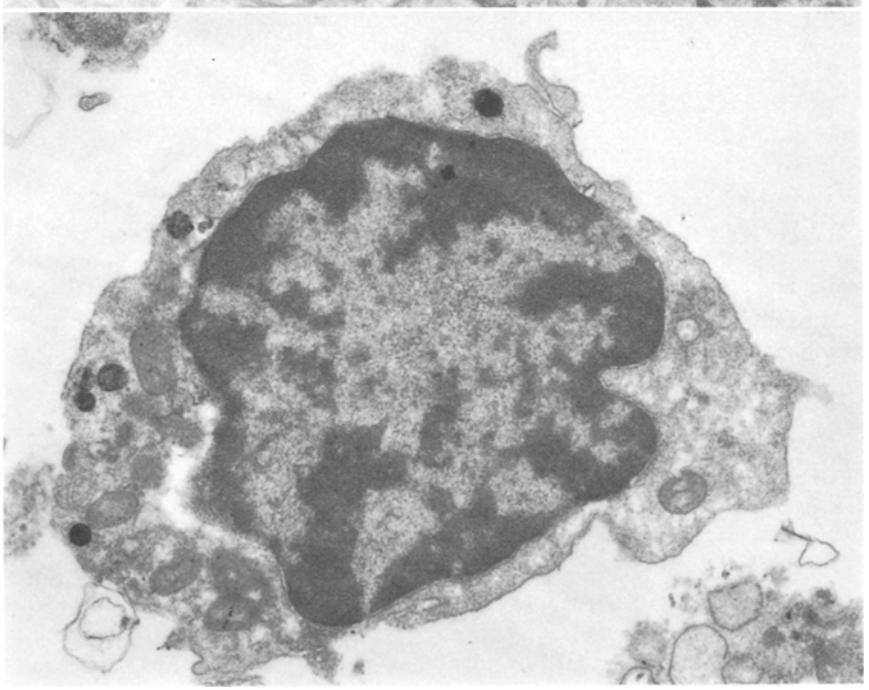

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Fig. 7. Case 3. An atypical cell in the lymph node with many long and slender projections. × 12,000

Fig. 8. Case 4. Acid phosphatase is positive in lysosomes of an atypical cell in the bone marrow by Gomori's method. × 12,500

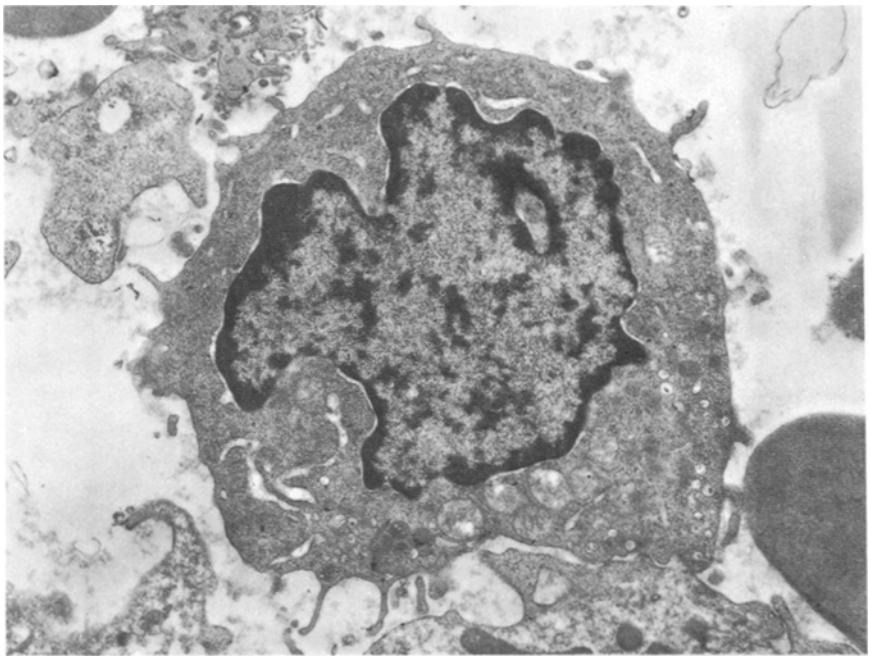

Fig. 9. An atypical cell in the bone marrow of case 4. Acid phosphatase is negative not only in the lysosomes but also in Golgi saccules by Katayama's method. ×10,500

Electron Microscopy. The atypical cells in the blood samples (cases 1 and 4) were mononuclear and irregular in outline, and had cytoplasmic projections. Some cells had many long and slender cytoplasmic projections (Fig. 5), others had short and slender projections, yet others had a few, short, wide projections (Fig. 6). The nuclei of these atypical cells were almost always irregular in outline and frequently showed deep indentations. Marginal chromatin in the nuclei appeared condensed and a conspicuous nucleolus was frequently visible. Oval mitochondria were moderate in number and free ribosomes and vesicles were abundant. Rough endoplasmic reticulum, Golgi apparatus and lysosomes could occasionally be found. Sometimes centrioles and fine fibrils were also observed. No ribosome-lamella complexes were observed in these atypical cells. The cells in the lymph nodes of case 3 were mixed with normal plasma cells, lymphocytes and histiocytes. These atypical cells were similar to those in the blood samples, but the cells which had long and slender cytoplasmic projections were present in larger numbers than in the blood (Fig. 7). The atypical cells were also found in the liver and spleen of case 4. Peroxidase reaction was negative in the two cases (cases 1 and 4) which were examined. Acid phosphatase was positive in some lysosomes of these atypical cells, by Gomori's method in cases 1 and 4 (Fig. 8) and the addition of tartrate in Gomori's medium inhibited this acid phosphatase reaction. On the other hand, acid phosphatase reaction was negative not only in the lysosomes, but also in Golgi saccules and cytoplasmic vesicles by the method using naphthol AS-BI phosphoric acid

as substrate in case 4 (Fig. 9). The addition of tartrate in Katayama's medium showed negative reaction in these atypical cells.

Discussion

The fine structure of hairy cells has been investigated by many investigators. They are characterized by many slender cytoplasmic projections, in particular numerous filamentous projections seen by phase contrast microscopy and by ribosome-lamella complexes in the cytoplasm. Although ribosoma-lamella complexes are found in patients with other hematologic disorders and are thus not specific for hairy cells, Katayama et al. (1977) report that ribosome-lamella complexes are not only more prevalent in hairy cells but also seen in a higher percentage of leukemic cells in LRE than in other hematologic disorders. In our cases, some cells had the slender projections, but others had a few wide and short projections. No ribosome-lamella complexes were observed in any case in this study. The nature of the hairy cells remains controversial. Some investigators (Haak et al., 1974; Haegert et al., 1974; Debusscher et al., 1975; Deegan et al., 1976; Vykoupil et al., 1976; Utsinger et al., 1977) have considered these cells are lymphocyte origin, but others (Fabre and Delsol, 1974; Jaffe et al., 1974; Golomb et al., 1975; King et al., 1975; Rozenszajn et al., 1976; Scheinberg et al., 1976; Seshadri et al., 1976) have favored a monocytic or histiocytic origin. The atypical cells in our cases resembled morphologically lymphocytes with regard to the nuclei and "reticulum cells" with regard to the cytoplasm. These cells ultrastructurally resembled "hairy cells" most among the known varieties of leukemic cells, apart from the presence of some wide and short cytoplasmic projections and the absence of ribosome-lamella complexes.

Cytochemically, peroxidase reaction was always negative in these atypical cells. Acid phosphatase reaction was positive in lysosomes by Gomori's method, but the addition of tartrate inhibited this reaction. All atypical cells were negative by the method which utilized naphtol AS-BI phosphoric acid as substrate. In particular, the tartrate-resistant acid phosphatase isoenzyme, which was regard as specific for hairy cells was negative in blood samples and the spleen of case 4.

Light microscopic observations of the spleen and the liver were similar to those of malignant histiocytosis with massive splenomegaly reported by Vardiman et al. (1975) although erythrophagocytosis was consistently present in their cases, while it was not a constant feature in our cases. Peripheral blood and bone marrow could not be compared. They described the initial manifestations of their malignant histiocytosis as massive splenomegaly without associated systemic symtoms, but whilst some of our cases had similar clinical manifestations, others had systemic symptoms other than splenomegaly. Both our report and theirs deal with only four cases each, and comparison of the age and sex distributions does not seem to be appropriate. Vardiman et al. did not carry out ultrastructural studies. It seems, nevertheless, that our cases roughly correspond to theirs on the basis of histological and clinical findings, though

there are some differences between the two group. We could reasonably assume that the ultrastructure of the proliferating cells of "malignant histiocytosis with massive splenomegaly in asymtomatic patients" would be similar to that seen in the cells of our cases. Further morphological, cytochemical and immunological investigations as well as a detailed clinical study are needed for the clarification of the interrelation between these chronic proliferative diseases of lymphoreticular series and of the origin of the leukemic cells.

References

Anday, G.J., Goodman, J.R., Tishkoff, G.H.: An unusual cytoplasmic ribosomal structure in pathologic lymphocytes. Blood **41**, 439–449 (1973)

Bockman, D.E., Wu, L.Y.F., Lawton, A.R., Cooper, M.D.: Altered fine structure of B lymphocytes correlated with defective terminal differentiation. Amer. J. Anat. **140**, 551–568 (1974)

Brunning, R.D., Parkin, J.: Ribosome-lamella complexes in neoplastic hematopoietic cells. Amer. J. Path. **79**, 565–578 (1975)

Burke, J.S., Mackay, B., Rappaport, H.: Hairy cell leukemia (leukemic reticuloendotheliosis) II. Ultrastructure of the spleen. Cancer (Philad.) **37**, 2267–2274 (1976)

Catovsky, D., Pettit, J.E., Galton, D.A.G., Spiers, A.S.D., Harrison, C.V.: Leukaemic reticuloendotheliosis ('hairy' cell leukaemia): A distinct clinico-pathological entity. Br. J. Haematol. **26**, 9–27 (1974)

Cawley, J.C., Emmines, J., Goldstone, A.H., Hamblin, T., Hough, D., Smith, J.L.: Distinctive cytoplasmic inclusions in chronic lymphocytic leukaemia. Europ. J. Cancer **11**, 91–92 (1975)

Daniel, M.T., Flandrin, G.: Fine structure of abnormal cells in hairy cell (tricholeukocytic) leukemia, with special reference to their in vitro phagocytic capacity. Lab. Invest. **30**, 1–8 (1974)

Debusscher, L., Bernheim, J.L., Collard-Rongé, E., Govaerts, A., Hooghe, R., Lejeune, F.J., Zeicher, M., Stryckmans, P.A.: Hairy cell leukemia: Functional, immunologic, kinetic, and ultrastructural characterization. Blood **46**, 495–507 (1975)

Deegan, M.J., Cossman, J., Chosney, B.T., Schnitzer, B.: Hairy cell leukemia: An immunologic and ultrastructural study. Cancer (Philad.) **38**, 1952–1961 (1976)

Diebold, J., Chomette, G., Reynès, M., Tricot, G.: La rate dans la leucémie à tricholeucocytes. Virchows Arch. A Path. Anat. and Histol. **372**, 325–336 (1977)

Djaldetti, M., Landau, M., Mandel, E.M., Har-Zaav, L., Lewinski, U.: Electron microscopic study of lymphosarcoma cell leukemia. Blut **29**, 210–215 (1974)

Fabre, J., Delsol, G.: Etude des lésions hépatiques de la "hairy cell leukemia". Virchows Arch. Abt. B Zellpath. **15**, 139–156 (1974)

Golomb, H.M., Braylan, R., Polliack, A.: "Hairy" cell leukaemia (leukaemic reticuloendotheliosis): A scanning electron microscopic study of eight cases. Br. J. Haematol. **29**, 455–460 (1975)

Gomori, G.: Microscopic histochemistry. Chicago: University of Chicago Press 1952

Haak, H.L., de Man, J.C.H., Hijmans, W., Knapp, W., Speck, B.: Further evidence for the lymphocytic nature of leukaemic reticuloendotheliosis (hairy-cell leukaemia). Br. J. Haematol. **27**, 31–38 (1974)

Haegert, D.G., Cawley, J.C., Collins, R.D., Flemans, R.J., Smith, J.L.: Leukaemic reticuloendotheliosis: A morphological and immunological study of four cases. J. clin. Path. **27**, 967–972 (1974)

Henry, K.: Electron microscopy in the non-Hodgkin's lymphomata. Br. J. Cancer (suppl. 2) **31**, 73–93 (1975)

Hoshino, M.: "Polysome-lamellae complex" in the adenoma cells of the human adrenal cortex. J. Ultrastruct. Res. **27**, 205–215 (1969)

Iijima, S.: Leukemic reticuloendotheliosis. In: Malignant diseases of the hematopoietic system. Gann monograph of cancer research. vol. 15, pp. 163. Eds. K. Akazaki, H. Rappaport, C.W. Berhard, J.M., Bennett, and E. Ishikawa. Tokyo: University of Tokyo Press 1973

Jaffe, E.S., Shevach, E.M., Frank, M.M., Green, I.: Leukemic reticuloendotheliosis: Presence of a receptor for cytophilic antibody. Amer. J. Med. **57**, 108–114 (1974)

Katayama, I., Li, C.Y., Yam, L.T.: Ultrastructural characteristics of the "hairy cells" of leukemic reticuloendotheliosis. Amer. J. Path. **67**, 361–370 (1972a)

Katayama, I., Li, C.Y., Yam, L.T.: Ultrastructural cytochemical demonstration of tartrate-resistant acid phosphatase isoenzyme activity in "hairy cells" of leukemic reticuloendotheliosis. Amer. J. Path. **69**, 471–482 (1972b)

Katayama, I., Schneider, G.B.: Further ultrastructural characterization of hairy cells of leukemic reticuloendotheliosis. Amer. J. Path. **86**, 163–182 (1977)

King, G.W., Hurtubise, P.E., Sagone, A.L.Jr., LoBuglio, A.F., Metz, E.N.: Leukemic reticuloendotheliosis: A study of the origin of the malignant cell. Amer. J. Med. **59**, 411–416 (1975)

Nabarra, B., Sonsino, E., Andrianarison, I.: Ultrastructure of a polysome-lamellae complex in a human paraganglioma. Amer. J. Path. **86**, 523–532 (1977)

Rozenszajn, L.A., Gutman, A., Radnay, J., David, E.B., Shoham, D.: A study of the nature of "hairy" cells, with emphasis on enzymatic markers. Amer. J. clin. Path. **66**, 432–441 (1976)

Scheinberg, M., Brenner, A.I., Sullivan, A.L., Cathcart, E.S., Katayama, I.: The heterogeneity of leukemic reticuloendotheliosis, "hairy cell leukemia": Evidence for its monocytic origin. Cancer (Philad.) **37**, 1302–1307 (1976)

Schmalzl, F., Huhn, D., Asamer, H., Braunsteiner, H.: Hairy cell leukemia ('leukemic reticuloendotheliosis'), reticulosarcoma, and monocytic leukemia: Cytochemical and ultrastructural investigations. Acta Haemat. **53**, 257–276 (1975)

Schnitzer, B., Kass, L.: Hairy-cell leukemia: A clinicopathologic and ultrastructural study. Amer. J. clin. Path. **61**, 176–187 (1974)

Seshadri, R.S., Brown, E.J., Zipursky, A.: Leukemic reticuloendotheliosis: A failure of monocyte production. New Eng. J. Med. **295**, 181–184 (1976)

Utsinger, P.D., Yount, W.J., Fuller, C.R., Logue, M.J., Orringer, E.P.: Hairy cell leukemia: B-lymphocyte and phagocytic properties. Blood **49**, 19–27 (1977)

Vardiman, J.W., Byrne, G.E.Jr., Rappaport, H.: Malignant histiocytosis with massive splenomegaly in asymptomatic patients: A possible chronic form of the disease. Cancer (Philad.) **36**, 419–427 (1975)

Vykoupil, K.F., Thiele, J., Georgii, A.: Hairy cell leukemia: Bone marrow findings in 24 patients. Virchows Arch. A Path. Anat. and Histol. **370**, 273–289 (1976)

Woessner, S., Rozman, C.: Ribosome-lamellae complex in chronic lymphatic leukaemia. Blut **33**, 23–28 (1976)

Yam, L.T., Li, C.Y., Finkel, H.E.: Leukemic reticuloendotheliosis: The role of tartrate-resistant acid phosphatase in diagnosis and splenectomy in treatment. Arch. intern. Med. **130**, 248–256 (1972)

Zucker-Franklin, D.: Virus-like particles in the lymphocytes of a patient with chronic lymphatic leukemia. Blood **21**, 509–512 (1963)

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