Leukemic Reticuloendotheliosis*

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To clarify the concept of so-called leukemic reticuloendotheliosis, pathological investigations of autopsy cases were performed, comparing with the neighboring pathological entities such as monocytic leukemia of the Naegeli-type, malignant lymphoma with tumoremia and myeloreticulosis accompanied with myelogenous leukemia. So-called leukemic reticuloendotheliosis can be divided into acute and chronic types. The acute type of leukemic reticuloendotheliosis is a variant of malignant lymphoma and its essential pathological feature is a diffuse, neoplastic proliferation of lymphatic reticulum cells in the lymphatic tissue. The disease is more or less frequently accompanied with a leukemic blood picture. In this connection it must be regarded as paralympathic leukemia. In the chronic type, morphological changes in the red pulp of the spleen are more dominant and these findings indicate that the primary lesion is in the spleen. Further investigations are, however, necessary to establish a logical relationship between the acute and chronic types.

The current confusion in concepts of 'leukemic reticuloendotheliosis'¹⁻¹⁴ has arisen from the disagreement in interpretations of the origin of the blood monocytes and of their relationship to the reticuloendothelial system. Moreover, as Rapaport¹⁵ has recently pointed out, the continued use of the term 'reticulum cell' for two entirely different cell types — one of which is a differentiated, free or fixed reticulum cell with specific functions, the other a pluripotential stem cell of mesenchymal nature — has obscured the views on various pathological conditions which take place in hemopoietic tissues. Akazaki^{16,17} and Kojima¹⁸ have clearly denied hemopoietic activities of the reticuloendothelial cells and proved distinct differences in the cytological character between the reticulum cells and blood monocytes. In this connection the concept of 'leukemic reticuloendotheliosis' becomes contradictory by itself and the term 'monocytic leukemia' must be limited in use to a leukemic state of the myelogenous blood monocytes, in other words, to the so-called Naegeli type of monocytic leukemia. In fact, however, we should like to present one rather larger group of leukemic conditions, which meets the following criteria, and we have no choice but to designate it as a sort of 'reticulum cell leukemia'. The criteria are as follows: 1) a definite number of pathologic

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cells appear constantly in the peripheral blood; 2) corresponding with the leukemic change of the peripheral blood, the infiltration of free pathologic cells is seen in organs, especially in the liver, spleen and lymphatic tissues; 3) the pathologic cells can neither be classified as granulocytes, blood monocytes nor as lymphocytes from the hematological and cytological viewpoints; 4) if possible, some attributes of the reticulum cell, such as phagocytosis, specific mobility, etc., are proved in the pathologic cells; 5) the proliferation of the pathologic cells in tissues is diffuse and makes no nodular lesion; and 6) other malignancies, and metabolic and infectious diseases can be excluded with sufficient evidence. The present report deals with the investigation of such problematic cases in order to clarify the category of the concept 'leukemic reticuloendotheliosis', by comparing with neighbouring pathological entities such as monocytic leukemia of the Naegeli type, malignant lymphoma with tumoremia and myeloreticulosis accompanied with myelogenous leukemia.

Leukemic Reticuloendotheliosis (Acute Type)

Most of the cases, which satisfy the above-mentioned criteria and are hereby designated as leukemic reticuloendotheliosis, are classified into the acute type with clinical courses of less than 6 months.

Case 1: 51-year-old male. Erythematous eruptions of the skin and pain in joints were noted at first, then swelling of the cervical, axillary and inguinal lymphnodes became manifest. Anemia was not severe, but the white blood cell count was 10,000–27,300 with ca. 85% abnormal reticulum cells. In autopsy findings, there was found systemic lymphadenopathy. The liver was 1,750 g, the spleen 280 g, and the kidneys 240 and 240 g in weight. Histological pictures were characterized by a diffuse hyperplasia of fixed reticulum cells and an infiltrative proliferation of free cells. The ground structure of the lymphnodes was modified by cellular hyperplasia, but was not intensively destroyed. In the spleen, infiltration of pathologic cells was most prominent in parafollicular areas.

Case 2: 53-year-old male. The illness began with splenomegaly and anorexia. One month later he had fever and the splenomegaly increased markedly. After a 2 months' clinical course the patient died. Red blood cell count was 4.8 million, Hb was 16.8 g/100 ml, white blood cell count was 1,400–36,000 with about 50% atypical reticulum cells. The liver was 1,320 g, the spleen 620 g, and the kidneys 130 and 150 g in weight. Moderate swelling was found in mediastinal, paratracheal, axillary, hepatic, retroperitoneal and mesenteric lymphnodes. The bone marrow was not severely affected by the infiltration of pathologic cells, and the changes of the spleen was also of the secondary nature. In the lymphnodes the normal architecture was fundamentally maintained, even though they were occupied by marked diffuse hyperplasia of fixed reticulum cells with proliferation of reticulin fibers.

Case 3: 29-year-old male. The whole clinical course was 3 months. The chief complaints of the patient were lymphadenopathy and splenomegaly. Red blood cell count was 3.3–4.3 million, white blood cell count was 10,600–61,900 with 80–90% pathologic cells. The liver was 2,500 g, the spleen 560 g, and the kidneys 250 and 280 g in weight. The swelling of the mesenterial, retroperitoneal, pancreatic, mediastinal, axillary and

cervical glands was rather systemic and moderate. They were occupied by diffuse hyperplasia of polygonal and larger fixed cells, in which free pathologic cells were recognizable. Mature reticulum cells (macrophages) remained independent of proliferating fixed and free cells. The leukemic infiltration of free pathologic cells was found in the bone marrow, spleen, liver and both kidneys.

Case 4: 47-year-old male. The clinical course was 4 months. Since one month before death the blood picture became leukemic with an appearance of atypical reticulum cells, which showed marked phagocytic activity. Swelling of the lymphnodes was found in the neck, retroperitoneum and mesenterium. Intensive leukemic infiltration attacked the liver, spleen and kidneys. The lymphnodes became hyperplastic, particularly due to the proliferation of the fixed phagocytic cell elements.

Case 5: 29-year-old female. The sickness began with hemorrhagic diathesis, chest pain and moderate fever. Red blood cell count was ca. 3.0–4.0 million, and white blood cell count was 27,300–800 with 10–80% of pathologic cells. In autopsy findings the liver was 2,100 g, the spleen, 1,385 g and the kidneys were 200 and 220 g. Cervical, retroperitoneal and peripancreatic lymphnodes were moderately swollen and histologically an infiltrative proliferation of larger free cells was prominent. The bone marrow was relatively free from infiltration of pathologic cells.

Pathologic hyperplasia of the reticulum cells in the lymphnodes as the primary lesion is common to the above-mentioned five cases. Moreover, in all cases, the clinical course is acute and less than 6 months. The blood picture is definitely leukemic, but anemia not so severe. The pathologic cells appearing in the peripheral blood are mononuclear and mostly abundant in cytoplasm, which is positive for acid phosphatase, negative for alkaline phosphatase and weakly positive for PAS staining. The oxydase and peroxydase reactions are negative. Sometimes small vacuoles are included in the cytoplasm and occasionally phagocytic activity is positive. These cytological attributes of the pathologic cells indicate an intimate relationship of the pathologic cells to the lymphatic reticulum cells. Morphological changes in the lymphnodes are characterized by diffuse, non-nodular hyperplasia of the reticulum cells without severe destruction or modification of the ground architecture of the lymphatic tissue, and the diffuse hyperplasia of the reticulum cells reveals two different, transitional phases; i.e., fixed cell type proliferation and free cell type infiltrative proliferation. The two phases coexist in one lymphnode in various ratios and they are different from case to case. In general, in the cases in which the fixed cell type proliferation is prominent, leukemic changes are not remarkable. On the other hand, if the free cell type infiltrative proliferation is dominant in the lymphnodes, splenomegaly develops markedly and the blood picture becomes highly leukemic. Mature reticulum cells or fixed and free macrophages remain in proliferative foci in the lymphnodes and also in other organs. No transition is observed between such mature reticulum cells and the pathologic proliferating reticulum cells. The diffuse hyperplasia of the pathologic reticulum cells in the lymphatic tissue must therefore be regarded as neoplastic in nature, and not as a systemic

hyperplasia of unknown etiology.

Malignant Lymphoma with Leukemic Blood Picture

In acute leukemic reticuloendotheliosis, the primary lesion of pathological proliferation of the reticulum cells is always found in the lymphatic tissue as mentioned above, and the nature of the proliferation seems to be neoplastic. From these findings the questions may arise as to whether the leukemic reticuloendotheliosis can be distinctly differentiated from the malignant lymphoma, especially from the reticulum cell sarcoma with leukemic blood picture.^{19,20} We can point out what makes the leukemic reticuloendotheliosis differ from the leukemic reticulum cell sarcoma, from the facts that 1) the normal architecture of the lymphatic tissue is not or little destroyed, 2) the proliferation of the reticulum cells is mainly diffuse and no definitive nodular lesion develops, and 3) metastatic foci in various organs are infiltrative as seen in other types of leukemia. But the border line between the leukemic reticuloendotheliosis and the leukemic reticulum cell sarcoma is not always clear. We have some border-line cases as shown in Table 1.

Leukemic Reticuloendotheliosis (Chronic Type)

Most cases of leukemic reticuloendotheliosis belong to acute types and are

TABLE 1. *Malignant lymphoma with leukemic picture*

No.	Sex	Age (yr.)	Duration (month)	RBC (million)	WBC	Atypical cell	Liver (g)	Spleen (g)	Histology of the lymphnodes
1	Male	49	5	3,6-3,9	10,200 -57,800	41-87%	2,350	990	Reticulum cell sarcoma
2	Female	19	5	3,2-3,4	3,000 -5,000	2-5%	1,000	180	Reticulosis terminated as reticulo-sarcoma
3	Female	50	7	—	18,600 -202,000	40-90%	1,350	11,50	Lympho-sarcoma
4	Male	26	6	1,9	14,000	92-95%	2,350	380	Lympho-sarcoma
5	Female	55	4	(Leukemic)			1,300	335	Reticulo-sarcoma (Hodgkin cell type)
6	Male	60	1		53,200 -52,100	85%	1,865	365	Reticulo-sarcoma (Hodgkin cell type)

essentially malignant in their clinical behavior. Some cases of the so-called leukemic reticuloendotheliosis are, however, chronic and their pathologic pictures are quite different from those of the acute type.²¹

Case 6: 52-year-old male. Ten years ago his illness was diagnosed as chronic lymphatic leukemia and for these 4 years splenomegaly increased markedly. But the swelling of the superficial lymphnodes was only to a slight degree. In the blood picture red blood cell count was 2.84–4.46 million, and white cell count 24,700–127,500 with 50–90% pathologic cells. The pathologic cells in the peripheral blood were relatively small in size and seemed to be lymphocytes. According to the cytological examinations performed by Dr. K. Matsui, the cells must be identified as reticulum cells, mainly from the findings of their movement pattern, positive phagocytosis and electronmicroscopic pictures. The most striking histological features were seen in the spleen and there was found a diffuse and irregular proliferation of small cell elements. The proliferating cells in the medullary cords seemed to have been mostly fixed ones, and free cells were liberated from them in the venous sinuses. Almost all cell elements of the lymphnodes in stamp preparations seemed to be mature lymphocytes, but from the histological point of view, a picture of a sort of lymphoreticulosis was recognized. In the liver a diffuse leukemic infiltration took place intensively in the Glisson's sheath and also in the liver parenchyma. The liver cell cords became extremely atrophic. The bone marrow was highly atrophic and no marked leukemic infiltration was found.

In the interpretation of this case, the chronic lymphatic leukemia cannot yet be excluded, because the cytological criteria for the lymphocyte are not so evident as are supposed in general.^{22–25} However, if positive phagocytosis is regarded one of the specific attributes of the reticulum cells, this case must be classified as leukemic reticuloendotheliosis of the chronic type. The related cases are referred to in the report of Bouroncle *et al.*, 1958.²⁶ Attention must be paid to the fact that the morphological changes are mostly recognizable in the red pulp of the spleen. These findings indicate that the primary lesion is in the spleen. If it is so, we come to have now a splenogenic, leukemic reticuloendotheliosis.

Leukemic Reticuloendotheliosis and Myelogenous Leukemia

From the above-mentioned findings it is now clear that the primary lesion of so-called leukemic reticuloendotheliosis is in the lymphatic tissue, and the cells participating in the proliferation are lymphatic reticulum cells. The changes of the spleen are undoubtedly of secondary character in all of the cases except for the case of the chronic type. The author has never seen cases of leukemic reticuloendotheliosis in which diffuse proliferation of the myelogenous reticulum cells in the bone marrow is regarded as primary and essential. So, most of the cases of leukemic reticuloendotheliosis are lymphatic in this respect.^{27,28} If the term 'Schilling-type leukemia' is equated with leukemic reticuloendotheliosis, the Schilling-type leukemia must be rather paralympathic or paralymploblastic leukemia than splenogenic or monocytic. Reticulum cell sarcoma originating from the bone marrow and also the diffuse hyperplasia of the myelogenous

reticulum cells are extremely rare. The author has found only one doubtful case of malignant reticulosis of the bone marrow, the blood picture of which, however, is completely aplastic and not leukemic. In this case, cancer metastasis to the bone marrow is undeniable. In our discussion on the reticulum cell of the bone marrow with respect to leukemic reticuloendotheliosis, it should be mentioned that, concerning the cases of chronic myelogenous leukemia at terminal stage, a diffuse proliferation of immature cells resembling the reticulum cells occurs and becomes acute leukemic.²⁹⁻³¹

Case 7: 23-year-old male. For 2.5 years he had a chronic myelogenous leukemia. After a certain acute phase, the patient died under severe anemia, emaciation and jaundice. In the autopsy findings, in addition to ordinary pictures of the chronic myelogenous leukemia, it was more characteristic that larger immature cells and also some giant cells were diffusely proliferated in the bone marrow, liver and spleen. The cells were thought to resemble the reticulum cells.

Case 8: 37-year-old female. In the course of 3 years' chronic myelogenous leukemia a tender tumor appeared at her left arm which caused a spontaneous fracture. In the autopsy findings there were noticed two kinds of pathological changes: one was a picture of chronic myelogenous leukemia and the other a reticulosarcomatous tumor of over a hen's egg size at the distal end of the left humerus. The proliferating cell elements of the latter tumor were mostly polymorphous and atypical, and its metastases were seen scattered in the bone marrow, liver, spleen, pancreas, kidney, uterus and ovaries. In the peripheral blood, many atypical cells could be demonstrated.

The nature of the proliferative lesion in these two cases can be considered either as 1) an essentially reactive reticulosis, 2) a reticulum cell sarcoma developing by differentiation or mutation of the leukemic cells or 3) an anaplastic, tumor-like type of the myelogenous leukemia cells by itself. The author would like to support the third possibility, because in the atypical cells he could not deny the attributes of myelogenous cells. However, the solution of this problem requires a further investigation in the future. In any case, this type of myeloproliferative processes has no direct relationship to leukemic reticuloendotheliosis.

Monocytic Leukemia of the Naegeli Type

In most Anglo-american literature 'leukemic reticuloendotheliosis' is equated with monocytic leukemia of the Schilling type.³²⁻⁴⁵ And both types of monocytic leukemia, i.e., the Schilling and the Naegeli types, are dealt with as a definite disease entity. From the viewpoint of separating the blood monocyte from the reticuloendothelial cell, however, both diseases are to be placed in quite different categories. In a typical monocytic leukemia of the Naegeli type, 1) the primary lesion of the malignant cell proliferation is located in the bone marrow, 2) there are no types of transition between reticulum and leukemic cells, 3) the latter reveals distinct, cytological characteristics as the blood monocyte (constantly positive peroxylase reaction), and 4) the changes of the lymphnodes are of

secondary nature as in the other types of myelogenous leukemia. Furthermore, 5) a severe anemia is notable in clinical symptoms.

SUMMARY AND CONCLUSIONS

1) The concept of leukemic reticuloendotheliosis is originally rather ideological. In fact, the essentially pathologic picture of the cases designated with this term can be found mostly in the lymphatic tissue as a diffuse proliferation of the lymphatic reticulum cells with a leukemic manifestation.

2) Clinically, most cases are acute and always malignant. The pattern of the proliferation of the lymphatic reticulum cells is neoplastic.

3) As to the criteria used in differentiating the disease from reticulum cell sarcoma with leukemic blood picture, it can be pointed out that in the leukemic reticuloendotheliosis a) the proliferation of the lymphatic reticulum cells is diffuse and not nodular, b) metastatic foci in organs are leukemic and composed of diffuse infiltration of free pathologic cells, c) the ground structure of the lymphatic tissue is modified or destroyed quite slightly and d) the atypism of the pathologic proliferating cells is less marked.

4) Leukemic reticuloendotheliosis can be distinguished from acute lymphatic leukemia and from lymphosarcomas through the cytological findings of the pathologic cells in the peripheral blood which show more or less distinct attributes of the reticulum cells.

5) The difference in the nature of the diseases described in 3) and 4) are, however, often obscure. It is necessary to clarify the lymphopoietic processes of the lymphatic reticulum cells and also the true relationship between the lymphocyte and mononuclear cells. At the present time, leukemic reticuloendotheliosis can be considered as a variant of malignant lymphomas.

6) Endothelial cells have no direct bearing on the essential pathological changes in the lymphatic tissue and other organs. From this point of view, the term 'leukemic reticulosis' seems to be correcter.

7) The adjective 'leukemic' is not so limited in its use and it comprises various conditions including simple tumoremia. If one wants to use the term strictly, one must ascertain the hemocytic nature of pathologic cells in the peripheral blood, and the lymphocytic nature of pathologic cells in leukemic reticuloendotheliosis must be here again problematic. Purely phenomenally, the extension of the free cell lesion in the lymphatic tissue seems to be related to the leukemic blood picture. Other factors such as the effects of radiation, chemotherapy and hormonal circumstances must be taken into consideration in studying the development of the leukemic picture.

8) With respect to the chronic type of leukemic reticuloendotheliosis, the author is looking forward to the presentation of other cases. From the findings of the above-mentioned case, particular attention must be paid to its relationship

to chronic lymphatic leukemia.

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Explanation of Figures

- Fig. 1. Case 5. Medullary cord of the lymphnode. A diffuse proliferation of large reticulum cells.
- Fig. 2. Case 5. Lymphnode. Proliferative and infiltrative lesion of free reticulum cells.
- Fig. 3. Case 4. Lymphnode. Pericapillary proliferation of phagocytic reticulum cells of the fixed type.
- Fig. 4. Case 6. Pathologic cells in the peripheral blood. Mononuclear cells with rather abundant cytoplasm. Phagocytosis positive.