Leukemic Reticulosis and Allied Disorders*

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(Received for publication, May 28, 1965)

The usage of the terms “leukemic reticulosis” and “leukemic reticulosarcomatosis” has been in confusion. They are applied to the cases with appearance of neoplastic reticulum cells in the peripheral blood.

However, their implications, clinical, pathological and diagnostic, are indistinct and controversial.

To define the concept of such conditions and pathological characteristics, the author investigated histological sections and blood films of 39 cases, which showed reticulum cells appearing in the peripheral blood. The following results were obtained:

1. Leukemic reticulosis is rapidly progressive and leads to the death of patients within four months. Histological features are characterized by diffuse medullary reticulosis of the lymph nodes and diffuse reticulum cell infiltration in various organs.

2. Leukemic reticulosarcomatosis is defined as hematogenous tumor cell dissemination of undifferentiated or reticular type reticulosarcoma at the terminal stage or as one of the results of chemotherapy or X-ray irradiation.

3. Even in Hodgkin disease-like granulomatous reticulosis, reticulum cells are observed in blood films. But these changes are regarded as cataplastic in nature.

4. In various reactive reticulosis, reticulum cells are observed in blood films. In association with various leukemias, reactive reticulosis exhibits malignant transition and neoplastic reticulum cells appear in peripheral blood at the terminal stage.

The term leukemic reticuloendotheliosis was first proposed by Ewald in 1923. But the first exact description of this disease had already been made in 1913 by Reschad and Schilling. They observed the case of a 33-year-old male with clinical symptoms of acute leukemia and with the appearance of many large mononuclear cells in the peripheral blood. They regarded the condition to...
represent a new systemic leukemia of reticuloendothelial origin, because these mononuclear cells showed the same morphological findings as those of Aschoff and Kiyono's histiocytes and negative peroxidase reaction.

After Fleischmann's description\(^3\) of the second case under the name of monocytic leukemia in 1916, Ewald\(^1\) reported a similar case and designated the disease as "leukemic reticuloendotheliosis", because it showed prominent reticuloendothelial cell proliferation.

Since then, the terms "monocytic leukemia" and "leukemic reticuloendotheliosis" were frequently used with identical meaning.\(^4\)-\(^{16}\) From the tritaristic viewpoint of leukopoiesis, leukemic reticuloendotheliosis means monocytic leukemia, and to unitarians it means stem cell leukemia.\(^17\)-\(^{20}\)

Moreover, the fact that some American authors use the term "stem cell leukemia" in the sense of acute undifferentiated leukemia, and the presence of reactive reticulosis in association with various leukemias makes the concept confusing.

But, in Japan, differences between monocytic and reticuloendothelial systems were clearly demonstrated in regard to their different origins and their different morphological and biological characters.

Akazaki\(^21,23\) showed that the reticuloendothelial system (RES) is composed of 1) reticulum cells, or histiocytes and 2) reticuloendothelia.

His opinion is that the apparent difference between the reticulum cell and the histiocyte is brought about by different environmental conditions.

Contrary to Aschoff and Kiyono's description about the blood histiocyte, he assumed that, under physiological conditions these cells did not appear in the peripheral blood.

On the other hand, Amano\(^23,24\) demonstrated that the monocyte is a kind of leukocyte and is independent from the RES.

From these reasons, monocytic leukemia and leukemic reticuloendotheliosis were recognized as independent disease entities and the names, "leukemic reticulosis or reticuloendotheliosis" and "leukemic reticulosarcomatosis" were applied to a disease which exhibits pronounced appearance of neoplastic reticulum cells in the peripheral blood. However, no distinction was made between reticulosis and reticulosarcomatosis.

An attempt is made in this report to elucidate the concept of the condition and the pathomorphological characteristics.

**GENERAL CONSIDERATIONS**

1. **Reticulosis and the term "leukemic"**

   In general, reticulosis means various pathological conditions of systemic reticulum cell proliferation, and various diseases of different natures and origins are comprised in this concept.
After Kojima's classification\textsuperscript{25–27} they were divided into the following groups:

1) Reactive reticulosis
2) Idiopathic reticulosis
   a) Cataplastic
   b) Neoplastic

The appearance of histiocytes, which belong to mesenchymal tissues and not to leukocytes, in the peripheral blood stream is sometimes noticed in a series of such pathological conditions.

However, most European and American authors who advocate the RES origin of monocytes describe them as monocytosis.\textsuperscript{16}

The term "leukemic" can be defined as indicating quantitatively and qualitatively irreversible proliferation of leukocytes, and as a rule, such conditions are accompanied by the appearance of these proliferated cells in the blood stream.

Whether it is justified to apply the term "leukemic" to the proliferation of histiocytes or not, which are in their nature not comprised in leukocytes, requires further comments.

When pathological plasma cells appear prominently in peripheral blood, the term "plasma cell leukemia" is usually used. In this meaning the term "leukemic" can also be used to characterize the condition where a large number of histiocytes is observed in the peripheral blood.

2. Reticulosis and reticuloendotheliosis

As it was mentioned above, the RES is composed of two kinds of cells, 1) reticulum cells or histiocytes, and 2) reticuloendothelia.

But in most cases of systemic RES proliferation, which are called reticulosis or reticuloendotheliosis, reticuloendothelia show no particular activity except for Kupffer cell proliferation, and the latter is usually reactive in nature. So it seems better to call such a condition "reticulosis".

But the term reticuloendotheliosis may be sustained in the meaning of RES proliferation.\textsuperscript{28}

\section*{MATERIALS AND THEIR REVIEW}

The first report of the leukemic reticulosarcomatosis in Japan was presumably that of Asami and Uragami's case,\textsuperscript{30} although no descriptions were found on hematological findings. After that, about 55 cases were reported under the name of leukemic reticulosis or leukemic reticulosarcomatosis.\textsuperscript{31–69} However, no attempts were made to discriminate leukemic reticulosis from reticulosarcomatosis, in general.

To establish a concept of the diseases, the author collected 39 cases, which showed reticulum cell appearance in the peripheral blood. Autopsy specimens
as well as blood smears of these cases were observed.

From histological findings, these cases were divided into the following four groups:

1) Cases which seemed to represent a disease entity, that can be called "leukemic reticulosis"
2) Leukemic reticulosarcomatosis
3) Cataplastic reticulosis with reticulum cell appearance in the peripheral blood (Hodgkin disease-like granulomatous reticulosis)
4) Reactive reticulosis with reticulum cell appearance in the peripheral blood
   a) Inflammatory (infectious) reticulosis
   b) Reticulosis in association with neoplastic diseases
   c) Reticulosis in association with some blood diseases.

The first group was characterized by diffuse medullary reticulosis of the lymph nodes and diffuse reticulum cell infiltration of various organs and was supposed to be an entity that can be called "leukemic reticulosis".

The features of the second group were those of undifferentiated or reticular type reticulosarcoma, and diffuse tumor cell infiltration was prominently observed in various organs.

The third group was characterized by Hodgkin disease-like granulomatous reticulosis, but no leukemic infiltrating tendency was recognized.

The fourth group showed reticulum cell proliferation of various natures. The reticulosis caused by infection was recognized as inflammatory reactive in nature, but some cases of reticulosis which were associated with various leukemias were thought to have neoplastic characters.

I. Cases which seemed to represent a disease entity that can be called "leukemic reticulosis"

Most of these cases were reported under the name of leukemic reticulosarcomatosis. But their hematological and histological features suggest that they do not belong to reticulosarcomatosis. Among 39 collected cases, 19 cases seemed to belong to this entity, and their details were shown in Table I.

Age and sex

Among the 19 patients, 9 patients (47.3%) were over 45, 6 patients (36.8%) were less than 15, but no patients was found from 30 to 45 years of age.

The same tendency was also noticed in the previously reported cases in literatures. Among the 30 other cases which were reported under the name of leukemic reticulosarcoma or reticulosis, 10 patients (33.3%) were over 45, and only 2 patients in the third decade, and 6 patients (20%) were less than 15 years of age.

The male-female ratio was 11 to 8 in collected cases. Most of the male patients were over 47 years old, and most of the females were between 12 and
<table>
<thead>
<tr>
<th>Case no.</th>
<th>Source</th>
<th>Age, sex</th>
<th>RBC (× 10^6)</th>
<th>Hb</th>
<th>WBC (× 10^9)</th>
<th>Reticulum cells (%)</th>
<th>Course (months or weeks)</th>
<th>Fever</th>
<th>Liver wt. (g)</th>
<th>Spleen wt. (g)</th>
<th>Lymph nodes</th>
<th>Hemorrhagic diathesis</th>
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<td>+</td>
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<td>740</td>
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<td>-</td>
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<td>+</td>
<td>1910</td>
<td>200</td>
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<td>+</td>
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<td>+</td>
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<td>280</td>
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<td>265-224</td>
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<td>4.8-97</td>
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<td>+</td>
<td>1590</td>
<td>380</td>
<td>+</td>
<td>-</td>
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<td>290-219</td>
<td>60</td>
<td>28-15</td>
<td>-45</td>
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<td>+</td>
<td>2400</td>
<td>520</td>
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<td>390-250</td>
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<td>24-32</td>
<td>91</td>
<td>3 m, 1 w.</td>
<td>+</td>
<td>1780</td>
<td>350</td>
<td>+</td>
<td>+</td>
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<tr>
<td>7</td>
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<td>47 M</td>
<td>390-250</td>
<td>6</td>
<td>6-2</td>
<td>3-54</td>
<td>4 m</td>
<td>+</td>
<td>1790</td>
<td>215</td>
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<td>212-393</td>
<td>51</td>
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<td>5-14</td>
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<td>1780</td>
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<td>42</td>
<td>17-8.2</td>
<td>48</td>
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<td>+</td>
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<td>331-231</td>
<td>53</td>
<td>30-61</td>
<td>80-95</td>
<td>2500</td>
<td>+</td>
<td>2500</td>
<td>560</td>
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<td>+</td>
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<td>75-90</td>
<td>8 m</td>
<td>+</td>
<td>1110</td>
<td>510</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>Okayama Univ.</td>
<td>13 F</td>
<td>78-223</td>
<td>8</td>
<td>8</td>
<td>56</td>
<td>2 m, 2 w.</td>
<td>+</td>
<td>1300</td>
<td>220</td>
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<td>307-227</td>
<td>46-33</td>
<td>12.7-18</td>
<td>3.5-49</td>
<td>2 m, 2 w.</td>
<td>+</td>
<td>1200</td>
<td>620</td>
<td>+</td>
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<tr>
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<td>112-109</td>
<td>3.7-21</td>
<td>1.5-49</td>
<td>7 m</td>
<td>+</td>
<td>340</td>
<td>100</td>
<td></td>
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<td>2 M</td>
<td>8</td>
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<td>3 m</td>
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<td>620</td>
<td>260</td>
<td>+</td>
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<td>600</td>
<td>180</td>
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</tbody>
</table>

* Detailed descriptions are found in page 9.
Hematological findings

Red cells and hemoglobin. Most cases showed moderate to marked anemia, particularly in their terminal stage. Red blood cell counts were over 3 million pccmm in only 4 cases, and 8 cases showed between 3 to 2 million. Hemoglobin concentration was usually between 50 and 60%.

Leukocytes (nucleated cells). Eight cases showed marked to moderate leukocytosis, 3 cases had normal counts, and 6 cases showed marked leukopenia.

Reticulum cell count. In 5 cases the count was over 80%, over 40% in 6 cases and in 3 cases it was less than 30%. In 2 cases, which showed similar histological features, no reticulum cell appearance was found, and these cases were recognized as having aleukemic variant of this entity.

From case to case, these reticulum cells showed various morphological pictures such as histiocytoid, monocytoid, lymphocytoid or plasmocytoid appearances, and comparing with reticulosarcoma cells in the blood, these cells usually showed some resemblance to blood cells. Various examinations such as histochemistry, supravital staining, and tissue culture also suggested that these cells were of RES origin (positive acid phosphatase activity, phagocytic activity, etc.).

The following descriptions are the findings of Giemsa stained preparations of the blood smear in various cases.

Histiocytoid variety. Markedly enlarged cells, ranging from 20 to 40μ in their long axes. Their shapes were oval, spindle or elongated, with irregular rim or pseudopod formation. The nuclei were round or oval, and 1 to 3 distinct nucleoli were observed. The nucleo-cytoplasmic ratio was markedly small.

No particular granulation was found in the cytoplasm but fine azur granulation was sometimes observed (Fig. 7).

Monocytoid variety. They were oval or slightly elongated in shape. The cytoplasm was sky-blue in color and usually broad and clear-cut, with few azur granulations. Sometimes a prominent vacuole formation was observed.

The nuclei were oval or indented with coarse chromatin network. Nucleoli were infrequently observed.

Lymphocytoid variety. Their size was 1.5 to 3 times the size of normal lymphocytes and they were round or oval in shape. The cytoplasm was scanty, sky-blue in color and sometimes irregular in outline.

The nuclei were round, oval and scarcely indented. The chromatin was markedly dense and showed some condensation. No nucleoli were usually observed (Fig. 8).

Plasmocytoid variety. Usually elongated or spindle in shape with markedly basophilic cytoplasm and distinct perinuclear halo. The nuclei were round, oval, and occasionally dumb-bell-shaped and eccentrically situated. The chromatin
structure was dense but relatively fine in network.

Nucleoli were infrequently observed.

Sometimes a pseudopodia formation was observed.

In such cases, the patients used to have hyperglobulinemia particularly hyper-γ-globulinemia, and occasionally Bence-Jones protein was demonstrated in the urine. Proliferated cells were usually pyronin positive on histological sections (Fig. 9).

**Clinical course**

The onset of the disease was usually insidious but its course was rapidly progressive and usually led to the death of patients within 4 to 6 months.

Cardinal symptoms were remittent fever of 38−39°C, various eruptions, hepatosplenomegaly and hemorrhagic diathesis.

Lymph nodes were usually enlarged up to finger-tip size, and compared with reticulosarcoma, they showed a slight adhering tendency. Conglomerated lesions were infrequently observed.

**Histological findings**

**Lymph nodes.** Examination of lymph nodes and lymphatic apparatus from various regions, revealed similar findings. In general, lymph nodes showed the appearance of the so-called diffuse medullary reticulosis. The medulla was occupied with the proliferation of uniform reticulum cells but scanty persisting lymphatic tissues were observed in the region of the lymph follicles.

Lymph nodes excised from two patients, showed still unestablished diffuse medullary reticulosis, and reticulum cell proliferation extended into the lymphatic tissues, which remained around the follicles and in the cortical region.

The proliferating cells were usually uniform in appearance and exhibited similar features to pathological cells in the blood.

Of cases in which pathological blood cells were histiocytoid or monocytoid in shape, the proliferating cells were markedly large and had oval or deeply indented nuclei which had distinct heavy membranes and prominent nucleoli. The chromatin structure was coarse and occasionally aggregated into many small clumps. The cytoplasm was usually broad and sometimes showed racket-like or tadpole-shaped appearances (Fig. 7). Prominent phagocytosis was sometimes observed.

Of cases in which lymphocytoid cells appeared in the blood, the proliferating cells had round, oval or sometimes indented nuclei with distinct nuclear membranes and fine chromatin structure. Nucleoli were usually not clear. The cytoplasm was scanty and connected to one another in a stellated pattern (Fig. 8).

Of cases in which plasmocytoid cells appeared in the blood, the proliferating cells were much the same as plasma cells, accompanied with eccentric nuclei,
radiated chromatin structure and basophilic, pyronin-positive cytoplasm (Fig. 9). Russel's bodies as well as Mott cells were frequently observed.

Above all, the basic structure of lymph nodes was essentially preserved and sinuses, medulles and follicles were usually demonstrated by silver impregnation (Figs. 4–6).

These findings seemed to represent the most remarkable difference between leukemic reticulosis and reticulosarcoma.

Liver. The above-mentioned cells were usually proliferated in Glisson's sheaths and on liver capsule in a stellated pattern, sometimes with giant cell formation. These cells used to invade into sinuoids, and blood vessels, bile ducts of the Glisson's sheaths, and adjacent hepatic cell cords were compressed by proliferating cells there.

These seem to be an activated proliferating condition of reticulum cells on these sites and not always leukemic cell infiltration, although it is difficult to identify the origin of proliferating cells (Figs. 10 and 11).

Remarkable swelling and proliferation of Kupffer cells were so intense that the reaction could be distinguished from reticulosis, which was occasionally observed in association with leukemia. Sometimes they filled the whole sinusoids, and multinuclear cells were observed, usually attaching themselves to reticulin fibers.

Spleen. In contrast to reticulosarcoma, in which commonly nodular proliferation of splenic cords and sarcomatous change of all the follicles were observed, cases with leukemic reticulosis showed diffuse reticulum cell proliferation of the Billroth's cords, and lymphfollicles were usually free from sarcomatous change and maintained, although they were small in number.

Venous sinuses were filled with such pathological cells and the emigration of these cells from Billroth’s cords into sinuses was sometimes observed. No activity was found on venous endothelial linings.

Bone marrow. Entire marrow was usually replaced by pathological cells, but sometimes hematopoietic cells or fatty tissues remained to be recognized.

Pathological cell infiltration was found also in interstitial tissues of various organs such as kidneys, adrenals, testes and lungs.

Pathological cells were also found in the capillaries of the lung, glomerular tufts of the kidney and peripheral vessels of other various organs, which demonstrated their leukemic nature.

These findings do not belong to the histological features of the reticulosarcoma in its conventional sense and suggest the presence of another disease entity "leukemic reticulosis", although some authors such as Dameshek and Gunz regarded the histiocytic leukemia as a leukemic counterpart of reticulosarcoma.

Representative cases are here presented with detailed descriptions of clinical and pathological findings.
Case 1. (Tohoku Univ.). 47-year-old male. The patient suffered from remittent fever of 38–40°C, lymphadenopathy and had multiple subcutaneous tumors up to the size of goose eggs. He died 4 months later.

His blood showed WBC of 6,700–2,000 and 54% of reticulum cells.

These reticulum cells were 20–40μ large in their long axis, and histiocytoid in appearance. Peroxidase reaction (−), phagocytic activity (+) (Fig. 7).

The biopsy of a lymph node, 2 months before his death, showed a not yet fully established diffuse medullary reticulosis (Fig. 3). At the autopsy, systemic lymph nodes, liver and spleen were markedly enlarged and many nodular growths were recognized on various organs. Histologically, medullary portion of all the lymph nodes were completely replaced with diffuse proliferation of large histiocytoid cells, but the basic structure was well preserved. Diffuse reticulum cell infiltration was recognized in various organs, particularly on the nodular growths. The bone marrow was replaced with reticulum cell proliferation.

Case 2. (Sapporo City Hosp.). 50-year-old male. The blood examination showed a WBC of 28,800 and 45% of plasmocytoid and a few monocytoid cells. The total serum protein was 8.0 (γ-globulin 42%) and Bence-Jones protein was positive in urine. At the autopsy, lymph nodes were up to small-finger-tip size, but diffuse reticulum cell proliferation was found in the lymph nodes, liver, spleen and bone marrow. They were connected to one another in stellated or sometimes in syncytial pattern, and multinucleated giant cells were frequently observed.

Case 3. (Keio Univ.). 49-year-old male. He suffered from systemic lymphadenopathy, a high fever (40°C) and hemorrhagic tendency. The blood examination revealed WBC of 19,800–31,850 and 98–91% so-called atypical lymphocytes (Fig. 8). Histologically, medulles of lymphatic tissues were completely replaced with uniform small cell proliferation. The proliferated cells had rounded nuclei with fine chromatin structure and scanty cytoplasm which were connected to one another in stellated configuration and recognized as reticulum cells. These cells were also infiltrated diffusely in various organs (Fig. 8).

II. Leukemic reticulosarcomatosis

Most of the cases reported under this name seemed to represent merely the dissemination of reticulosarcoma cells into the blood stream at their terminal stage, or as one of the results of chemotherapy or X-ray irradiation.

Only 10 cases belonged to leukemic reticulosarcomatosis in the opinion of the author (Table II).
TABLE II. Leukemic Reticulosarcomatosis

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Source</th>
<th>Age, sex</th>
<th>RBC $(\times 10^4)$</th>
<th>Hb (g/dl or %)</th>
<th>WBC $(\times 10^4)$</th>
<th>Reticulum cell counts (%)</th>
<th>Course (m: months)</th>
<th>Fever</th>
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</tr>
<tr>
<td>9</td>
<td>*Niigata Univ.</td>
<td>36 M 282</td>
<td>62</td>
<td>2.1-1.1</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>10</td>
<td>*Tokyo Med. Dent. Coll.</td>
<td>25 F</td>
<td>214</td>
<td>55</td>
<td>9.5</td>
<td>6</td>
<td>3 m</td>
<td>+</td>
</tr>
</tbody>
</table>

* Nasal tumor and its dissemination

**Age and sex**

Among the 10 patients seven (70%) were over 58, and no cases were found under 25 years of age. The male-female ratio was 6 to 4.

A similar tendency was also observed in literatures. Out of 30 patients, 12 patients (40%) were over 50 years of age, and only 4 patients (13%) were between 20-39 years of age, although attempts were seldom made to discriminate reticulosis from reticulosarcoma. The male-female ratio was 22 to 8.

**Hematological findings**

**Red blood cells and hemoglobin concentration.** Red cell counts showed marked deviation from case to case. In 6 cases RBC was over 3 million pccmm and hemoglobin concentration was over 70%. Marked anemia was found in only 2 cases.

**Leukocytes (nucleated cells).** Marked leukocytosis was found in 3 cases and leukopenia in only one case.

**Reticulum cells.** In 2 cases, the counts were over 70%. Most cases showed marked deviation in their clinical courses. However, reticulum cell counts were smaller compared with leukemic reticulosis, and were elevated only at the terminal stage. In general, pathological reticulum cells in the blood stream showed characteristic features of tumor cells and prominent polymorphism (Fig. 12).

Some of these were markedly large and some were of the size of a lymphocyte. The nuclei were usually large compared with cytoplasm. They were oval, reniform, lobulated or globoid in shape and their chromatin structure was coarse and spongy in appearance and was sometimes associated with large chromatin clumps.

The cytoplasm of these cells was basophilic and not homogeneous and it had
no granules, but occasional vacuoles.

Bizarre-shaped giant cells were frequently observed.

Clinical findings

The major symptoms were lymphadenopathy, hepatosplenomegaly and remittent fever. Subcutaneous tumors were sometimes observed. Lymph nodes were markedly enlarged and usually conglomered as in reticulosarcoma. Their clinical course varied from case to case. In rapidly progressive cases, death took place in only a month, but in some cases patients survived 2 years or more.

The reticulum cell appearance was sometimes observed after X-ray irradiation or chemotherapy, but usually it was found at the terminal stage.

In Cases 5 and 7, intensive X-ray irradiation was performed, and Case 3 was treated with 60Co and a large amount of Endoxan, and pathological cells were found after these treatments.

Histological findings

In general, histological pictures of various organs showed the morphology of undifferentiated or reticular type reticulosarcoma, with a tendency toward nodular proliferation.

Lymph nodes. Reticulosarcoma cells proliferated diffusely in mosaic pattern or sometimes in stellated form and the basic structures of the lymph nodes were completely destroyed and sinuses, medulles and follicles were no longer identified.

The biopsied lymph nodes, taken from a patient 6 months before his death, showed nodular follicular reticulum cell proliferation (Fig. 13).

Compared with leukemic reticulosis, proliferated reticulum cells were markedly pleomorphic and their nuclear chromatin structures were coarse, and prominent nucleoli were frequently observed (Fig. 14).

Spleen. The lymphfollicles were usually replaced by sarcoma cell proliferation and reticulum cell proliferation in splenic cords made nodules in general.

Liver. Tumor cell infiltration was frequently observed in Glisson's sheaths compressing the adjacent hepatic lobules.

Kupffer cell proliferation was not so prominent compared with leukemic reticulosis.

Bone marrow. In most cases, myeloid tissues were replaced by tumor cells.

III. Cataplastic reticulosis with reticulum cell appearance in the peripheral blood

The term cataplasia was applied by Waugh74 (1937) to the proliferation of reticulum cells, which exceeded reactive hyperplasia without conclusive neoplastic nature.

The following two cases seemed to be included in this category.

Case 1. (Red Cross Central & Musashino Hosp.).72 59-year-old male. He suffered from lymphadenopathy and remittent fever of 38°C and died after 8 months.
Blood examination showed a WBC of 3,200 with 39% unclassified pleomorphic cells resembling reticulum cells or Hodgkin-cells (Fig. 15).

Lymph nodes were generally enlarged up to 3 cm in diameter and were completely replaced with granulomatous tissues of Hodgkin type, which were characterized by diffuse reticulum cell proliferation, fibrosis and many Hodgkin cells, Sternberg-Reed cells and many bizarre giant cells.

In spite of such pleomorphic proliferation and marked fibrosing tendency, the sinuses usually remained uninvolved and the findings appeared to be different from common neoplastic diseases.

The spleen weighed 410 g and revealed porphyritic appearance.

The liver weighed 1,480 g and numerous patches of whitish grey nodules could be seen throughout the cut surface. Their nodular lesion looked the same as those seen in the lymph nodes but they were more nodular in nature. Many giant cells were encountered in sinusoidal spaces (Figs. 16 and 17).

Case 2. (Nagasaki Univ.). 34-year-old female. She complained of general malaise, remittent fever of 38°C, eruptions, cervical lymphadenopathy and hepatosplenomegaly. The patient died 4 months later.

Blood examination showed a WBC of 136,000 with 64% pathological cells.

The liver was 1,310 g and the spleen was 1,040 g in weight and many whitish nodules were observed on the cut surfaces of the organs.

Histological findings were similar to those of the first case except for a slight fibrosing tendency.

Neoplastic nature was not recognized in these 2 cases.

The disease apparently belonged to Hodgkin disease-like reticulosis of an unknown etiology.

A similar case was previously reported by Muto et al. under the name of leukemic pleomorphic reticulosis.

The entity of Hodgkin disease itself is under debate about its inflammatory or neoplastic nature.

Whether it is neoplastic or cataplastic, the appearance of reticulum cells or Reed-Sternberg cells in peripheral blood is rarely observed, but the relationship between this condition and leukemic reticulosis was discussed by some authors.

The first description was made by Reed (1902) about the presence of intravascular giant cells by histological sections and a similar report was given by Jeanselme and Marchal in 1926.

In 1944, Isaacs referred to occasional finding of Reed-Sternberg cells in peripheral blood films.

In the same year, Bersack reported a case which showed fulminent cutaneous dissemination of nodular lesions. Although terminal hematogenous spread was suspected, no pathological cells were observed in blood films.
In 1957, Ludman and Spear\textsuperscript{78} reported a case, which showed 10\% Reed-Sternberg cells in peripheral blood on a single occasion, although the patient had been successfully treated with chemotherapy and X-ray irradiation.

In 1960, Varadi\textsuperscript{79} described a patient with the appearance of 1–3\% histiocytes and Reed-Sternberg cells. Chrobáč and Horáček’s\textsuperscript{80} case in the same year had 5–24\% atypical reticulum cells in the peripheral blood.

Keiser,\textsuperscript{81} reported a case with 5\% peripheral reticulum cells and suggested the influence of X-ray irradiation.

Libansky et al.\textsuperscript{82} (1962) reported a case with a long-term treatment, in which Reed-Sternberg cells and atypical reticulum cells appeared in the blood at the terminal stage.

Recently, Scheerer\textsuperscript{83} (1964) reported a case, in which Reed-Sternberg cells appeared up to 17\% persistently in the last week, and named the disease "Reed-Sternberg cell leukemia".

These reticulum cells or Reed-Sternberg cell appearance in the peripheral blood could be interpreted as follows: 1) Hematogenous tumor cell dissemination takes place at the terminal stage of the disease or as a result of various treatments. 2) All these cases had marked involvement of the bone marrow, which leads to the appearance of Reed-Sternberg cells in the peripheral blood. 3) The relationship between Hodgkin disease and its leukemic condition is analogous to that observed between lymphosarcoma and lymphatic leukemia.

However, the following facts seem to support the view that these reticulum cell appearance in the blood is induced by treatments.

a) The histological lesions in Hodgkin disease are usually of granulomatous character and no leukemia-like infiltration is confirmable. b) Reticulum cells and Reed-Sternberg cells in the peripheral blood are found only at the terminal stage of the disease, and only 9 such cases were hitherto reported. c) Cases of Ludman and Spear, Keiser, Libansky and Scheerer were intensively treated with X-ray irradiation and cytostatic drugs, and Reed-Sternberg cell appearance in the peripheral blood occurred only after these treatments.

Although some authors, Craver\textsuperscript{84} (1936), Soyka\textsuperscript{85} (1951), Marchal\textsuperscript{86} (1957), Greenberg\textsuperscript{87} (1962) and Lacher\textsuperscript{88} (1963), reported simultaneous occurrence of Hodgkin disease and histiocytic or monocytic leukemia, our knowledge of the problem is still quite insufficient on account of the limited number of reports, and further evidences are still required to confirm the leukemic expressions of Hodgkin disease.

IV. Reactive reticulosis with reticulum cell appearance in the peripheral blood.

In this category, the author described the reticulosis induced by various causes with the appearance of proliferated reticulum cells in the peripheral blood.

On account of their various origins, reactive reticulosis can be divided into
the following groups.

1) Inflammatory (infectious) reticulosis
2) Reticulosis in association with neoplastic diseases
3) Reticulosis in association with some blood diseases.

1. Inflammatory (infectious) reticulosis

Since the first description by Eichhorst\(^8^9\) (1874) of histiocyte (reticulum cell) appearance in the peripheral blood of a case with typhoid fever, a considerable number of such cases were reported.

In 1907, Rowley\(^9^0\) found such phagocytic cells in the blood of patients with malaria and lymphatic leukemia and regarded them to be phagocytic lymphocytes.

In the same year, Van Nuys\(^9^1\) and in 1911, Leede\(^9^2\) found phagocytic cells in subacute bacterial endocarditis, and in 1912, Connal\(^9^3\) reported similar findings in trypanosomiasis, malaria, small pox and in ankylostomiasis.

But some European authors, who advocate reticuloendothelial origin of monocytes, describe the condition as monocytosis, and cases associated with a leukemia-like condition, were included in leukemoid reaction of monocytic type.

However, monocytes did not originate from reticulum cells or histiocytes, as it was already pointed out.

The condition, in which peripheral blood is flooded with free reticulum cells to such an extent, is comparable to leukemoid reaction, and should better be called "reticulemoid reaction".

Reticulum cell is not a kind of leukocyte, and corresponding to the term leukemia and leukemoid reaction, it seems better to use the terms reticulemia, and reticulemoid reaction.

The term reticulemia was already applied by French schools to the cases which showed leukemic reticulum cell appearance in the blood. (Sézary,\(^9^4\)–\(^9^6\) Cazal,\(^9^7\)–\(^9^8\) Toba\(^9^9\))

The following three cases were recognized as belonging to reticulemoid reaction.

Case 1. (Tohoku Univ.). 31-year-old female. She complained of general malaise, remittent fever of 37–38°C, and hepatosplenomegaly. Blood examination revealed a WBC of 27,000 with 60% pathological cells. From cytological findings these cells were recognized as reticulum cells and the diagnosis of leukemic reticuloendotheliosis was given, although clinical picture was that of sepsis (Fig. 18, a-c).

Treatments were unsuccessful and the patient died 3 months later.
Pathological diagnosis: Septicoppyemia with bacterial embolus in various organs. No lymph nodes were enlarged and no particular findings were found in the
liver and spleen. The bone marrow showed marked reticulum cell proliferation but not neoplastic in nature, and these cells slightly infiltrated in the kidney.

Case 2. (Tohoku Univ.). 2-year-old female. She complained of remittent fever of 38–39°C, diarrhea, cervical lymphadenopathy and marked hepatosplenomegaly.

The blood showed marked leukopenia (WBC 3,400, 2,400, 750) and severe anemia. The bone marrow was pancytopenic. Many monocytoid cells and phagocytic cells were frequently observed in blood films.

At the autopsy, the cells of the RES were markedly proliferated in liver, spleen, lymph nodes and bone marrow, and frequently, these proliferated cells showed prominent phagocytic activities. Lymph nodes showed histiocytic medullary reticulosis, but the basic structure was clearly demonstrated.

The pathological findings corresponded to the so-called histiocytic medullary reticulosis of Robb-Smith and Marshall (Fig. 21).

Case 3. (Tohoku Univ.). 40-year-old male. He suffered from general malaise, fever and systemic lymphadenopathy. Lymph nodes were up to finger-tip in size and no adhesion, nor tenderness were observed.

The peripheral blood revealed marked leukocytosis (WBC 26,400—53,700), and up to 43% pathological reticulum cells (Fig. 19).

At the autopsy, diffuse medullary reticulum cell proliferation was recognized in lymph nodes, but these proliferations were accompanied by many necrotic foci. The proliferated reticulum cells were markedly swollen and various kinds of giant cells were observed among them (Fig. 20). No particular findings were observed in the liver and spleen.

2. Reticulosis in association with neoplastic diseases

The proliferation of reticulum cells was commonly observed in various neoplastic conditions particularly in various leukemias although they were usually reactive in nature.

But, sometimes, reticulosis of neoplastic nature was found in the course of leukemia, and the author recognized them as a malignant change of such associated reticulosis.

The following cases seemed to be included in this group (Table III).

Case 1. (Keio Univ.). 44-year-old male. He suffered from refractory severe anemia and leukopenia and because of the appearance of many myeloblasts, promyelocytes as well as erythroblasts, erythroleukemia or chronic myeloid leukemia was diagnosed. The patient died 3 years later. Before his death, 3–5% reticulum cells and atypical giant cells were found in the peripheral blood.

At the autopsy, hepatomegaly (2,334 g) splenomegaly (1,076 g) and up to thumb-tip sized systemic lymph node enlargement was recognized. Many whitish-grey nodules were scattered throughout the cut surface of liver and spleen.
TABLE III

<table>
<thead>
<tr>
<th>No.</th>
<th>Source</th>
<th>Age, sex</th>
<th>WBC</th>
<th>Reticulum cells in blood</th>
<th>Diagnosis</th>
<th>Duration</th>
<th>Liver</th>
<th>Spleen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Keio Univ.</td>
<td>44 M</td>
<td>3,100 - 5 × 10^6 (Mb1. 9%)</td>
<td>3-5%</td>
<td>CML or EL</td>
<td>3 y</td>
<td>2,334</td>
<td>1,076</td>
</tr>
<tr>
<td>2</td>
<td>Keio Univ.</td>
<td>23 M</td>
<td>22,900</td>
<td>+</td>
<td>CML</td>
<td>2 y</td>
<td>2,350</td>
<td>3,950</td>
</tr>
<tr>
<td>3</td>
<td>Niigata Univ.</td>
<td>40 M</td>
<td>50 × 10^4</td>
<td>+</td>
<td>CML</td>
<td>3 y - 6 m</td>
<td>1,090</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Fukushima Univ.</td>
<td>45 F</td>
<td>8 × 10^4</td>
<td>+</td>
<td>CML</td>
<td>3 y - 4 m</td>
<td>1,790</td>
<td>1,330</td>
</tr>
</tbody>
</table>

EL; Erythroleukemia, CML; Chronic myeloid leukemia, Mbl.; Myeloblast

Lymph nodes. Besides diffuse myeloid cell infiltration, marked sinus reticulum cell proliferation was observed and these proliferated cells were markedly pleomorphic and various kinds of giant cells were found among them. But the basic architectures of the lymph nodes were well preserved.

Liver. Nodular reticulum cell proliferation was found in various sites particularly in the Glisson’s sheaths and many large reticulum cells were found in the sinusoidal spaces. Diffuse myeloid cell infiltration was found particularly in Glisson’s sheaths. But no connections were found between reticulum cell and myeloid cell proliferation (Fig. 24).

Spleen. Nodular reticulum cell proliferation and diffuse myeloid cell infiltration were recognized but lymph follicles were usually maintained.

Bone marrow. Focal reticulum cell proliferation was found in diffuse juvenile myeloid cell proliferation but these two systemic proliferations were sharply demarcated from each other (Fig. 27).

Histologically, this case revealed reticulosis and myeloid cell proliferation (erythroleukemia). Although Lubbers100 (1938), Chevaillier101 (1943), Cazal102 (1946), Silver103 (1954) and Mancini104 (1957) reported similar cases and called them “polyblastic leukemic reticuloendotheliosis”, no connections were found between these reticulum cells and leukemic cells. However, reticulum cell proliferation seemed to be reactive in nature.

Case 2. (Keio Univ.)23 23-year-old male. He suffered from nasal bleedings, fever and splenomegaly, and chronic myeloid leukemia was diagnosed and was successfully treated with Myleran. But two years later, he died from acute exacerbation. Before his death, his WBC was 22,900 and contained 15% myeloblasts, 1% promyelocytes, 4% myelocytes and 5% metamyelocytes. Bone marrow aspiration revealed 57.8% myeloblasts.

At the autopsy, the liver weighed 2,350 g and the spleen 3,950 g and the systemic lymph nodes were enlarged to small-finger-tip size.

Histologically, the lymph nodes showed marked proliferation of sinus
reticulum cells, and these cells showed marked atypism and various giant cells were frequently observed, although slight destructive tendency was recognized (Figs. 22 and 23).

Spleen; The basic structure was completely replaced with Hodgkin disease-like granulomatous pleomorphic reticulum cell proliferation (Fig. 26).

Bone marrow; Focal reticulum cell proliferation.

Leukemic myeloid cell infiltration was found in various sites, liver, spleen and lymph nodes.

Moreover, many bizarre-shaped giant cells and reticulum cells of pyknotic nuclei were frequently observed in the sinusoidal spaces of the liver, glomerular tufts of the kidney and pulmonary capillaries. These findings suggested that proliferated reticulum cells were terminally disseminated into the blood stream.

Case 3. (Niigata Univ.). 40-year-old female. For 3 years before her death, she suffered from chronic myeloid leukemia (WBC 50×10^4, 6–25% myeloblasts, 57% myeloblasts in bone marrow aspiration) but she was successfully treated. Six months before her death, she noticed a tumor on the 6th rib on the left side, and many mono- and multi-nucleated giant cells appeared in the peripheral blood.

At the autopsy, this case showed similar histological findings with the above-mentioned two cases.

These cases were recognized as representing malignant changes of reactive reticulosis associated with chronic myeloid leukemia and erythroleukemia, because they showed leukemic hematological findings and pleomorphic reticulum cell proliferation.

Their common features were: 1) Similar clinical course (chronic myeloid leukemia of 2–3 years duration). 2) Sinus reticulum cell proliferation with marked atypism and various kinds of giant cells, with slight nodular proliferating tendency and only little destructive tendency. 3) Marked splenomegaly (1,076–3,950 g) with granulomatous or destructive proliferation of pleomorphic reticulum cells in splenic cords and rarely in the liver. 4) Atypical reticulum cells and occasional giant cells in the blood stream at the terminal stage.

Recently, similar pleomorphic reticulum cell proliferation was reported by Nagahara\(^{105}\) (1963), Fujimoto\(^{107}\) (1964) and Asano\(^{150}\) (1965) in cases of chronic myeloid leukemia, and by Ishii and Yagawa\(^{106}\) (1957) in acute myeloid leukemia, although, from histological features, most of these cases were usually considered to be tumor-forming leukemia or leukemoid reaction which was associated with reticulosis. But from their hematological pictures of marked leukocytosis and numerous blastic myeloid cell appearances (WBC 8×10^4, and 20.5% myeloblasts, 35.5% of promyelocytes as was seen in Nagahara's case), it seemed better to consider them as true myeloid leukemia. Their histological pictures exhibited markedly pleomorphic reticulum cell proliferation with various kinds of giant cells, and these proliferated reticulum cells were also observed
in peripheral blood.

Since the first descriptions of Richter (1928), many such reports on the coexistence of leukemia and reticulosis as well as reticulosarcoma were published. Such simultaneous occurrence of the two pathological processes can be interpreted in different ways.

1) Associated reticulum cell proliferation, independent from leukemia (Benecke, "Myeloretikulose"; Apitz, "Lymphoretikulose"; Oberling and Guérin, "réticuloses associées").

2) There is some cytogenetic relationship between leukemic cells and reticulum cells (Fresen, "retikuläre Myelose", "retikuläre Lymphadenose").

3) Accidental combination of two independent disease entities.

4) These pleomorphic cells are not of RES origin but undifferentiated leukemia cells (Kojima and Iijima).

Most of these authors, who acknowledge the RES as composed of undifferentiated pluripotent mesenchymal cells, considered the apparent combination as a transition of reticulosis to leukemia.

In the reports of the combination of lymphatic leukemia and reticulosis, Richter (1928), Apitz (1939), and Pließ (1957) considered that these two changes are independent from each other, and others such as Ahlström (1938), Roulet (1930), Rössle (1932), Asami and Uragami (1937), Nasu (1951), and Arutyunoff (1956) assumed the existence of a cytogenetic relationship between them.

The combination of myeloid leukemia and reticulosis was also reported by many authors such as Benecke, Fresen (1957), Yarigin (1960), Interozzi (1955), Wilken (1957), Wildhack (1959), and Fritsch (1964).

The term "Myeloretikulose" was first applied by Benecke (1940) to an independent combination of two systemic diseases. But after that, this term was misinterpreted as meaning the transition of myeloid leukemia to reticulosis, and most authors used the term in unitaristic meaning. From such unitaristic viewpoint, Fresen called the combination "retikuläre Myelose."

A review of the cases in previous reports on "Myeloretikulose" or "Lymphoretikulose", in the sense of the presence of independent associated reticulosis with lymphatic or myeloid leukemia, (cases of Benecke, Apitz, Fresen and Fritsch), and the four cases of the present author reveal some common characteristics.

a) Transition of the reticulosis to that of a neoplastic nature was always observed (Figs. 22 and 23).

b) Reticulum cells in these cases were markedly pleomorphic and various kinds of giant cells were frequently observed.

c) The structure of lymph nodes was relatively sustained but the destruction of the spleen is prominent with granulomatous pleomorphic reticulosis (Fig. 26).

d) Neoplastic reticulum cells, particularly giant cells, were always observed...
in the bloodstream and in the peripheral vessels such as hepatic sinusoidal spaces (Fig. 25).

The secondary focal transition of reticulosis from hyperplastic to neoplastic nature was previously observed in various cases such as Rössle (1939), Benecke (1940), Feller (1954), Janssen (1956) and Kovacs and Kropass (1954), and Stein (1957), and morphological features in such cases differed somewhat from those of ordinary reticulosis in distribution and nature.

The neoplastic change of sinus reticulosis is scarcely reported in the literature, but previously mentioned cases seemed to be included in this entity, as reported by Muresan (1958), although he interpreted sinus reticulum cells as reticuloendothelia. These problems on the histogenesis of reticulosis will be described later.

There is a possibility, that these proliferated pleomorphic cells are not reticulum cells but undifferentiated leukemia cells.

But, from their peculiar morphological features, negative peroxidase reaction, and prominent phagocytosis of hemosiderin pigments and red cells, these cells were considered as reticulum cells.

Concerning monocytic leukemia, there are descriptions by Hittmair, who had proposed the word histiocytic or mesenchymal reaction. He explained that in monocytic leukemia, mesenchymal tissues were involved and accompanying reticulosis was induced, transformed to leukemia and these cells entered into bloodstream making a mixed form of monocytic leukemia, a type of Hittmair. The cases of Wagner (1951, 1954) and Villinger-Kwerch (1952) seemed to be included in this category. Jasinsky reported a case which showed the appearance of reactive histiocytes in the peripheral blood. However no such reports were found in Japan.

3. Reticulosis in association with some blood diseases

The proliferation of reticuloendothelial cells in the course of pernicious anemia was first observed by Ferrata and his schools. After that, Castellio (1923), DiGuglielmo (1923), Vasilieu (1923) and Lambin (1924) described similar cases.

In these cases, so-called monocytes, monoblast or sometimes hemohistioblast (Ferrata) were frequently observed in peripheral blood.

DiGuglielmo described primitive migrating cells, which can be observed in embryonal primitive stage of hematopoiesis.

Similar reticuloendothelial proliferation and invasion in the blood were also observed in various diseases such as agranulocytosis, panmyelophthisis and carcinoma metastases in bone marrow.

But no such reports were found in the case of myelofibrosis.

The following case seemed to belong in this category.

Case: 49-year-old female. After an operation on the intestinal phlegmone, she
suffered from remittent fever, marked anemia and purpuric eruptions and died one month later. The blood contained $242 \times 10^4$ RBC, 2,200 WBC and 15–20% unclassified pathologic cells (Fig. 28).

At the autopsy, marked hemorrhages were found on various organs but no remarkable change was found except for diffuse reticulum cell proliferation in bone marrow, and the diagnosis was panmyelophthisis.

**COMMENTS**

From histological features, the author divided leukemic reticulosis from leukemic reticulosarcomatosis.

Cases which were considered to have leukemic reticulosis, usually showed diffuse medullary reticulosis of lymph nodes, and leukemic nature was indicated by infiltrating tendency of reticulum cells.

But pathological cells in the peripheral blood were of various appearances such as histiocytoid, monocytoid, lymphocytoid, or plasmocytoid and recognized to be derived from lymph nodes.

From their histological features, however, these cells were considered as reticulum cells, because they were connected to one another in stellated configuration, and showed phagocytic activities and some relation to reticulin fibers.

Previous authors who recognized such hematological varieties, in the states of reticulosis, considered that, the reticulum cell is a hematopoietic pluripotent mesenchymal cell and it can produce various blood cells.

Moreover, the presence of a malignant change of an associated reactive reticulosis with various leukemias lead to such confusions.

So, it seemed better to consider that the reticulum cell can be transformed in such various leukocyte-like shapes and there are many varieties of leukemic reticulosis, such as 1. histiocytoid, 2. monocytoid, 3. lymphocytoid, 4. plasmocytoid appearances.

There are many evidences of the transformation of reticulum cells to such various appearances.

*On the transformation of reticulum cells to lymphocytoid cells*

From electronmicroscopic studies, some authors believe that lymphocytes originate from reticulum cells (Amano\textsuperscript{134} and Tanaka etc.). But some investigators regarded that the view is not sufficiently substantiated (Akazaki etc.).

Even in pathological conditions, such as reticulosarcoma, reticulum cells show lymphocytoid appearance and sometimes it is difficult to differentiate reticulosarcoma from lymphosarcoma (Akazaki and Hino).

Morelli\textsuperscript{146} (1953) reported a case, which had at first histioleukemia and showed a WBC of 56,000–120,000 and 75–92% histiocytes in the blood, but 2 months...
later the disease turned to a typical lymphatic leukemia with a WBC of 13,900 and the lymphocyte count was 81.5%.

Marmont147 (1947) described the name “istiolencemia linfatica” (histioleukemia lymphatica) and considered that, there are many variations from reticulosis to lymphadenosis, and histioleukemia lymphatica is a transitional form between them.

Previously, the author experienced a case of lymphatic leukemia in which only mesenteric lymph nodes and nodular growths in the liver showed the features of reticulosarcoma.

The second well documented case of macroglobulinemia Waldenström in Japan, which was kindly submitted from Hiroshima Red Cross Hospital (Figs. 29 and 30), also showed diffuse lymphocytoid cell proliferation, but by means of silver impregnation, these cells were recognized as reticulum cells (Figs. 29 and 30). The electron microscopic studies of this case also suggested that proliferating cells are reticulum cells (Tanaka134).

On the transformation of reticulum cells to plasmocytoid cells

Some hematologists (Rohr,135 Rotter,136 Fagraeus,137 etc.) considered that plasma cells originate from reticulum cells and it can be included in the RHS (RES), although excellent works of Amano and Hanaoka showed that plasma cells originate from adventitial cells.

However, in various pathological conditions, reticulum cells can be very much plasma cell-like in appearance.

The following cases seemed to have such plasmocytoid reticulum cell proliferation (Table IV).

Case 1. The remarkable findings were the systemic lymph node enlargement and a marked porphyritic spleen.

Lymph follicles of the lymph nodes and spleen were markedly enlarged (up to 5 mm in diameter) and composed of polygonal large reticulum cell proliferation. The cells of peripheral sites of these follicles of the spleen, were very similar to plasma cells and Russel's bodies as well as Mott cells were frequently observed. Pyronin staining was positive only on these peripheral sites (Fig. 34). Lymph nodes showed diffuse proliferation of plasmocytoid pyroninophilic cells.

Similar cases were previously reported by Brücher139 (1955) as lymphatic plasmacellular reticulosarcoma.

Case 4. Solitary reticulosarcoma of the sternum. The proliferating cells were connected to one another in stellated configuration, and reticulin fibers were recognized by silver impregnation.

But these cells had eccentric nuclei and basophilic and pyronin positive cytoplasm, and they were plasmocytoid in appearance (Fig. 33).
TABLE IV

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>WBC ($\times 10^9$)</th>
<th>Serum globulin</th>
<th>Gamma-globulin</th>
<th>Bence-Jones protein</th>
<th>Course (m. month)</th>
<th>Pathological diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>M</td>
<td>7</td>
<td>61.1%</td>
<td>26</td>
<td>-</td>
<td>17 m.</td>
<td>Diffuse reactive reticulosis</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>M</td>
<td>50. (97%)</td>
<td>76%</td>
<td>57</td>
<td>-</td>
<td>4 m.</td>
<td>Leukemic reticulosis</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>M</td>
<td>28.8 (35%)</td>
<td>25.5%</td>
<td>42</td>
<td>+</td>
<td>2 m. alive</td>
<td>Leukemic reticulosis</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>Myelogenous reticulosarcoma</td>
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<tr>
<td>5</td>
<td>52</td>
<td>M</td>
<td>8</td>
<td>67-82%</td>
<td>68</td>
<td>+</td>
<td>3 y. 6 m.</td>
<td>Morbus Waldenström</td>
</tr>
</tbody>
</table>

* Proliferating reticulum cells were plasmocytoid in appearance and usually pyronin positive except for Case 3.

These plasmocytoid reticulosarcoma and transition or combination of reticulosarcoma and plasmocytoma were also observed in the literatures.\(^{140,143-145}\)

Case 5.\(^{142}\) Systemic lymph nodes were markedly enlarged and goose-egg-sized tumors were observed on the mediastinum and on the left arm.

From frequent biopsies of lymph nodes and tumors, the disease was diagnosed as plasmocytoma.

At the autopsy, however, the lymph nodes and tumors were recognized as diffuse reticulum cells proliferation and much amount of reticulin fibers and collagenous fibers were found around these tumor cells. These tumor cells were pyronin positive and many PAS positive inclusion bodies were observed in the nuclei (Figs. 31 and 32). No descriptions were found on such intranuclear inclusion bodies except for the myeloma cells of Ito and Katsumu's case.\(^{141}\)

Macroglobulinemia Waldenström usually shows various pathological conditions such as lymphosarcoma, lymphatic leukemia, reticulosarcoma and plasmocytoma.\(^{138}\) The above-mentioned case of macroglobulinemia was at first recognized as having plasmocytoma, but at the autopsy, proliferating cells seemed to be plasmocytoid reticulum cells. The histological features of this case seemed to support the transformation of plasmocytoma to reticulosarcoma.

The entity “leukemic reticulosis” can be defined as irreversible reticulum cell proliferation in the medulla of lymph nodes and leukemic dissemination of these cells.

The diagnostic criteria are: a) diffuse medullary reticulosis of lymph nodes, b) reticulum cell appearance in the blood, c) acute leukemia-like symptoms and d) rapid course.
CONCLUSION

It was recognized that the following diseases can be accompanied by irreversible proliferation of reticulum cells and their appearance in the peripheral blood.

1. Leukemic reticulosis
2. Leukemic reticulosarcomatosis
3. Cataplastic reticulosis (Hodgkin disease-like granulomatous reticulosis)
4. Malignant change of associated reticulosis of various leukemias.

Leukemic reticulosis is rapidly progressive and leads to the death of patients usually within 4–6 months.

Histological features are characterised by diffuse medullary reticulosis of the lymph nodes and leukemic reticulum cell infiltration in various organs.

The proliferating reticulum cells exhibit various features such as histiocytoid, monocytoid, lymphocytoid or plasmocytoid appearances, but the basic structures of lymph nodes are usually preserved.

In spite of such manifold cytological manifestations, these cells are assumed to belong to reticulum cells.

No particular activities are found in reticuloendothelia and it seems more preferable to call it "reticulosis" than "reticuloendotheliosis".

Leukemic reticulosarcomatosis is a condition characterized by hematogenous tumor cell dissemination of reticulosarcomatosis at the terminal stage or as the results of chemotherapy or X-ray irradiation.

Reticulum cell appearance in the peripheral blood is observed in Hodgkin disease-like reticulosis but it is granulomatous in character and cataplastic in nature.

In association with various leukemias, reactive reticulosis exhibits malignant transition and neoplastic reticulum cells appears in peripheral blood at the terminal stage.

Acknowledgment

The author expresses his cordial gratitude to Prof. Akazaki for his kind guidance and to Prof. Kojima, Assist. Prof. Watanuki for their kind advices.

The author is also indebted to the following Universities and Hospitals, which had kindly submitted their precious materials. Sapporo City Hosp. (Dr. Ohtani), Hirosaki Univ. (Prof. Usubuchi), Iwate Med. Coll. (Prof. Yagawa), Res. Inst. tuberclo. (Dr. Nagai), Fukushima Med. Coll. (Prof. Kojima), National Cancer Inst. (Drs. Ohboshi, Itakura, Shimoyama), Tokyo Univ. (Prof. Miyake, Dr. Mori), Keio Univ. (Prof. Kobayashi), Toho Univ. (Prof. Nakayama), Tokyo Med. Dent. Coll. (Prof. Shimamine), Nihon Univ. (Prof. Takeuchi), Tokyo Womens' Med. Coll. (Prof. Mikami), Tokyo Tsushin Hosp. (Dr. Hino), Red Cross Central & Musashino Hosp. (Drs. Tanaka & Chin), Tokyo National Ist Hosp. (Dr. Kaneko), Kanto labor accident Hosp. (Dr. Ushio), St. Luke's Hosp. (Dr. Yamana), Nagoya Univ., Niigata Univ. (Drs. Ohnishi & Sakuragawa), Okayama Univ. (Prof. Seno), Hiroshima Univ. (Prof. Iijima), Hiroshima prepect. Hosp. (Dr. Monzen), Hiroshima ABCC, (Dr. Yamamoto), Kyushu Univ., Kumamoto Univ. (Prof. Takeuchi), Nagasaki Univ. (Prof. Matsuoka, Dr. Matsuo).
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LEGENDS TO FIGURES

Fig. 1–11. Leukemic reticulosis.

Fig. 1–3. Diffuse reticulum cell proliferation was found in the medullary portion but lymphatic tissues remained in follicular sites (Fig. 1. Case 10. lymphocytoid variety, Fig. 2, Case 11, and Fig. 3. Case 4. histiocytoid variety).
Fig. 3. Biopsied lymph node 2 months prior to death. Still unestablished diffuse medullary reticulosis, but at autopsy, diffuse reticulosis was completely established.
Fig. 4–6. Silver impregnation of lymph nodes. The basic architecture of lymph nodes, such as sinuses, medulla and follicles was well recognized (Fig. 4. Case 15. lymphocytoid variety, Fig. 5. Case 7. plasmocytoid variety, Fig. 6. Case 6. lymphocytoid variety).
Fig. 7–9. Left: Proliferating cells in lymph nodes. Right: Pathological cells in the blood stream.
Fig. 7. Histiocytoid variety: Pathological cells in the blood were large histiocytoid cells, ranging from 20–40μ in their long axis. Nuclei were round and 1–3 distinct nucleoli were observed. Proliferating cells in various organs were identical with pathological cells in the blood.
Fig. 8. Lymphocytoid variety: Pathological cells in the blood were lymphocytoid in appearance but a histological picture showed that these proliferating cells were reticulum cells.
Fig. 9. Plasmocytoid variety: Pathological cells in the blood had eccentric nuclei and basophilic cytoplasm with perinuclear halo. On histological sections, proliferated cells were pyronin positive and connected to one another in stellated configuration.
Fig. 10, 11. Hepatic lesions of leukemic reticulosis. Pathological cells were proliferated in Glisson's sheaths and invaded into sinusoidal spaces.

Fig. 12–14. Leukemic reticulosarcomatosis.

Fig. 12. (a-c) Pathological cells in the blood, showed pronounced tumor cell-like appearances, with large bizarre-shaped nuclei and pleomorphic appearances.
Fig. 13. Biopsy material. Nodular proliferation of reticulum cells. Six months later, the proliferation acquired the character of reticular type reticulosarcoma (Fig. 14). Compare to Fig. 3. (Leukemic reticulosis, 2 months prior to death).

Fig. 15–17. Cataplastic reticulosis (Hodgkin disease-like granulomatous reticulosis).

Fig. 15. Polymorphic reticulum cells as well as Hodgkin cells (a) were observed in the blood.
Fig. 16. Lymph nodes: Marked fibrosis with appearance of Hodgkin cells as well as Reed-Sternberg cells.
Fig. 17. Hepatic granulomatous lesion.

Fig. 18–21. Infectious reactive reticulosis.

Fig. 18 (a,b,c). 19. Reticulum cells in the blood in cases of septicopyemia.
Fig. 20, 21. Lymph nodes: Reticulum cell proliferation.

Fig. 22–27. Reticulosis in association with various leukemias.

Fig. 22, 23. Pleomorphic sinus reticulum cell proliferation in chronic myeloid leukemia.
Fig. 24. Nodular reticulum cell proliferation (left) and erythroleukemic infiltration in
Glisson’s sheath (right).

Fig. 25. Chronic myeloid leukemia: Giant cell appearance in sinusoidal spaces.

Fig. 26. Chronic myeloid leukemia: Pleomorphic destructive reticulum cell proliferation in the spleen.

Fig. 27. Bone marrow: Nodular reticulum cell proliferation in diffuse erythroleukemic cell proliferation.

Fig. 28 (a-d). Various reticulum cells, which appeared in a case of panmyelophthisis.

Fig. 29-34. Transformation of reticulum cells.

Fig. 29, 30. The second case of macroglobulinemia Waldenström in Japan. The proliferated cells seemed to be lymphocytes (29), but by silver impregnation (30), these proliferated cells were recognized as reticulum cells.

Fig. 31, 32. The fourth case of macroglobulinemia Waldenström, which was kindly submitted by Dr. Ushio. The proliferated cells were pyronin positive but connected to one another and with reticulin fibers (31). The arrows indicate PAS positive intranuclear inclusion bodies (32).

Fig. 33. Plasmocytoid reticulosarcoma of the sternum. The proliferated cells had eccentric nuclei and pyronin positive basophilic cytoplasm. But these cells were connected to one another and attached themselves to reticulin fibers.

Fig. 34. Splenic lymph follicle (F) in diffuse lymphatic plasmocytoid reticulosis. The arrows indicate pyronin positive cells in the peripheral region of the follicles (pyronin staining).