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Neoplastic Reticulosis Associated with Chronic Myelogenous Leukemia*

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Neoplastische Retikulose nach chronischer myeloischer Leukämie

Zusammenfassung. Bericht über 12 Fälle von chronischer myeloischer Leukämie mit neoplastischer Retikulose. Alle 12 Patienten waren langzeitig mit Cytostatica und Bestrahlungen behandelt worden. Erst terminal kam es zur Ausschwemmung blastenartiger Reticulumzellen in die Blutbahn. Die neoplastische Retikulose bestimmte weitgehend den Obduktionsbefund.

Die sekundäre maligne Retikulose ist anatomisch gekennzeichnet durch 1. eine Proliferation pleomorpher Reticulumzellen mit Bildung von Riesenzellen, 2. eine terminale Ausschwemmung atypischer Reticulumzellen in die Blutbahn, 3. organcharakteristische Reticulumzellwucherungen in Lymphknoten, Milz und Knochenmark. Die Lymphknoten zeigen das Bild der neoplastischen Sinusretikulose, die Milz das Bild der herdförmigen granulomatösen Reticulumzellwucherung, das Knochenmark sowohl noduläre wie geschwulstige Wucherungen von Reticulumzellen.

Die Beziehungen der Leukämie zur Retikulose werden überprüft. Es ist wahrscheinlich, daß diese terminalen neoplastischen Retikulosen durch die Behandlung der Leukämien mit Cytostatica und Bestrahlungen ausgelöst worden sind.

Summary. Twelve cases of neoplastic reticulosis associated with chronic myelogenous leukemia were reviewed. These leukemic patients received long-term treatment with cytostatics and irradiation. Blastomatous reticulum cells appeared in the peripheral blood terminally. Neoplastic reticulosis was prevalent in post-mortal findings.

This particular type of reticulosis was characterized by: 1. marked proliferation of pleomorphic reticulum cells with formation of giant cells, 2. a terminal dissemination of atypical reticulum cells by the blood stream, and 3. histological patterns specific for the lymph nodes, spleen and bone marrow. The lymph nodes showed a sinus reticulosis, blastomatous in nature. Lesions in the spleen were granulomatous, and the bone marrow had nodular lesions and tumors suggestive of reticulum cell sarcoma.

A relationship between leukemia and reticulosis was discussed from various view-points. The treatment of leukemia with cytostatics and/or irradiation was considered to be most important in inducing a neoplastic reticulosis from a reactive one.

Recent progress in cytostatic and radiation therapies has brought about a long-term remission in some patients with neoplastic disease particularly of chronic myelogenous leukemia.

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On the other hand, serious or sometimes fatal diseases such as myelofibrosis, agranulocytosis and myelophthisis have been observed as undisirable iatrogenic effects of the treatments (HAYHOE and KOK, 1957). The effects on the lymphatic and reticuloendothelial tissues may be significant. In 1965, the author reported 4 cases of chronic myelogenous leukemia with peculiar reticulosis, which had been successfully controlled by treatments. Histologic findings of these cases suggested a neoplastic character apparently simulating Hodgkin's disease or reticulum cell sarcoma (FUKUDA, 1965). Since then, several reports of similar cases have appeared and at least 12 cases are available in the Japanese literature (ASAI, KANAI, OHTA and MURAKAMI, 1965; Case Record, 1966; FUJIMOTO, ISHIDA, TOKUDA and TATEICHI, 1964; TANIMOTO, NIHO, HATORI and HISHIMOTO, 1967).

Such *secondary reticulosis* was used to be detected only by postmortal examinations, and in most of the cases coexistent reticulum cell sarcoma or tumor-forming leukemia was assumed. But histological features of reticulum cell proliferation in such cases were so particular as being rarely observed in the literature. Furthermore, the patients unexceptionally had received a long-term treatment with cytostatics and irradiation. Therefore, it was suggested that these lesions of reticulosis were secondarily induced by chemotherapy and/or radiotherapy. TERBRÜGGEN (1965) reported similar lesions in cancer patients who had received a radical removal of the tumor and a prolonged administration of cytostatics.

The present paper deals with a review of 12 cases available in Japan. Characteristics of clinical and postmortal findings of the disease and histogenesis of reticulum cell proliferation will be discussed in reference to therapeutic procedures.

Materials

Materials employed were composed of 8 autopsy and 1 biopsy cases in which clinical records and specimens for histologic examinations were generously submitted to the author and 3 additional cases in which only clinical and pathological records in the Japanese literature were available (Table).

In these cases undoubtful chronic myelogenous leukemia was diagnosed from clinical and hematological findings (positive Ph^1-chromosome, low alkaline phosphatase activity etc.). Long-term treatments with cytostatics, such as 6-MP, Myleran and Tespamin, X-ray or Co^{60} irradiation, and steroid administration were carried out. The patients exhibited a long-term remission, but died of acute exacerbation of the disease 2—5 years later.

A particular disease with reticulosis was first confirmed by postmortal examinations, but clinical findings of the patients were also different from ordinary chronic myelogenous leukemia in the following points;

1. severe splenomegaly (1—5 kg) with unusual histological features which were different from splenic lesions of myelogenous leukemia, 2. appearance of atypical (blastic) reticulum cells including giant cells in the blood stream, particularly at the late stage (Fig. 1), and 3. frequent induction of a bone tumor with proliferation of atypical reticulum cells.

The splenomegaly in the early stages is susceptible to therapeutic procedures but gradually becomes refractory at the late stage. Bone tumors were also noticed at the late stage or first at the autopsy.

Table

Case	Age (yr)	Sex	Clinical diagnosis	Course	WBC	Mbl. (%)	Reticulum cells (%)	Liver (g)	Spleen (g)	Site of bone tumors	The therapy
1	40	♀	CML	2 yr, 10 mo	500,000	35	7	2,230	1,090	rib	Myleran, X-ray
2	44	♂	EL, CML	3 yr,	3,100	10	5	2,334	1,076	none	6 MP
3	40	♀	CML	2 yr, 10 mo	340,000	0,5	0,5	2,050	750	left humers	6 MP, Myleran, Mitomycin
4	45	♀	CML	3 yr, 6 mo	84,000	25	1	1,790	1,230	pelvic bone	Tespamin, Co^{60}
5	19	♀	CML	4 yr	6,500	88	20	1,450	150	mandibule	6 MP, X-ray
6	62	♂	CML	5 yr	117,200	5,5	+	3,400	1,700	none	Myleran, 6 MP, X-ray
7	57	♀	CML	2 yr	44,000	20	+	2,100	5,150	none	Myleran, 6 MP
8	23	♂	CML	2 yr	22,900	15	+	2,350	3,950	vertebrae	Myleran
9	59	♀	CML	10 yr (alive)	18,900	14	++			none	Myleran, Co^{60}
10	10	♂	CML	2 yr, 10 mo	5,100	38	+	1,420	200	none	6 MP, Myleran
11	47	♂	CML	2 yr, 9 mo	2,900	3,2	++	1,480	500	pelvic bone	Myleran
12	34	♀	CML	3 yr, 8 mo	20,200	29	++	3,840	5,950	pelvic bone	Myleran, Mitomycin

CML = chronic myelogenous leukemia; EL = erythroleukemia; + = Histologically detected; ++ = Clinically detected.

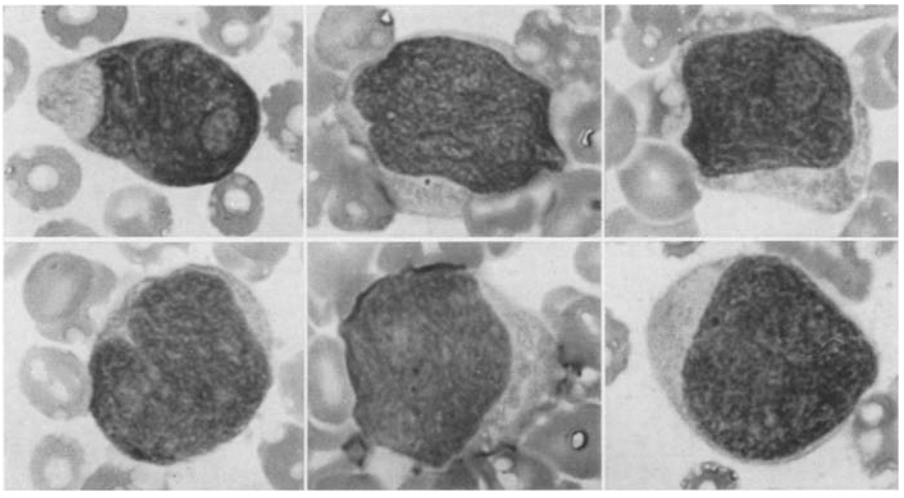

Fig. 1. Various blastomatous reticulum cells appeared in the peripheral blood

Case Reports

Hematogenous dissemination of atypical reticulum cells in the present cases was apt to be overlooked by hematologists. But histopathological evidence sufficient for a dissemination through the blood stream was disclosed in every case, as an embolism in the peripheral blood vessels.

Followings are brief clinical and pathological descriptions on 4 cases in which reticulum cell dissemination through the blood stream was actually discovered at the terminal stage.

Case 1. A 40-year-old Japanese female. At the age of 32, she suffered from uterine carcinoma and received a radical operation and X-ray irradiation of 2400 r in total.

Six years later, hepatosplenomegaly and extensive leukocytosis (50×10^4) appeared and the diagnosis of chronic myelogenous leukemia (CML) was established. But she was successfully treated with Tespamin. After a remission of 3 years, a fist-sized tumor appeared on her left 6th rib. At this time, her WBC was 5,000 to 9,000 without juvenile forms, but a bone marrow puncture revealed prominent myeblastosis with a few large abnormal reticulum cells and giant cells. She became febrile and marked leukocytosis (50,000) and hepatosplenomegaly reappeared. She died 3 months after the recurrency. At the terminal stage, 35.5% myeloblasts and 7% mono- and multinucleated giant cells were found in the blood smear.

At *postmortal examination*, numerous nodular lesions, small-finger-tip-sized, were remarkable in the cellular bone marrow, and a fist-sized tumor involving the vertebral end of the 6th rib was found on the left side. The nodules were composed of large uniform cells with vesicular nuclei, prominent in nucleoli. The tumor of the rib showed a feature similar to pleomorphic reticulum cell sarcoma. The spleen, weighing 1,090 g, was porphyry in appearance and an irregular proliferation of pleomorphic reticulum cells associated with various giant cells was marked in the Billroth's cords.

The lymph nodes were not enlarged and basic structure was found well preserved. The lymphatic tissue was atrophied with a proliferation of pleomorphic reticulum cells in the sinus.

Beside infiltration of leukemic myelogenous cells, reticulum cells were found infiltrating in various organs forming reticulum cell embolisms in peripheral blood vessels.

Case 2. A 44-year-old Japanese male. Three years before death, petechial bleedings, cervical lymphoadenopathy and hepatosplenomegaly were noticed and the patient was admitted to a hospital. Hematological examinations revealed hyperchromic anemia (RBC 183 mills.,

Hb 40%, C.I. 1.1) and leukopenia (WBC 4,800) with an appearance of a few macro- and normoblasts and 6.5% myeloblasts.

A bone marrow specimen showed an increase of megaloblasts (57%) and myeloblasts (15.6%).

At first, anemia was transiently improved by transfusions and administrations of folic acid and Vitamin B_{12}. Severe anemia re-appeared 5 months later and it became refractory to all therapeutic procedures.

One year after the entrance, hepatosplenomegaly increased in grade and the liver and spleen felt firm in consistency. Erythroleukemia was suspected and the patient received 6 MP with a little beneficial effect. After that a bone marrow puncture revealed 28.8% myeloblasts, 9.4% promyelocytes and 3.4% myelocytes, but megaloblasts were no longer observed.

The patient continuously run a downhill course and died in the 28th month of his hospitalization under the diagnosis of CML. At the terminal stage, a hematological examination revealed a WBC of 49,400 with 9% myeloblasts and 3—5% reticulum cells.

Autopsy revealed distinct enlargement of lymph nodes up to a finger-tip-size. The liver weighed 2,340 g and the spleen 1,090 g. The spleen was porphyry in appearance and multiple nodules, finger-tip-sized, were found in the cellular marrow.

Histological examinations revealed diffuse and nodular proliferations of atypical reticulum cells besides leukemic infiltration of myelogenous cells in various organs. The site of prevalent reticulum cell proliferation was the sinus of the lymph nodes and the Billroth's cords of the spleen. The nodular lesions in the bone marrow were irregularly distributed. Embolisms of atypical reticulum cells were frequently observed in the blood spaces of various organs, particularly in the sinusoids of the liver.

Case 3. A 40-year-old Japanese female. After the last delivary at the age of 37, general malaise, palpitation and a left hypochondral tumor appeared. Five months later, severe anemia and leukocytosis (WBC 348,000) were noticed, which showed a remission by the treatment with 6 MP and Busulfan.

Two and a half years later, she was readmitted to the hospital because of severe pain and swelling on the left upper arm. The blood counts showed WBC of 65,000 to 10,000, but no signs of acute exacerbation were observed. After three months, pathologic fracture occured in the left humerus and reticulum cell sarcoma was diagnosed on a biopsy specimen from the tumor.

The tumor was gradually enlarged and she died after the course of 3 years' duration. Her last WBC was 13,500 with 0.5% tumor cells, 0.5% myeloblasts and 0.5% metamyelocytes.

Autopsy revealed a fist-sized tumor on the left humerus with a feature similar to that of reticulum cell sarcoma and numerous finger-tip-sized nodules in the bone marrow. A marked proliferation of pleomorphic reticulum cells with leukemic infiltration of myelogenous cells was also observed in the liver, spleen and lymph nodes.

Case 4. A 45-year-old Japanese female. Three years prior to death, splenomegaly and leukocytosis (WBC 87,000) were noticed and she was treated successfully with Tespamin under the diagnosis of CML.

In the last 4 months, she suffered from bleeding tendency and a fist-sized tumor was noticed on her left gluteal region. Blood examination revealed a WBC 84,000 with 25% myeloblasts, 5% promyelocytes, and 24.5% myelo- and metamyelocytes. The tumor was gradually enlarged and it was refractory to treatments with irradiation and cytostatics.

The patient ran a downhill course and died in the 3rd year of her clinical course. At the terminal stage large unclassified atypical cells were found 1% in the blood smear.

Autopsy revealed a tumor, man's head in size in the pelvic bone, invading the sacroiliac joint and its adjacent adipose tissues. Histologically, it was composed of large atypical cells with distinct pleomorphism suggesting reticulum cell sarcoma.

These large atypical cells markedly proliferated in the spleen, 1,230 g in weight and lymph nodes, but infiltration of leukemic myelogenous cells was also observed in various other organs.

Pathomorphological Findings

As a common feature of chronic myelogenous leukemia, proliferation and infiltration of leukemic myelogenous cells were more or less observed in the bone

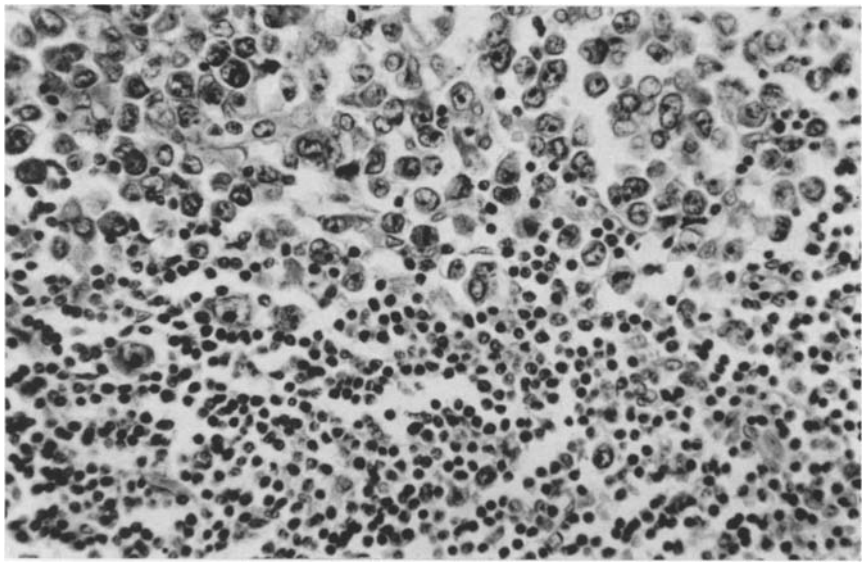

Fig. 2. Lymph node. Blastomatous reticulum cells were markedly proliferated in the sinus space

marrow, liver, spleen and lymph nodes. These leukemic cells were varied from blastic cells to more mature forms and showed a positive Peroxidase reaction. The unusual feature of these leukemic patients is diffuse and nodular proliferation of large atypical reticulum cells in the lymph nodes, liver, spleen and bone marrow. Consequently, following particular gross and microscopic findings characterized all the examined cases with or without clinical detection of the atypical reticulum cell in the peripheral blood.

1. Lymph Nodes. The lymph nodes varied in size from case to case, but in most instances, they were enlarged up to the size of a small-finger-tip particularly in the paraortic region, but conglomerated lesions were scarecely observed.

Histologically, reticulum cells in the sinus were swollen and markedly proliferated with compression of the lymphatic tissues. The basic structure of lymph nodes was relatively preserved with well distinguished follicles and medulla. But a destructive invasion was occasionally observed and a neoplastic character was prevalent in such cases.

The proliferating cells were generally large and prominently pleomorphic. The nuclei were large and vesicular or hyperchromatic in appearance and frequently contained prominent nucleoli. The cytoplasma was broad and irregular in outline. Bizarre or multinucleated giant cells and large cells similar to Hodgkin's cells were frequently observed among them. Mitotic figures were frequently encountered (Fig. 2).

In 4 cases, small lymph nodes showed features of sinus reticulosis with slight atypism, but other lymph nodes had reticulosis of more neoplastic character with numerous mitotic figures. The findings suggested a transition of hyperplastic reticulosis of the lymph node to a neoplastic lesion.

2. Spleen. In general, the spleen was markedly enlarged, weighed 1 to 5 kg and was firm in consistency. The capsule was smooth and dark red in color.

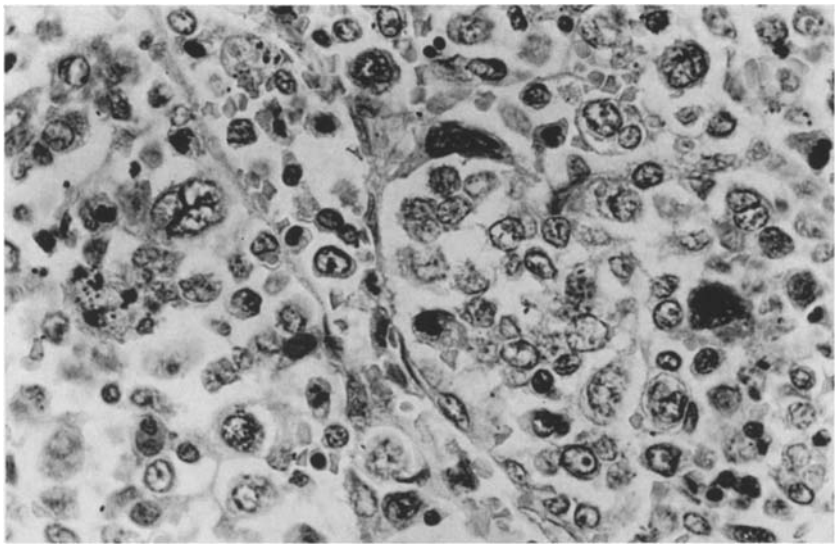

Fig. 3. Spleen. Pleomorphic reticulum cells including giant cell were markedly proliferated in the Billroth's cords

Multiple whitish grey nodules of 2—5 mm in diameter were scattered on the cut surface. Up to finger-tip-sized infarction foci were frequently observed in the subcapsular region.

Histologically, the basic structure was markedly destroyed with a granulomatous appearance similar to that in Hodgkin's disease (Fig. 3).

Large pleomorphic reticulum cells were irregularly proliferated in the Billroth's cords. The nuclei were large, vesicular or hyperchromatic and frequently had prominent nucleoli. Giant cells were also observed. They had various appearances and resembled Hodgkin's cells, Reed-Sternberg cells and megakaryocytes. So-called mirror-figures were also encountered. These proliferating cells had intensive phagocytic activities, and impaired red cells and hemosiderin pigments were frequently observed within the cytoplasm.

The argyrophilic fibers had an intimate relationship to these proliferating cells and consequently the architectures of the fibers were markedly deranged. The Malpighian follicles were preserved, but they were atrophied, and free from reticulum cell proliferation.

3. Liver. The sinusoidal spaces were markedly distended and contained numerous atypical cells including giant cells (Fig. 4). These cells sometimes formed nodular foci, but the lesions were sharply demarcated from leukemic cell infiltration (Fig. 5). No signs of transition between these cells and leukemic myelogenous cells were confirmed. The presence of such various atypical cells in the sinusoidal spaces gave evidence upon hematogenous dissemination at least at the terminal stage.

4. Bone Marrow. Multiple greyish nodules up to a small-finger-tip in size were found in the cellular marrow. They were composed of monotonous proliferation of large reticulum cells. But these foci were sharply demarcated from diffuse

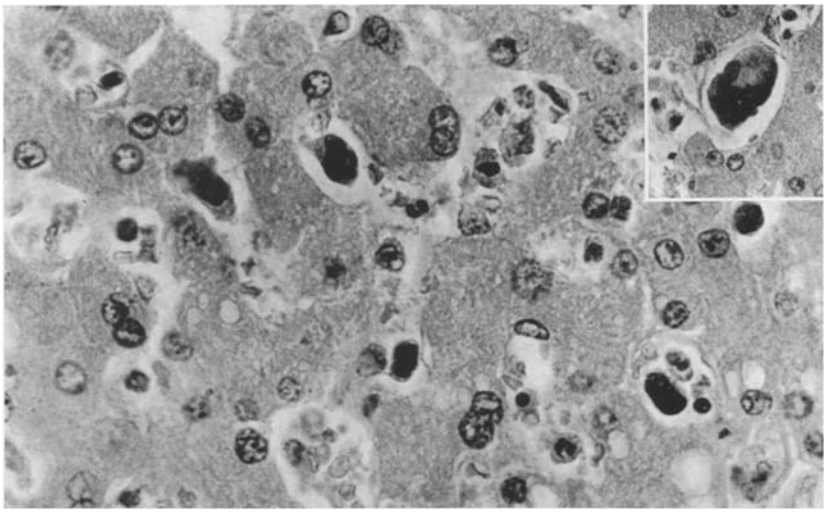

Fig. 4. Liver. Many atypical reticulum cells and giant cells were found in the sinusoidal spaces

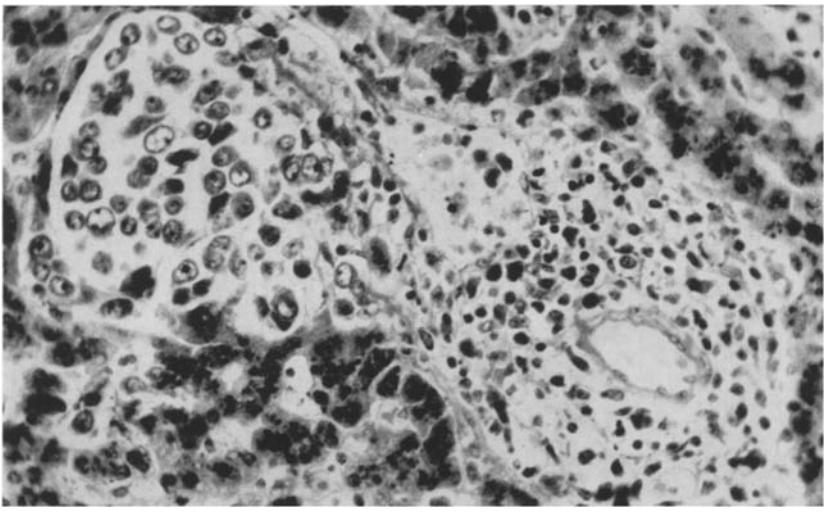

Fig. 5. Liver. Nodular foci of reticulum cell proliferation were sharply demarcated from leukemic cell infiltration (portal area)

proliferation of myelogenous cells and there was no evidence of transition between reticulum cells and leukemic cells (Fig. 6).

In 7 cases a marked proliferation of large reticulum cells associated with a tumor formation was observed. These tumors showed an extensive destruction of bone structures and led occasionally to pathologic fractures. The histological features were similar to those of undifferentiated or pleomorphic reticulum cell sarcoma, and actually in these cases clinical diagnosis was tumor forming leukemia or reticulum cell sarcoma of the bone marrow in association with chronic myelogenous leukemia (Fig. 7).

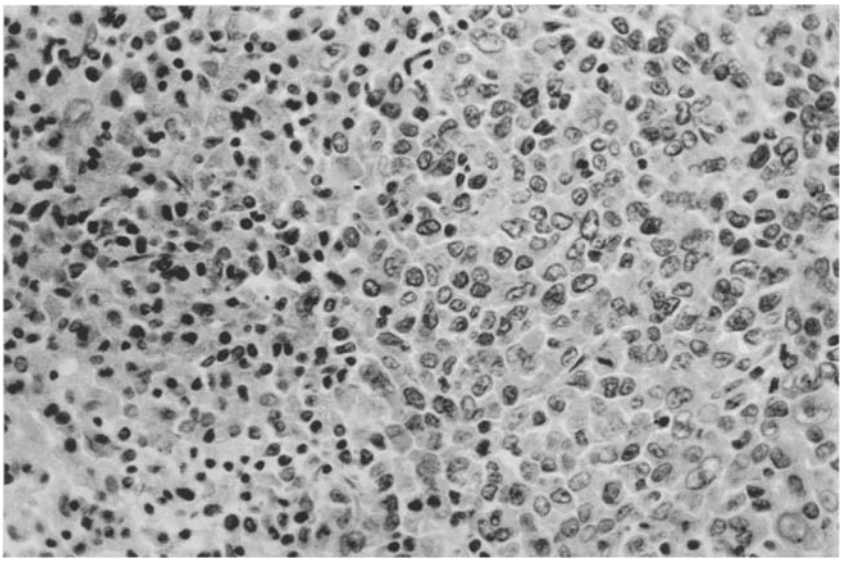

Fig. 6. Bone marrow. Nodular foci of reticulum cells (right) were sharply demarcated from surrounding leukemic myelogenous cell proliferation (left)

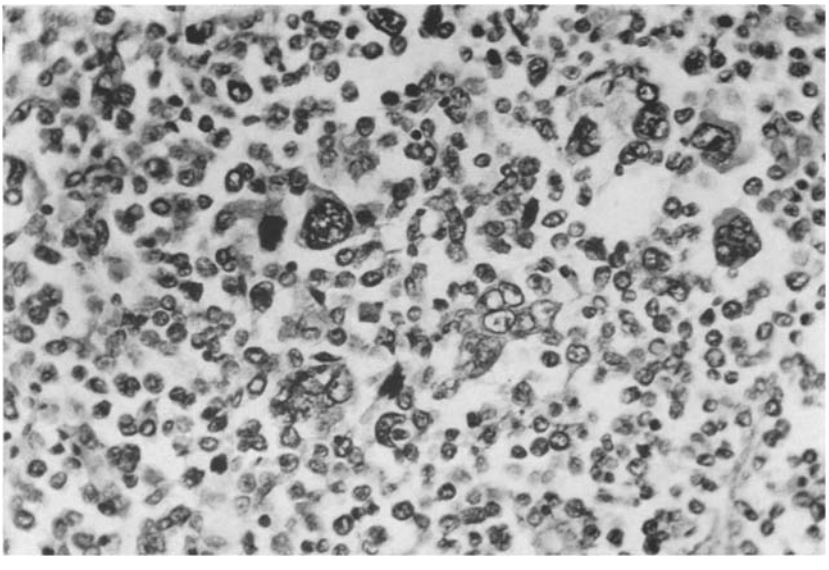

Fig. 7. Bone tumor. The feature is similar to pleomorphic reticulum cell sarcoma

5. *Other Organs.* Besides diffuse infiltration of leukemic myelogenous cells, atypical reticulum cells were also found infiltrating in the interstitial tissues of various organs, such as the kidneys, ovaries, adrenals and pancreas. The embolism of these cells was more frequently encountered in the peripheral blood vessels, such as glomerular tufts of the kidney and pulmonary capillaries. The findings suggested a dissemination of the reticulum cells through the blood stream at the terminal stage.

From clinical and histological observations, it was confirmed that a peculiar reticulosis of neoplastic nature had occurred several years after the onset of chronic myelogenous leukemia.

This reticulosis is characterized by:

1. proliferation of pleomorphic reticulum cells with formation of various giant cells, 2. a terminal dissemination of atypical reticulum cells through the blood stream, and 3. differences of histological features among the lymph nodes, spleen and bone marrow.

The lymph nodes show a sinus reticulosis, blastomatous in nature. The splenic lesion is granulomatous in appearance and the bone marrow has a nodular proliferation and tumors suggesting reticulum cell sarcoma.

Comments

The coexistence of leukemia and neoplastic reticulosis is an unsolved interesting problem and following four possibilities can be proposed concerning their histogenetic relationships.

1. Accidental coincidence of chronic myelogenous leukemia and neoplastic reticulosis or reticulum cell sarcoma (Double malignancies!) (BENECKE, 1940; LÜSCHER, 1960).

2. Metamorphosis of myelogenous leukemia.

a) The origin of proliferating large atypical cells is not the reticulum cell but undifferentiated leukemic cells (KOJIMA, 1963).

b) Transition of myelogenous leukemia to reticulum cell sarcoma (BELOLIPETSKAJA and GEZ, 1960; HELBIG and LOHSE, 1965; INTROZZI, 1955).

3. Leukemoid reaction associated with neoplastic reticulosis. The intrinsic nature of myelogenous cell proliferation is not that of "genuine" leukemia but a leukemoid reaction, which is induced by neoplastic reticulosis.

4. Malignant change of reticulosis associated with chronic myelogenous leukemia (FRITSCH, 1964; FUKUDA, 1965).

1. Accidental Coincidence. In 7 of the 12 presented cases, bone tumors appeared in various regions at the late stage. These tumors showed histological features similar to reticulum cell sarcoma of the bone marrow and such cases were usually regarded as representing an accidental coincidence of leukemia and reticulum cell sarcoma. But the findings in the lymph nodes and the spleen were quite different from those of metastatic lesions of reticulum cell sarcoma of bone marrow origin and also of systemic lymphatic reticulum cell sarcoma.

As the incidence of myelogenous reticulum cell sarcoma is extremely low, such a high coincidence of the tumor with chronic myelogenous leukemia is statistically unreasonable. No such tendency was confirmed in the extensive reports of GUNZ and ANGUS (1963) and of FABER and BORUM (1962) on the coincidence of leukemia and cancer.

2. Metamorphosis of Leukemia. There is a discussion about the origin of the above-mentioned large atypical cells. Some regard them as not belonging to reticulum cells but as undifferentiated leukemic cells. According to them, leukemic cells are transformed into more juvenile forms and lose their nature as blood cells and sustain the general mesenchymal character only (KOJIMA, 1963). Consequently, their histological appearance become similar to that of reticulum cell sarcoma. But metamorphosis of leukemic cells, which is frequently induced by cytostatic

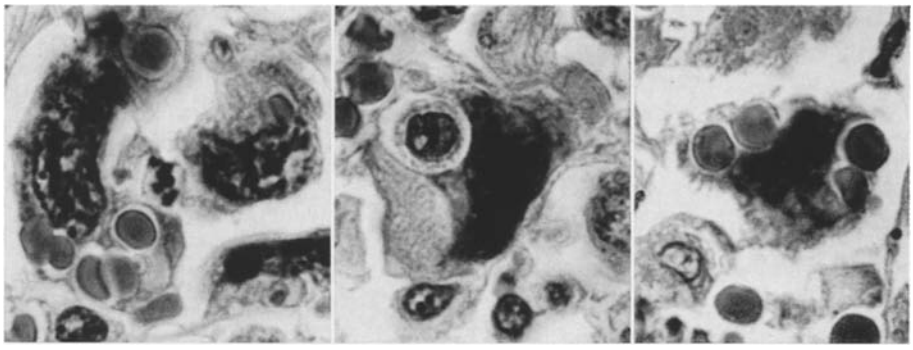

Fig. 8. Feature of phagocytosis. Various reticulum cells and giant cells contained many red cells within their cytoplasma

agents, is not so prominent and usually observed only in the bone marrow (KUNDEL and NIES, 1965). These atypical cells had prominent phagocytic activities (Fig. 8) and a negative peroxidase reaction. The histological features of the lymph nodes and spleen were quite different from those of leukemic cell infiltration.

All these findings support the assumption that the origin of these atypical cells are reticulum cells and not leukemic myelogenous cells. The lesions of large atypical cells are sharply demarcated from the surrounding proliferation of leukemic myelogenous cells without any transition. This fact is against the theory that these atypical cells are derived from leukemic cells.

3. Leukemoid Reaction Induced by Neoplastic Reticulosis. It is unlikely that the proliferation of myelogenous cells represents a leukemoid reaction which is secondarily induced by neoplastic reticulosis. It is rather an expression of "genuine' myelogenous leukemia.

The onset of myelogenous cell proliferation is always 2 to 5 years ahead of reticulosis. The findings of clinical and hematological examinations including the positive Ph^1-chromosome and low alkaline phosphatase activity of leukocytes indicate genuine myelogenous leukemia.

Histological findings endorsed this concept.

4. Malignant Changes of Reticulosis, in Association with Chronic Myelogenous Leukemia. Malignant changes of an associated reticulosis seem to be the most reasonable assumption. In cases of various leukemias reticulum cells in the sinus of the lymph nodes used to show a marked proliferation, occasionally exhibiting pleomorphism even with multinucleated giant cells.

In the present study, the author found not rarely in one and the same case that sinus reticulosis in lymph nodes had both hyperplastic and neoplastic patterns. A significant difference in the histological feature was observed among the lymph nodes, spleen and bone marrow, and this was rarely noticed in previous literature. These facts suggest that in the present cases associated reactive reticulosis changed to neoplastic one.

Various descriptions were found on independent coexistence of myelogenous leukemia and reticulosis or so-called reticulum cell sarcoma. BENECKE and FRESEN called such a condition "Myeloretikulose" (BENECKE, 1940; FRESEN, 1953).

They presumed a transition of hyperplastic reactive reticulosis to blastomatous neoplastic reticulosis, but no attention was paid to the histological and histogenetic differences between such associated reticulosis and ordinary lymphatic reticulum cell sarcoma.

In general, lymphatic reticulum cell sarcoma predominantly affects all the lymph follicles and initially shows the features of follicular reticulosis. But neoplastic reticulosis associated with various types of leukemia had no such tendency, and the follicles in lymph nodes and spleen were atrophied and free from reticulum cell proliferation. The hematogenous dissemination of reticulum cells, which is an exceptional finding in ordinary reticulum cell sarcoma, was observed in the present cases as well as in the previously reported cases of coincidence of leukemia and reticulosis or reticulum cell sarcoma (BARTH, 1925; BENECKE, 1940; INTROZZI, 1955).

The influence of cytostatics and irradiation must be considered to be important causative agents of such neoplastic transition (CHIARI, 1964; FRITSCH, 1964; FUKUDA, 1965). Almost all cases had long been treated with 6MP, Myleran or Tespamin and some patients had received X-ray or Co^{60}-irradiation. TERBRÜGGEN (1965) described similar neoplastic reticulosis in 3 cancer patients, who had received radical operation and had long been treated with cytostatics. There was no recurrent tumor, but atypical pleomorphic reticulum cells were markedly proliferated in the lymph nodes, spleen and bone marrow. These cells showed a prominent phagocytic activity, and a hematogenous dissemination was also confirmed by histological examinations.

The alkylating agents, such as Myleran and 6MP were known to produce a marked chromosomal damage, and cellular abnormalities, particularly cellular gigantism, were demonstrated in several case reports. WALLER described an appearance of numerous giant reticulum cells in a leukemia patient treated with Myleran (WALLER, 1960). ANGUS and GUNZ (1963), NELSON and ANDREWS (1964) and KOSS et al. (1965) recognized a development of carcinoma in leukemia patients, who were treated with Myleran. HUNSTEIN succeeded in induction of "generalized blastic leukemia" in 3 rats among 60 animals by administration of Myleran (HUNSTEIN, 1965). These facts seemed to show the carcinogenic activity of cytostatics, although no predilection for the reticuloendothelial system (RES) was demonstrated.

"Are cytostatics specifically carcinogenic to RES?" is an important problem and awaits further experimental evidence.

Concerning the histogenesis, reticulosis of the lymph nodes can be divided into three types; sinus medullary and follicular reticulosis. In general, a sinus reticulosis is considered to be purely reactive in nature, and neoplastic reticulosis or its precursor is known to show the feature of follicular or medullary reticulosis.

The existence of blastomatous sinus reticulosis was scarecely acknowledged previously and the single exception was "reticulose syncytiale", which was described by DUSTIN and WEIL (1936). Although their case was not related to leukemia and cytostatics, histological features were very similar to these of the above-mentioned cases.

The presence of such neoplastic sinus reticulosis as well as medullary and follicular ones seems to demonstrate that difference of histogenesis make different

histological features. This seems to make an analysis possible in future on the relationship between histogenesis and pathogenesis of the reticuloendothelial diseases.

Some agents may specifically activate reticulum cells of the follicles and others may provoke medullary or sinus reticulum cell proliferation. The difference of agents and/or difference of nature and histogenesis of reticulum cells seems to make distinct reticulosis.

Different modes of reticulum cell proliferation among lymph nodes, spleen and bone marrow also seem to indicate the organ specificity of the reticuloendothelial system.

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