An Autopsy Case of Reticulosarcomatosis Cutis*

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Reticulosis cutis in a wide sense represents the proliferation of the lymphoid-reticular cells in the skin and may be devided into two main groups; one is the inflammatory or reactive proliferation (reticulosis in a narrow sense) and the other is the neoplastic one. On the histological appearence, Gall and Mallory[1] devided the neoplastic proliferation of the lymphoid-reticular cells into the monomorphous and polymorphous group. In the former, the tumors are composed entirely of lymphoid-reticular cells, while in the latter group, the tumors show an admixture of inflammatory cells. These neoplastic proliferations of the lymphoid-reticular cells frequently occur in the lymphnode, but in the skin they rarely arise autochthonously.

We recently autopsied a case of reticulum cell sarcoma which primarily arised in the skin multicentrically, and showing leukemic picture, made wide-spread metastases.

CLINICAL COURSE

The patient was 59-year-old office man. He first noted two hen's egg-sized nodular elevation on the left thigh in June, 1963. These nodular masses were faintly red colored, but painless, so he gave them no concern. In August similar tumors appeared on the left fore-arm and in September he noted the painless swelling in the left orbital region. At the beginning of October, he had chill and fever for ten days. At the end of October, he noted other several cutaneous tumors on the face and abdominal wall. About three days before admission, the swelling of the left orbital region suddenly increased in size and began to

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have nasal obstruction, so he admitted to the Yamaguchi Prefectural Central Hospital on November 1, 1963.

At the time of admission, the patient was a moderately developed, rather healthy appearing man, and physical examination was negative, except the cutaneous tumors. These tumors were of various size and scattered over the face, fore-arms, lower extremities and abdominal wall, and most of them had the same characteristics: round, elastic hard, red to liver colored, painless and of no ulceration (Fig. 1). Because of the cutaneous tumor in the left orbital region, the

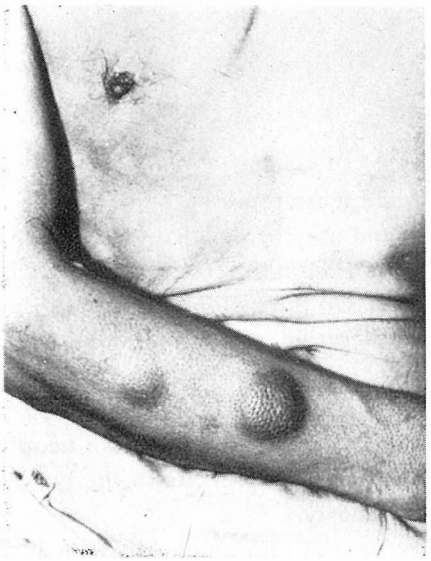

Fig. 1. Cutaneous tumors

Table 1. Peripheral Blood Examination

Date	11-2-'63	12-10	12-30	1-21-'64	2-18	3-24	4-28
RBC	328×10^4	319	364	371	184	335	327
Ht	32%	27	30	27.5	17.5	35.5	31.5
Thromb.	148	104	43	33	32	22	28
WBC	6000	5800	5800	3100	3200	3000	10400
N. band	0	0	4	3.5	3.5	8	0
N. segment	57	42	31	15.5	22.5	53	3
Eosioph.	3	18	1	0	1.5	3	0
Basoph.	1	2	0	0	1	0	0
Lymphocyte	31	28	36	48.5	25.0	27	34
Monocyte	8	5	3	6.0	10.5	3	11
Atypical cell	0	5	25	26.5	36.0	5	42

Table 2. Systemic Blood Chemistry

Date		11-4-'63	1-27-'64	4-20
Hemoglobin	(g/dl)	10.7	8.5	12.5
Serum protein	(g/dl)	7.2	7.0	6.0
Albumin	(g/dl)	3.6	2.9	2.8
Globulin	(g/dl)	3.6	4.1	3.2
A/G ratio		1.0	0.71	0.88
Blood sugar	(mg/dl)	73	80	125
Icteric index		4	4	6
Alk. phosphatase	(U.)	1.6	1.4	2.1
Cholesterol	(mg/dl)	184	171	376
Phenol turb.	(u.)	12.4	14.8	31.6
N P N	(mg/dl)	25.5	29.5	46.0
Urea N	(mg/dl)	13.0	15.5	28.2
G P T	(u.)	4.5	1.8	16.0

left palpebral fissure was completely closed. Laboratory studies such as hematological examination (Table 1), blood chemistry (Table 2), paperelectrophoresis of serum protain and urinalysis were not diagnostic. A chest film and alimentary examination of the gastrointestinal tract revealed no abnormalities. Histological findings of the biopsy specimen of the cutaneous tumor revealed masses of loosely packed tumor cells in the lower dermis and subcutaneous tissue. Infiltration of the tumor cells in the upper dermis was slight. Tumor cells possessed pale-staining cytoplasm and round, oval or kidney-shaped nuclei with distinct nuclear membrane and one or two prominent nucleoli. A moderate number of mitotic figures were present. Reticulum network was moderately developed and in some area reticulum fibers were intimately bound with the tumor cells, connecting by fine processes. Diagnosis of "reticulosis cutis" was made and then injection of Mytomycin and Toyomycin was begun. Examination of the peripheral blood and systemic blood chemistry during the hospitalization are summarized in Table 1 and 2.

On October 10, atypical cells were found in the peripheral blood, but not in large number. These atypical cells were two or three times larger than the red cells and had soft chromatin texture with two or three prominent nucleoli. A few number of the cells had several vacuoles in the cytoplasm (Fig. 2). Peroxidase reaction and phase-microscopical examination of these atypical cells were not carried out. At that time leukocyte count was 5800, and slight degree of normocytic, normochromic anemia was revealed. On October 28, examination of the sternal bone marrow was done, which showed very cellular marrow and megakaryocytes appeared normal, but the differential count showed a predominance of the atypical cells. These atypical cells had almost the same

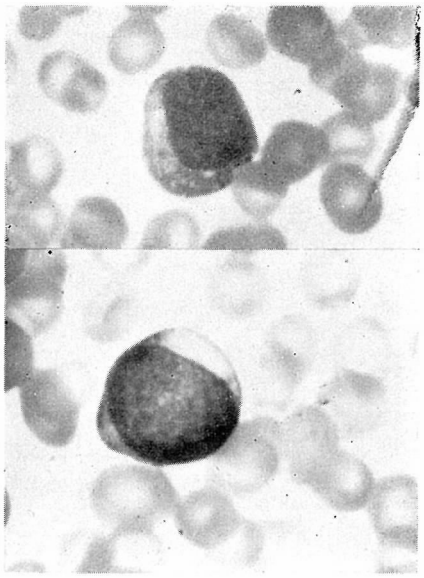

Fig. 2. Atypical cells in the peripheral blood

characteristics as those were recognized in the peripheral blood. The examiner made a tentative diagnosis of "lymphosarcoma cell leukemia". A few weeks later, examination of the bone marrow was done again. The findings were almost the same as before except for the great increase of atypical cells (58%).

Toyomycin, mytomycin and tespamin or of these combination were unsuccessful; atypical cells in the peripheral blood gradually increased in number and the cutaneous tumors showed the tendency to increase in size and number. Furthermore, leukopenia became prominent. So, in January 1964, combined use of endoxan and predonin was begun. These drugs showed dramatic effect to the cutaneous tumor and the general condition of the patient was gradually improved. However, atypical mononuclear cells still remained in the peripheral blood varying from 36 to 3%. At the terminal stage, leukocyte count was 10400 of which 42% was atypical cells.

On April 15, he suddenly became semicomatose with cramp. Gradually he became deeply comatose and his condition deteriorated, and died on May 1,1964, showing the clinical symptoms of cerebral bleeding. Throughout the course of the disease, there was no enlargement of the lymphnodes, spleen and liver. Hemorrhagic tendency was not evident clinically.

POST-MORTEM EXAMINATION and HISTOLOGY

An autopsy was performed three hours after the death. There was no external

abnormalities, except for the cutaneous tumors. The cutaneous tumors were only prominent on the face, neck and the left inguinal region. The heart was 340 gm in weight and the left ventricle was moderately dilatated. The aorta showed marked arteriosclerotic changes with calcified plaques and ulceration of the intima. The lungs were normal. The spleen was 75 gm and section revealed dark red pulp. The liver weighed 1600 gm and section showed no significant gross changes. The left kidney weighed 180 gm and the right 155 gm. On the surface of the both kidneys, there were sharply circumscribed pin point to small pea-sized grayish white foci. Such foci were not seen on section. Both adrenals were normal in size, but markedly thin in width. Cut surface of the cutaneous tumor was grayish white, firm, and showed the infiltrative growth into the subcutaneous tissue and muscle. No enlargement of the lymphnode was recognized anywhere. To our regret, permission of the autopsy of the central nervous system was not obtained.

Microscopically, cutaneous lesion was consisted of compact masses of the tumor cells, and comparing to the biopsy specimen, growth of the tumor cells was extensive and the whole dermis and subcutaneous tissue were completely replaced by the tumor cells (Fig. 3). The tumor cells had almost the same characteristics as those were recognized in the biopsy specimen. The cytoplasm was eosinophilic pale staining, but not so abundant. The border of the cytoplasm was irregular, some were round, oval or spindle shaped and some were polygonal. The nuclei also differed in configuration, some were round, but most of them were oval or kidney shaped with distinct nuclear membrane and one or two prominent nucleoli (Fig. 4). A moderate number of the mitotic figures were present. Phagocytic qualities of the tumor cells were not evident, but occasionally the cytoplasm contained small particles. Reticulum network was moderately developed, especially around the small blood vessels, and in some places, reticulum fibers were intimately bound with the tumor cells connecting by the fine processes (Fig. 5). However, in the other places, reconstruction of the reticulum was relatively scanty. In some area, tumor cells showed invasive growth into the small blood vessels (Fig. 6). In the upper dermis, blueish pink staining homogeneous material which appeared like amyloid substance was recognized between the tumor cells (Fig. 7). This material stained pale yellow with van Gieson stain, grayish blue with Azan-Mallory stain and slightly pink with periodic acid Schiff reaction. Though metachromatic staining with gentianaviolet was negative, this substance had the possibility to be amyloid, if not so, it might be degenerated collagen or elastic fibers.

Metastatic lesions were recognized in the kidney, lung, liver, testis and bone marrow. In the kidney, tumor cells were forming small masses in the cortex and showed the tendency to infiltrate into the interstitial tissue (Fig. 8),

and to make masses around the small blood vessels. The same small masses of the metasized tumor cells were also seen in the lungs, especially around the small blood vessels (Fig. 9). In the liver, a lot of the tumor cells were scatteringly seen in the sinusoid, rarely forming a small clump (Fig. 10). No tumor cells were recognized in the portal area. The hepatic cells in the central zone showed slight degree of fatty degeneration. In the testis, remarkable proliferation of the tumor cells was recognized in the interstitial tissue (Fig. 11) and the seminiferous tubules showed moderate atrophic changes. The bone marrow of the rib was highly cellular, but markedly involved. Because of the marked proliferation of the tumor cells, the myeloid and erythloid cells were remarkably decreased and no megakaryocytes were recognized at all (Fig. 12, 13). Such tumor cells were seen in the blood vessels of every organs, occasionally forming tumor cell emboli (Fig. 14).

The spleen was markedly congestive and normal follicles were scarcely visible. In the sinus, tumor-like cells were scatteringly seen, but it was hardly possible to distinguish the tumor cells from the monocytes which normally existed. The adrenal cortex on both sides revealed remarkable atrophy with degenerative changes, which might be caused by the excessive administration of predonin. In the epithelium of the esophagus, candida with moderate cell reaction was recognized.

COMMENTS

Giving careful consideration to the clinical course of the disease and on the basis of the histological findings, we made a diagnosis of reticulosarcomatosis cutis with leukemic modification and wide-spread metastases. In this case, however, there are several problems that must be discussed.

At first, in the differential diagnosis monocytic leukemia, leukemic reticuloendotheliosis and reticulosarcoma primarily arised in the bone marrow must be considered. Most cases of monocytic leukemia are recognized by the presence of a large number of monocytes in the peripheral blood, with frequent accompany of hepatosplenomegalia. In the monocytic leukemia of the Naegeli type, the infiltrate of the cutaneous lesion is composed mainly of monocyte-like cell[2], and in the blood the cells of the myelocytic series are present in addition to the monocyte-like cell, and the bone marrow shows myeloblastic hyperplasia without changes in the reticular cells[3]. Leukemic reticuloendotheliosis is characterized by hyperplasia of the reticulum tissue in the blood forming organs with the appearence of reticuloendothelial cells in the blood, and some authors regard this disease as one variety of monocytic leukemia[4]. As a rule, the reticulum cells of this disease are not malignant in nature, so they do not show invasive or de-

structive growth and lack cellular pleomorphism. Reticulosarcoma which primarily arised in the bone marrow may make metastatic lesions to the various organs with the appearence of leukemic manifestation. Histological findings of the bone marrow may be helpful to the differential diagnosis, though sometimes it may be difficult, especially at the terminal stage of the disease. In reticulosarcoma of the bone marrow, involvement is diffused and the bone marrow is almost completely destructed by the tumor cells which occasionally form tumor mass. As the result, severe anemia and hemorrhagic tendency are clinically evident, sometimes even at the beginning of the disease. In this case from the clinical and histological standpoint, it seems likely that the bone marrow was not primarily involved.

Some authors doubt or deny the possibility of arising of malignant lymphoma primarily in the skin. On this problem, Lever[2], Gall and Mallory[1] suggest that there is the possibility of arising of lymphoma autochthonously in the skin, reffering to the common lymphoid stem cell which has the ability to develop into either a lymphoid cell or a reticular cell. Furthermore, one cannot deny the assumption that the primary lesion was monocentric and showing leukemic picture, made wide-spread metastases to the skin and the other organs. If it was so, why the skin was much more frequently the site of metastasis than were others, such as the lung, liver, spleen and lymphnodes which have abundant blood and lymphatic supply. Though it may not be so convincing, this is the only reason we thought this to be multicentric in origin. As to this problem, Lever describes that lymphoma may start as a solitary lesion, but as a rule the lesions are mutiple from the beginning and this multiplicity is due to the systemic nature of the disease and usually not to metastasis.

Leukemia is merely the result of a release of immature tumor cells into the blood system and does not represent a separate form of disease. Leukemia is frequent with some type, and rare with other type of lymphoma. According to Mitus[5], the lymphoproliferative tumors are frequently associated with the dissemination of the cells in the peripheral blood and show leukemic picture, but on the other hand, solid tumors of reticulum cell does not usually show this characteristic. Rosenberg[6] also reported that the incidence of leukemia was the highest among cases of small cell lymphosarcoma (12.6%) and reticulum cell sarcoma showed the least tendency for leukemic modification (2.4%). As Berman[7] says, it may be possible that the syncytial arrangement of the reticulum cells prevent them from being easily washed out into the peripheral blood. But at the same time, we must consider the invasive tendency of the tumor cells especially into the blood vessel.

In a review of 618 cases of lymphoma, Gall and Mallory found leukemic blood changes in 17% and indicated that the blood picture was very often inconstant and varied from time to time during the course of the disease. In this

case the blood picture was aleukemic, but at the end of the disease it developed subleukemic pattern.

According to Herbut[8], if leukemia develops in reticulum cell lymphoma, it is of the monocytic variety, since the blood monocyte is derived from the reticular group of cells. However, it is not so easy to decide the cell-type in fixed preparation, because they often acquire a more undifferentiated appearence and in this abnormal form appear in the peripheral blood. Mitus and Mednicoff[5] applied the term "neoplastic lymphoid reticulum cell" to these abnormal appearing cells found in case of generalized malignant proliferation of the reticulum cell system. In this case, the tumor cells in the peripheral blood showed monocyte-like appearence in stained preparation, but in order to decide the type of the cell more definitely, the study of the living cell preparation will be very helpful.

SUMMARY

1) An autopsy case of reticulosarcoma which primarily arised in the skin multicentrically and showed leukemic picture was presented. Metastatic lesions were found in the lung, liver, kidney, testis and bone marrow.

2) The relationship between reticulosarcoma and leukemic modification has been briefly discussed.

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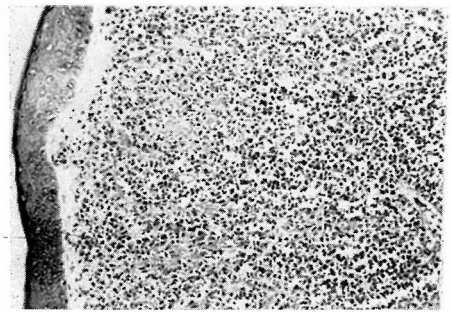

Fig. 3. Remarkable proliferation of the tumor cells in the dermis. H. E. ×100

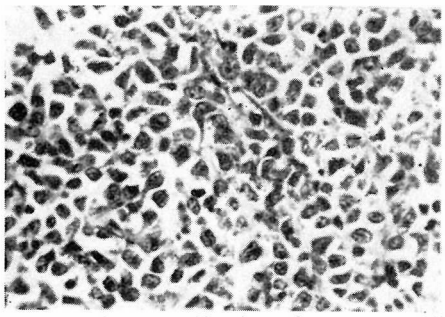

Fig. 4. High magnification of the tumor cells which have distinct nuclear membrane and two or three prominent nucleoli. H. E. ×400

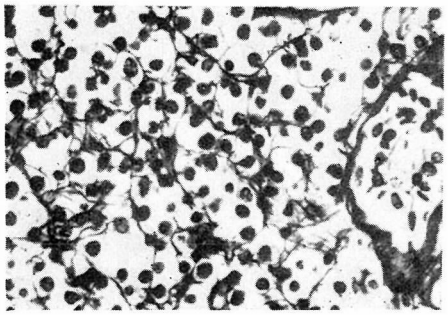

Fig. 5. Reticulum fibers are intimately bound with the tumor cells connecting by the fine processes. Pap's silver stain. ×400

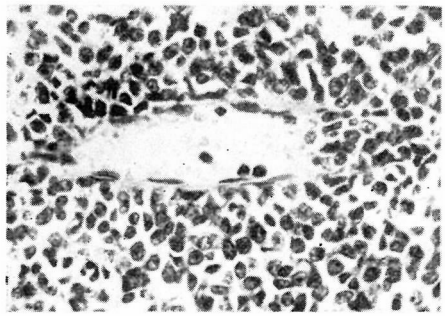

Fig. 6. Tumor cells show the invasive growth into the blood vessel. H. E. ×400

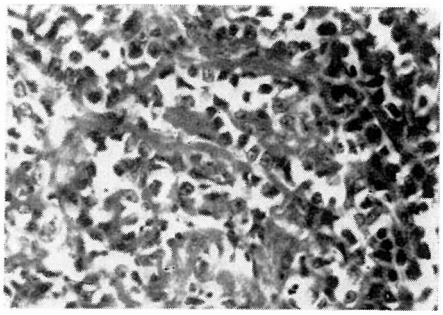

Fig. 7. Amyloid-like substance between the tumor cells. P. A. S. ×400

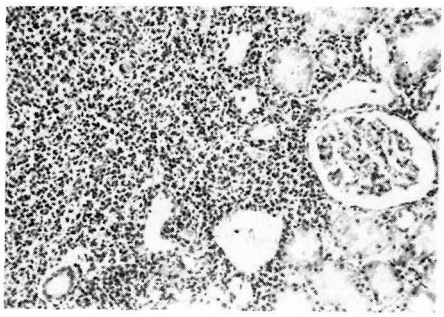

Fig. 8. Metastatic lesion in the kidney. H. E. ×100

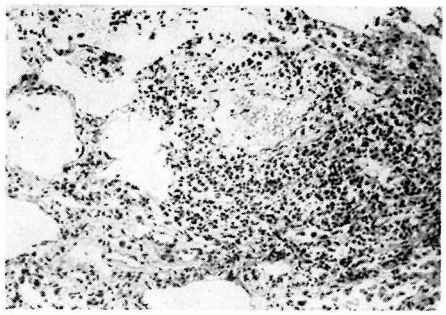

Fig. 9. Metastatic lesion in the lung. Tumor cells tend to accumulate around the small blood vessels. H. E. × 100

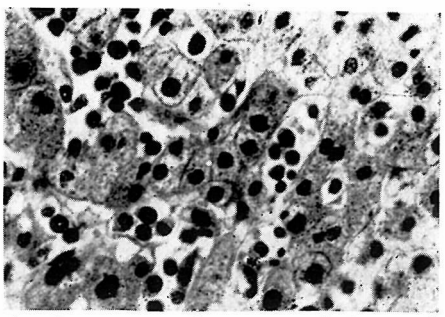

Fig. 10. Tumor cells are scatteringly seen in the sinusoid of the liver. H. E. × 400

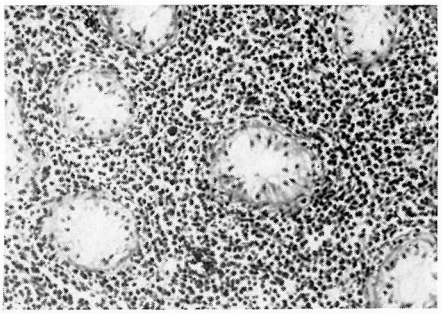

Fig. 11. Marked proliferation of the tumor cells in the testis. H. E. × 100

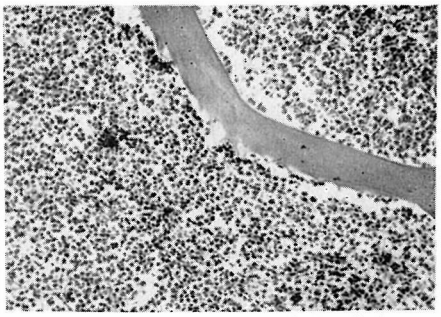

Fig. 12. The bone marrow of the rib is completely replaced by the tumor cells. H. E. × 100

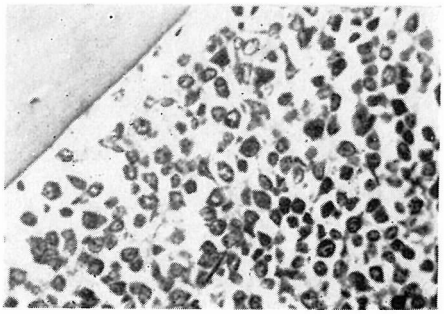

Fig. 13. High magnification of the bone marrow. The myeloid and erythloid cells are hardly visible. H. E. × 400

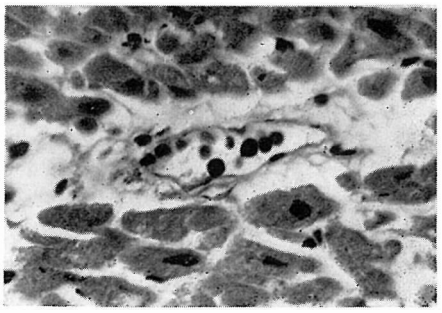

Fig. 14. Several tumor cells are seen in the small blood vessel in the myocardium. H. E. × 400