Idiopathic Panmyelophthisis with Hyperplastic Marrow. A Case Report.

45th Hematological Paper.

By

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Introduction.

Panmyelophthisis is a severe condition characterized by 3 cardinal features in peripheral blood: Aplastic anemia, malign neutropenia and thrombocytopenia. The disease occurs in an idiopathic or primary form of unknown etiology, and as a condition secondary to certain bone marrow poisons (benzol, arsenic, X-ray and radium etc.) or to replacement causes (leukemias, sarcoma, osteosclerosis and carcinomatous deposit etc.). But the final and conclusive diagnosis of panmyelophthisis is based upon the histologic findings of the hemopoietic tissues. There is hypofunction and most often almost complete aplasia, so that the greater part of the bone marrow is converted into a watery, fatty substance. All bone marrow precursory cells are reduced in number; nucleated red cells, myelocytes and megakaryocytes may be few or absent. If the bone marrow and the hemopoietic organs reveal hyperplasia and metaplasia of leucopoietic tissue which will be of the same nature of leukemic changes, the disease is called in the term of aleukemic leukemia. In a preceding paper Kimura¹⁾, one of the present co-workers, reported such a case of aleukemic myelosis.

On the other hand, it is a frequent fact that, notwithstanding that a case shows evidently cellular marrow, the case is not an example of

1) Sh. Kimura, Tohoku J. Exp. Med., 1940, 38, 522.

leukemia, but one of panmyelophthisis, (Whitby and Britton²⁾ and others, see later).

Such a case will be reported in the present article.

The Present Case.

The patient H.S., a boy aged 6 years and 2 months, was admitted to our Hospital on September 22, 1938, with a 2 months' history of remittent fever ($37^{\circ}\text{C}\sim 40^{\circ}\text{C}$) and of increasing weakness and pallor. There had been no nose bleedings and no purpuric spots. 2 months prior to Hospital admission he suddenly had a convulsive fit and then the fever was generally remittent. And he complained of faintness and depression. He was breast-fed in infancy and had had measles and whooping cough already. His family history gave nothing to note especially.

Physical examination upon admission revealed a pale, poorly nourished child with suffering facial expression, but the face was not puffed. The lips and the conjunctiva were pale and the tongue dry and whitely coated. No ulcerous and necrotic focus in the oral cavity. The cervical, submaxillar and inguinal lymph nodes were enlarged—some of the size of a bean, others of the size of a pigeon's egg—, but axillary, cubital and occipital nodes were not felt. The heart was slightly enlarged, but no anemic murmurs were heard. No masses were palpated in the abdomen, and the liver, the spleen and the kidneys could not be felt. No purpuric spots were seen anywhere on the skin. The urine: Acid; free from albumin, sugar, acetone, urobilin and urobilinogen; negative to diazo reaction. The stool gave a positive test to benzidine and no helminthic eggs were found. Blood gave the negative Wassermann and the Ide³⁾ reaction. The Mantoux reaction was negative in 1:1000 and slightly positive in 1:100. Blood cultures were always sterile.

The patient's condition slipped gradually toward fatal termination 27 days after admission, the entire course being characterized by a steady, moderate fever, which rose to a height of $39^{\circ}\sim 40^{\circ}\text{C}$ during one week before death. A total of 20 blood transfusions was given in the amount of 1100 cc..

The treatment consisted of the above mentioned blood transfusions and arsenic preparation (liquor Fowleri), but these had no appreciable

2) L.E.F. Whitby and C.J.C. Britton, *Disorder of the blood*, 2nd edit., London 1937, 346.

3) S. Ide and F. Ide, *Tokyo Iji Shinshi*, 1935, 59, 3085.

effect on the general condition of the patient and on the blood picture.

The blood examination was performed only thrice during the entire course. The blood picture on September 19, 3 days prior to Hospital admission was as follows:—Hemoglobine 40 (Sahli's value); red cells 2,240,000; total white cells 1,250; lymphocytes 1,050 per cmm. (84 %); neutrophiles 179 (14.3 %); plasma cells 21 (1.7 %); no basophiles, no eosinophiles, and no single monocyte was seen. Metamyelocytes occurred in 3.3 % (absolute count 40), but none of more immature cells. Very slight polychromatophilia was seen, but anisocytosis, poikilocytosis and basophilic stippings were not seen. A few normoblasts (200 per cmm.) were seen. Hemosedimentation rate was so accelerated that the hour value could not be measured by Yoshida's⁴⁾ micro method (Cf. 3rd Hematological Paper). It was 30 mm. in 35 minutes by this method (Cf. Table).

TABLE. Result of blood examination.*

			19. IX	23. IX	7. X	
Hemoglobin (Sahli's value)			40	33	41	
Erythrocytes per cmm.			2,240,000	2,240,000	2,450,000	
Leucocytes per cmm.			1,250	830	3,800	
Varieties of leucocytes	Neutrophiles	per cent	14.3	6.7	3.5	
		Absolute number	179	55	123	
	Basophiles	0	0	0		
	Eosinophiles	0	0	0		
	Monocytes per cent	0	2.4	0		
	Lymphocytes	per cent	84	87.1	96.1	
		Absolute number	1050	723	3662	
	Plasma cells	per cent	1.7	3.8	0.4	
		Absolute number	21	32	15	
Arne's nuclear shift	I	M	0	0	0	
		W	3.3	0	0	
		T	56.5	28	60	
	II	33.0	42	40		
	III	3.3	30	0		
	IV	3.3	0	0		
	V	0	0	0		
	Thrombocytes (Fonio) per cmm.					1,500
	Normoblasts per cmm.			200	200	0
	Anisocytosis			—	—	—
Poikilocytosis			—	—	—	
Polychromatophilia			+	+	—	
Basophilic stippings			—	—	—	
Sedimentation rate (the value of 30') with Yoshida's micro method			35	35	30	

* For blood examination the Tohoku-Pediatric Method, a modification of Sato-Sekiya's copper Peroxidase Reaction, was very frequently used (Cf. A. Sato and T. Suzuki, 1st Hematological Paper, Tohoku J. Exp. Med., 1936, 29, 92).

4) M. Yoshida, Tohoku J. Exp. Med., 1936, 29, 400.

The second (on September 23) and the third (on October 7) blood examinations gave almost the same results as the above, as is shown in the Table. Neutrophiles, remarkably decreased in number, were only 55 per cmm. on September 23, and 123 on October 7. The platelet count was reduced exceedingly and it was only 1,500 per cmm. by Fonio's method on October 7. Regenerative reactions of red cells were not seen at all on October 7 (Cf. Table). Blood coagulation began 3 minutes after blood taking and it was completed in $5\frac{1}{3}$ minutes by Oki's⁵⁾ method. Bleeding time was slightly prolonged.— $7\frac{1}{3}$ minutes by Duke's⁶⁾ method.

On September 26, the sternal puncture was performed. The marrow contained cells with deeply basophilic and vacuolated cytoplasm and with large swollen nuclei containing several indistinct nucleoli. I held these cells for degenerated myeloblasts, in spite of the fact that most of the cells did not give the peroxidase reaction* except for a few cells in each visual field. But the small bit of tissue removed from the sternum will hardly allow definite conclusion as to the condition of the bone marrow in general.

On September 29, the inguinal lymph gland was examined histologically and showed the following change: "Hyperaemia, bleeding and deposition of hemosiderin. The germinating centre was enlarged and clear, and the epitheloid cells were very scarce, and the necrobiosis was not distinct. Generally reticulum cells increased, and the endothels of small vessels increased in number and were swollen. Lymphocytes in medullary fasciculus were very scarce—a disturbance of lymphopoiesis. Dr. Yotsuyanagi,** Assistant Professor of the Department of Pathology of our University, who examined the histological changes of the lymph gland, stated that a conclusive assertion as regards the blood picture of the patient could not be drawn from the above described histological findings.

From September 26 on, the ulcer of the gingiva grew worse and sometimes bleedings from it were seen. From October 9 on, the patient suffered from toothache and sleep was disturbed. On October

5) T. Oki, Tokyo Igakkai Zasshi, 1931, 45, 1627.

6) W.W. Duke, Arch. of Intern. Med., 1912, 10, 445.

* I used the Tohoku Pediatric Method,⁷⁾ a modification of Sato-Sekiya's⁸⁾ original copper peroxidase reaction.

7) A. Sato, T. Suzuki and Ry. Shibata, Tohoku J. Exp. Med., 1934, 24, 195.

8) A. Sato and S. Sekiya, Tohoku J. Exp. Med., 1926, 7, 111.

** We are indebted to Dr. Yotsuyanagi, Assistant Professor, and Dr. Osada of the Department of Pathology in our University, for their examination of our case.

13, the tooth extraction was performed very carefully under the diagnosis of osteomyelitis of the lower jaw. Fortunately the bleeding after the extraction was not very severe. The patient's condition became worse and worse, the appetite was almost nil and sleep was markedly disturbed. He died on October 18, with the final diagnosis of panmyelophthisis.

Post-mortem examination. Macroscopical findings: Mesenterial lymph nodes were remarkably enlarged and hyperaemic. The liver was not enlarged, the spleen was enlarged, as large as that of an adult. In the thoracic cavity there were about 200 c.c. of bloody exudation. Intensive bleeding of the lungs was seen; these were hyperaemic and edematous. The mucous of the stomach was hyperaemic and hemorrhagic. Many petechial hemorrhages were seen in the kidneys. The intestines were hyperaemic and hemorrhagic (especially in the neighbourhood of the Peyer plaques).

The microscopic examination of the bone marrow of the femur and the ribs showed that it appeared soft and reddish brown. Microscopically the marrow was very cellular. The cells were composed almost all of large lymphoid elements with narrow homogenous or finely vacuolated cytoplasm. Most of the cells did not give the oxidase reaction, and the copper peroxidase reaction was also negative except a few cells in each visual field. The nucleus swelled and the nucleoli were indistinct. There were no cells to be regarded as myelocytes or as more developed cells. Megakaryocytes were scarcely seen. The deeply stained nucleated red cells with 1% safranin solution were seen in a considerable number.

In the other organs, there was seen no evidence of leukemic changes.

Comment.

Panmyelophthisis is a severe condition characterized by an extreme anemia, leucopenia and thrombocytopenia, due to aplasia or hypoplasia of the bone marrow tissue. The disease occurs in an idiopathic or primary form of unknown etiology, or as a condition secondary to an affection with certain bone marrow poisons.

The bone marrow examination of a case of agranulocytosis and panmyelophthisis reveals practically two conditions of the tissue. One of them is true aplastic condition of the marrow tissue; a true aplasia of erythroblastic tissue, no evidence of leucoblastic activity and no presence of megakaryocytes. The other of them is the defect of

maturing process of the marrow tissue; the marrow is filled with immature red cells, shows a marked myeloblastic reactions and contains numerous megakaryocytes despite the lack of nucleated red cells, granulocytes and having only a very few platelets in the peripheral blood stream.

There are many reports concerning the cases of agranulocytosis in which the bone marrow is found to be normal or even hyperplastic without apparrent injury to the granulopoietic tissue. In 1925 David⁹⁾ described a case of marked neutropenia (salvarsan agranulocytosis) in which the bone marrow contained many myeloblasts, myelocytes and neutrophile leucocytes. He suggested a disturbance of emigration of mature leucocytes from the bone marrow. Oppikofer¹⁰⁾ performed the histo-pathologic examination of 3 cases of agranulocytosis and found that there were no leucocytes and myelocytes in the bone marrow, and that the nuclei of numerous myeloblasts were oval and showed various degenerative changes in the bone marrow. He stated that there were some noxious influences of yet unknown toxin on myeloblasts of the bone marrow, and that these damages were shown through various degenerative forms up to necrobiosis. Zikowsky¹¹⁾ had at his disposal numerous carefully studied cases of agranulocytosis and opined that there was a blockade of the bone marrow which prevented the mature granulocytes from entering the blood stream. If this blockade persisted over a longer period of time, the parental cells of granulocytes, he stated, degenerated and broke down. Reichenbach¹²⁾ published the bone marrow picture of a case of agranulocytic angina showing at autopsy a fatty bone marrow with cellular areas which composed chiefly of promyelocytes. These promyelocytes were well preserved, and only a few of them he said, contained vacuoles. Fitz-Hugh and Krumbhaar¹³⁾ reported a case of agranulocytic angina in which "myelocytes and myeloblasts were found in the bone marrow at necropsy in more than normal numbers in a case of typical granulocytic angina, and at whose antemortem blood count was 200 white cells per cmm. (all lymphocytes), *i.e.*, a marked absolute reduction of lymphocytes and absence of all other white cells." They performed necropsy in the case within 2 hours of death, and fresh bone

9) W. David, *Med. Klin.* 1925, 21, 1929.

10) E. Oppikofer, *Beitr. path. Anat.*, 1930, 85, 165.

11) J. Zikowsky, *Wien. klin. Wschr.*, 1931, 44, 203, 226 and 259.

12) G. Reichenbach, *Folia Haemat.*, 1931, 45, 376.

13) T. Fitz-Hugh and E. B. Krumbhaar, *Am. J. Med. Sc.*, 1932, 183, 104.

marrow, spleen and lymph nodes smears were obtained immediately lest post-mortem changes of the marrow tissue might occur. They proposed a hypothesis: 'Maturation arrest' to explain the primary pathologic mechanism of the disease. They considered it likely that a disorder of maturation was at work either arresting the development of the white cells or producing degenerative changes in them before sufficient development had taken place for the migration into the blood stream. Fitz-Hugh¹⁴⁾ again reported with his co-worker, Comroe, the post-mortem bone marrow features in 9 agranulocytic cases, out of all their 18 cases. They concluded: "Necropsy study has shown in more than half the cases thus examined by us a plentiful supply in the leucopoietic centers of the progenitors of the blood leucocytes. This virtual hyperplasia is in marked contrast to the profound peripheral leucopenia characteristic of the disease, and strengthens the previous suggestion of an hypothesis of primary 'maturation arrest', rather than primary 'aplasia' to account for the hematologic phenomena of the disease." Jaffé¹⁵⁾ examined the bone marrow picture of 9 agranulocytic cases and found that in 4 of all his 9 cases the marrow was much more cellular than the age of the patients would lead one to expect. In this hyperplasia the granulopoietic tissue took an active part, and it seems, therefore, that in some instance the agranulocytic catastrophe, he stated, is preceded by proliferation of the young myelocytes. The autopsy was performed by himself with great care within 3 hours after death so as to prevent the artefacts due to the post-mortem change in fixing the marrow. So he knew that there were not the peculiar swelling and dissolution of the granules into vacuoles which he had stressed, and he was therefore inclined to believe that the dissolution of granules was an intravital phenomenon. Willi¹⁶⁾ examined 4 agranulocytic cases and found in 2 cases of them that the bone marrows were myeloblastic-myelocytic. He found that the hemopoietic tissue was not disturbed, but that the maturing process was disturbed, so there were no immature forms of neutrophiles in peripheral blood, though the parental cells were numerous in the bone marrow.

Recently Kuthan¹⁷⁾ discussed the aplastic condition of the bone marrow and mentioned at least 2 kinds of conditions. One of them is

14) T. Fitz-Hugh and B. I. Comroe, *Am. J. Med. Sc.*, 1933, **185**, 552.

15) R. H. Jaffé, *Arch. of Path.*, 1933, **16**, 611.

16) H. Willi, *Jahrb. Kinderheilk.*, 1934, **142**, 102.

17) St. Kuthan, *Dtsch. med. Wschr.*, 1939, **65**, 332.

a fatty changed marrow and the other was a "packed" marrow with parental cells. In the latter case the blood picture is aplastic, not only because of the disappearance of parental cells, but because of the disturbance of maturation and emigration of these parental cells. Such cases as with the bone marrow in which the maturation disturbance of granulocytes is presented, will, he added, be very difficult to differentiate from myeloid leukemia.

As seen in the references described above, we knew that there were many agranulocytic cases whose bone marrows did not show the alleged aplasia, but was rather hyperplastic and showed a defect of maturing conditions of progenitor cells with partly degenerative changes in cytoplasm and nucleus.

The present case of ours, as will be seen from the 3rd blood examination, had a remarkable anemia with entire absence of regenerative reactions, a marked granulocytopenia and a severe thrombocytopenia, and also showed a hemorrhagic diathesis. The case showed thus obviously a clinical feature of panmyelophthisis. But the marrow tissues from the sternum at biopsy and from the ribs and the femur at autopsy were found to be "packed" ones with swollen mononuclear cells (perhaps slightly degenerated myeloblasts with vacuolus in cytoplasm and in nucleus). The great majority of the cells was negative to copper peroxidase reaction as well as to oxidase reaction. Megakaryocytes were scarce but normoblasts were seen in a considerable number. The antemortem histologic examination of the inguinal lymph node, and the postmortem examination of the hemopoietic organs except the bone marrow showed no characteristic changes of leukemia. This condition was absolutely different from that of a leukemic leukemia, which Kimura,¹⁾ one of the present co-workers, reported in a preceding paper, with clinical guise of aplastic anemia or panmyelophthisis. It might be considered that the hyperplastic bone marrow seen in the present case of panmyelophthisis was in the condition of primary 'maturation arrest' suggested by Fitz-Hugh and Krumbhaar,¹²⁾ and by several other authors related in this paper. In our case autopsy did not, as shown above, reveal any replacement cause for agranulocytosis, nor was it a case of sepsis. And the bone marrow examination showed it to be a case due to 'maturation arrest' of parental cells as primary etiology—with the peripheral blood picture of agranulocytosis or panmyelophthisis. A hyperplastic marrow was not only seen in agranulocytosis, but, as Thompson¹⁸⁾ and his co-

18) W. P. Thompson, M. N. Richter and K. S. Edsall, *Am. J. Med. Sc.*, 1934, 187, 77.

workers stated, seen in the cases of aplastic anemia. We are of opinion that in the case of agranulocytosis and panmyelophthisis with hyperplastic marrow, the diagnosis is, as Kuthan¹⁷⁾ stated, very difficult and is erring, so we must use prudence in making the diagnosis in such cases.

It is said that the prognosis in the case of aplastic condition of the streaming blood with cellular marrow is rather hopeful, and also blood transfusion is said to be most effective. The present case of panmyelophthisis with cellular marrow did not improve even in spite of repeated blood transfusions. We believe that, however cellular the bone marrow of our case might have been, it is very natural that blood transfusions exerted no improving effect on the patient's condition, as the bone marrow was in a state of 'maturation arrest' and as it already showed the somewhat degenerative condition of the parentel cells.

Summary.

A case with clinical features of panmyelophthisis revealed, instead of aplastic marrow, a hyperplastic marrow at biopsy and at autopsy. The myeloblastic marrow was in a state of 'maturation arrest' and the cells showed partly degenerative conditions. There were no changes of characteristic leukemia in the other organs. Therefore, the present case was believed an example of panmyelophthisis with "packed" marrow.