Contribution to Hematology of Glandular Fever. A Case Report.

46th Hematological Paper.

By

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Introduction.

The clinical entity known as glandular fever was first described under the title "Drüsenfieber" by Pfeiffer¹⁾ in 1889. According to his description, the disease may be recapitulated briefly, as follows: (1) acute infectious disease which occurs in small epidemics and especially in "house epidemics"; (2) rapid enlargement of cervical lymph glands; (3) a less striking enlargement of liver, spleen and other glands.

Up to the present, glandular fever has long been recognized an entity, particularly abroad, although there are also reports of cases from Japan. On reviewing literature on this subject in our country, this disease was described in 1885, under the title "Kagaminetsu"²⁾. In spite of a number of observations from our country, there was no report of this disease from the north-eastern district of Japan.

The case reported here was a girl, and is, we believe, of interest from the hematological standpoint.

Case Report.

T.C., a girl, aged 1 year and 3 months, was brought to our Pediatric Clinic on account of the presence of tumors of the cervical, submental, axillary and inguinal lymph glands.

1) E. Pfeiffer, *Jahrb. f. Kinderheilk.*, 1889, **29**, 257.

2) K. Sato, T. Otawara, T. Yamada and H. Kataoka, *Kumamoto Igakkai Zasshi*, 1925, **1**, 14.

TABLE
Blood picture* in our own

Date	Day of illness	Erythrocyte count (millions)	Hemoglobin (Sahli's value)	Reticulocytes (%)	Polychromasia	Punctata basophilia	Anisocytosis	Poikilocytosis	Sedimentation of erythrocytes (Yoshida's micro method)				Thrombocytes (thousands)	Total white cell count per cmm.
									15'	30'	45'	60'		
22. IX	10	3.76	65		+	+	+	+	3.0	10.0	12.0	15.0	—	8,550
23. "	11	3.83	70	19	++	+	++	+	3.0	8.0	12.0	16.0	191	9,300
30. "	18	3.55	70		+	—	—	—	2.0	5.0	9.0	14.0	188	7,000
5. X	23	4.15	80		+	+	—	—	0.5	3.0	5.0	7.5	411	12,000
12. "	30	4.77	83		—	—	—	—	1.5	2.0	4.0	6.0	305	12,500
21. "	39	4.07	90		—	—	—	—	0.5	3.0	15.0	19.0	355	11,000
28. "	46	4.74	88		—	—	—	—	1.0	2.0	4.0	7.0	379	8,700
19. XI	67	4.46	88		—	—	—	—	1.5	3.5	5.0	9.0	267	12,000
9. XII	87	4.80	100		—	—	—	—	0.5	1.5	3.5	5.0	285	11,000

* Blood morphology was mainly examined by the Tohoku-Pediatric Method, a T. Suzuki, 1st Hematological Paper, Tohoku J. Exp. Med., 1936, 29, 92).

Family History.—Negative.

Past History.—The child was born at full term. She was chiefly bottle-fed (with goat's milk) and partly breast-fed for about 10 months with mixed feeding thereafter.

On May 10, she was vaccinated. On the 29th of the same month, she was admitted to our Clinic as a case of measles complicated with broncho-pneumonia and dyspepsia. About 6 weeks later she recovered and was discharged. On August 12, she suffered from a cough but got well in a few days.

Present illness.—Was first seen on September 23, after having complained of feeling sick for about 10 days. For the last 3 days prior to entrance, she had a high temperature showing 39°C in maximum. The parents noticed swelling in the neck of the patient on September 24th. Appetite and sleep were both bad. On September 23, she was admitted to the Clinic with complaints of fever and enlargement of lymph glands.

Physical examination.—She had a distressed, weak look, and appeared quite sick. Yellowish-white patches were to be seen on the tongue. The abdomen was prominent and tense. The liver and the spleen were not palpable. The heart, lungs, and throat were normal. The patellar reflexes were normal.

In an area between the body of mandibular bone and the sterno-mastoid muscle, a distinct swelling was seen which palpation showed to be a chain of swollen lymphatic glands. This was painful on pressure. Postero-cervical, axillar, inguinal and other lymph glands were also swollen. The urine showed a small amount of albumine, microscopically no white or red cell. Diazo reaction was negative.

Before admission, a blood count was made on September 22. The most striking features were: erythrocyte count was 3,760,000, hemoglobine (Sahli's

1.
case of glandular fever.

Varieties of leucocytes*											
Basophiles		Eosinophiles		Neutrophiles		Monocytes		Lymphocytes		Plasma cells	
%	Absolute count	%	Absolute count	%	Absolute count	%	Absolute count	%	Absolute count	%	Absolute count
0	0	0	0	29.6	2,500	3.3	280	67.1	5,700	2.0	160
0.4	40	0.8	70	15.5	1,440	1.2	110	82.1	7,630	1.0	90
0	0	3.8	270	30.7	2,150	11.6	810	53.9	3,770	0	0
0.2	20	2.4	290	20.8	2,500	12.8	1,540	63.8	7,660	+	+
0.6	80	0.3	40	34.7	4,340	10.6	1,330	53.8	6,730	0	0
0.8	90	4.2	460	20.7	2,280	7.4	810	65.4	7,110	2.3	250
0	0	5.6	490	15.5	1,330	5.9	510	52.9	4,600	0.3	30
0.9	110	7.3	880	21.4	2,570	7.5	900	62.7	7,520	0.2	20
0.6	70	8.3	1,010	18.0	2,200	6.3	770	66.6	8,130	0.2	20

modification of Sato-Sekiya's Copper Peroxidase Reaction (Cf. A. Sato and

value) was remarkably reduced; and polychromasia, punctata basophilia, anisocytosis and poikilocytosis were present. The sedimentation rate of erythrocytes (Yoshida's micromethod, Cf. 3rd Hematological Paper³⁾), was moderately accelerated. White blood cell count showed a lower value. A differential count showed as follows: neutrophiles 30%, monocytes 3% and lymphocytes 67%. Plasma cells were 2%. A remarkable nuclear shift of neutrophiles to the left followed, and young forms were 4%. The majority of lymphocytes were large. Pathologic granules of neutrophiles were within normal limits. At the time, the diagnosis of lymphatic leukemia was suggested.

Clinical Course:—On September 23, she was admitted to our Clinic. The temperature rose to 38°C. Urticarial eruptions appeared on the trunk. Blood examination on this date gave the following results: Erythrocyte count and hemoglobine was almost the same as the above. Reticulocyte counts were 19%. Polychromasia and anisocytosis were remarkable. Thrombocyte count showed 191,000, a value lower than the normal. White cell count slightly increased. The percentage of lymphocytes showed a higher value than the above, the majority of them being large lymphocytes. Lymphoblasts were 4 per cent. Pathological granules of neutrophiles slightly increased. Clotting time was normal and bleeding time was slightly delayed. Smudges appeared in a remarkable number. On this second blood examination, we could not help thinking still more of acute lymphadenosis. Therapeutic measures were directed against an anemic condition. Direct transfusion of 30 cc. of blood was performed. Injections of vitamin B and C preparations were performed. At the same time, "Therapol"* was injected.

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

* A preparation of p-aminobenzolsulfonamide.

TABLE 1. (Continued)

Date	Day of illness	Arneth nuclear shift*								Pathological granules of neutrophiles (%)	Smudges of nuclei	Remarks
		I			II	III	IV	V				
		M	W	T								
22. IX	10	0	4	34	55	5	2	0	5	++	Bleeding time, 5' 30'; clotting time, begin 2 and end 3' 30''	
23. " "	11	1	3	30	41	13	2	0	14	++		
30. " "	18	0	0	23	62	14	1	0	9	±		
5. X	23	1	1	30	42	20	6	0	20			
12. " "	30	0	0	11	29	40	13	7	14			
21. " "	39	0	0	20	41	30	4	5	12			
28. " "	46	0	1	12	39	38	8	2	9			
19. XI	67	0	0	8	40	42	8	2	6			
9. XII	87	0	0	10	27	45	16	2	6			

September 25, the temperature fell and the eruption disappeared. For about 4 days there was no fever.

September 29 and 30, the temperature rose to 38°C again. An intradermal test with tuberculin (0.1 c.c. of 1:1000) was negative. Roentgen finding showed an enlargement of the hilum of the lungs.

September 30, blood examination was performed. Erythrocyte count, hemoglobine and thrombocyte count showed a lower value than before. White cell count was 7,000. The percentage of eosinophiles and neutrophiles increased more than normal. Lymphocytes, however, decreased both relatively and absolutely. A few myelocytes appeared. Lymphoblasts were 3%. Large lymphocytes decreased remarkably and their percentage was 26. Pathologic granules of neutrophiles became normal and smudges of nucleus diminished remarkably. October 1, the second intradermal test with tuberculin (0.1 c.c. of 1:100) was negative. October 3, roentgen-examination was performed again and there was an enlargement of the hilum of lungs as before. The swelling of the lymph glands diminished slightly.

October 5, blood was examined. Erythrocyte count and hemoglobine increased slightly. Polychromasia and punctata basophilia were still present. Sedimentation rate of erythrocytes was accelerated slightly. Blood platelets showed also an increase. White cell count increased remarkably. The percentage of monocytes rose remarkably. Plasma cells were still present, though in a slight degree. The majority of lymphocytes were mature, although lymphoblasts and large lymphocytes were present. Pathologic granules of neutrophiles moderately increased. October 9, the temperature rose to 38°C. There was no pathologic findings of the urine on repeated examination.

October 12, the fifth blood examination was done. As erythrocyte count and hemoglobine increased slightly, abnormal red picture as polychromasia, punctata basophilia, anisocytosis and poikilocytosis disappeared. Blood platelets were normal. The percentage of eosinophiles, monocytes and neutrophiles were the same as above. The majority of white cells were poly-

TABLE 2.
Picture of lymphocytes (figures are percentage)

Date	Day of illness	Lymphoblasts				Large lymphocytes				Mature lymphocytes			
		Ordinary type		Rieder type		Ordinary type		Rieder type		Ordinary type		Rieder type	
		Azurophile granules		Azurophile granules		Azurophile granules		Azurophile granules		Azurophile granules		Azurophile granules	
		+	-	+	-	+	-	+	-	+	-	+	-
22. IX	10	0	0	0	0	21.0	28.0	1.0	3.0	6.0	39.0	0	2.0
23. "	11	0	4.0	0	0	20.0	28.0	1.0	4.0	12.0	27.0	0	3.0
30. "	18	0	3.0	0	0	6.0	11.0	0	9.0	8.0	52.0	0	1.0
5. X	23	0	0.5	0	0	6.5	17.0	0	1.0	4.5	67.0	0.5	2.0
12. "	30	0	0	0	0	6.0	13.0	1.0	5.0	10.0	40.0	5.0	20.0
21. "	39	0	0	0	0	7.0	20.0	3.0	12.0	6.0	40.0	5.0	7.0
28. "	46	0	0	0	0	3.0	11.0	1.0	4.0	8.0	57.0	7.0	9.0
19. XI	67	0	0	0	0	1.0	6.0	1.0	6.0	8.0	50.0	9.0	19.0
9. XII	87	0	0	0	0	2.0	12.0	1.0	8.0	10.0	45.0	6.0	16.0

morphnuclear leucocytes and the nuclear shift were normal. The percentage of lymphocytes relatively decreased, and the majority were mature. Blood examination and clinical features on this date led us to the right diagnosis of "Glandular fever." Since the admission, Fowler's solution had been administered perorally every day in order to cure anemia. But as a diagnosis was determined, the Fowler's solution was stopped. Although "Therapol" was injected 7 times to treat enlargements of lymph glands, no effect was seen. October 15, she caught cold and was found to be suffering from bronchitis the next day. The temperature rose to 39.4°C. In a few days she recovered from bronchitis.

October 21 and 28, blood examination was performed.

October 25, Wassermann reaction for serum was negative.

October 31, roentgen-examination was performed, and the enlargement of the hilum of lungs became smaller.

November 1, the intradermal test with tuberculin (0.1 c.c. of 1:100) was negative again. The swelling of the glands became gradually smaller, though these were still palpable. Notwithstanding that the blood feature of glandular fever was noticeable in a slight degree, she was discharged on November 21. The other children of the family were not affected probably because the parents had isolated them early enough.

November 19, blood examination was performed. At this time, lymph glands were scarcely palpable. Erythrocyte count and hemoglobine increased slightly, still above the upper limits of the normal value. Sedimentation rate of erythrocytes was slightly accelerated. Blood platelets were normal. White cells showed a high count. Eosinophilia and monocytosis were still seen. The proportion of neutrophiles to lymphocytes became normal. Pathologic granules of neutrophiles were also normal.

December 9, she came to the Clinic for medical examination without complaints though blood was examined; this time blood picture returned to normal.

Comment.

Frequent examinations of blood pictures from week to week, were of greater value in this case than were the clinical features. As mentioned at the beginning of the article, Pfeiffer¹⁾ did not describe blood findings. Türk⁴⁾ in 1907, called attention to the lymphatic blood picture in cases of septic disease with a decrease of granulocytes. Later, in 1912, the disease was described by Bloedorn and Houghton⁵⁾ as "acute benign lymphoblastosis." They stated that the blood picture was similar to that of acute lymphatic leukemia, with the difference that all cases took a benign course.

In Germany, this disease was first described by Schwarz⁶⁾ as "Infektiöse Mononukleose"—"Drüsenfieber"—"Angina mit lymphozytärer Reaktion als einheitliche Infektionskrankheit," and he stated that this disease was characterized by appearance of lymphoblasts and an increase of plasma cells. Sato, Otawara, Yamada and Kataoka²⁾ reported that "Kagaminetsu" and glandular fever ought to belong to an entity, and they made the first report on the blood picture of this disease in our country. Since this publication a few cases of the disease have been reported.

Now, we shall state the hematological findings of our own case in comparison with the results hitherto published in literature.

1. Red blood cell:—In the cases of glandular fever, Sato, Otawara, Yamada and Kataoka²⁾, Akashi⁷⁾, Majima⁸⁾ and Takahashi⁹⁾ said that erythrocyte count was within the normal limits. According to Tominaga¹⁰⁾, red cell count was reduced in a slight degree. In the case of Takahashi⁹⁾ red cell count was 4,140,000 on the first blood examination, and this value is below the under limit of the normal count, viewed from Sato-Suzuki's¹¹⁾ Standard Table of Blood Picture for Every Age. Tidy and Morley¹²⁾ said that red cell count was within normal limits, and Schwarz¹³⁾ stated that erythro-

4) W. Türk, Wien. klin. Wschr., 1907, 20, 157.

5) W. A. Bloedorn and J. E. Houghton, Arch. of Intern. Med., 1921, 27, 315.

6) E. Schwarz, Klin. Wschr., 1929, 42, 98.

7) S. Akashi, Nippon Densenbyogakkai Zasshi, 1927, 1, 421.

8) R. Majima, Rinsho Shonika Zasshi, 1931, 5, 353.

9) K. Takahashi, Jika Shinryo, 1938, 9, 664.

10) T. Tominaga, Zikken Iho, 1931, 17, 1139.

11) T. Suzuki, Tohoku J. Exp. Med., 1937, 30, 378.

12) H. L. Tidy and H. B. Morley, Brit. M. J., 1921, No. 26, 452.

13) E. Schwarz, Klin. Wschr., 1930, 9, 2355.

poesis was not influenced at all. Lehndorff and Schwarz¹⁴⁾ said that red cell count was normal in most cases except for severe or prolonged cases. In our own case distinct anemia was seen on the 10th day of illness (on the first examination). Red cell count showed an increase gradually reaching the normal limits on the 30th day of illness (on the 5th examination). Reticulocyte count was 19⁰/₁₀₀ on the 11th day of illness. Polychromasia, basophilic stippling, anisocytosis and poikilocytosis were present during the period accompanied by anemia.

2. Hemoglobin:—Sato, Otawara, Yamada and Kataoka²⁾, Akashi⁷⁾ and Tominaga¹⁰⁾ related that hemoglobin was within the normal limit. Takahashi⁹⁾ said that it showed a low value, being 72 in the minimal value. According to Lehndorff and Schwarz¹⁴⁾ hemoglobin shows normal value excepting in severe or prolonged cases. In our own result, hemoglobine showed a low value until the 18th day of illness.

3. Blood platelets:—Takahashi⁹⁾ examined blood platelets and the count was 272,000 toward the end of the second week. In our own case, thrombocytes were reduced slightly until the 18th day of illness and returned to the normal limits after showing a temporary increase on 4th blood examination.

4. Hemosedimentation rate of erythrocytes:—Within our knowledge, there has been no reference concerning hemosedimentation.

In our own case, hemosedimentation rate was moderately accelerated until the 18th day of illness and attained gradually the normal limits, after showing a moderate acceleration at one time when the patient was attacked by bronchitis.

5. White blood cells:—Sato, Otawara, Yamada and Kataoka²⁾ said that in their 12 cases, leucopenia in slight degree resulting from neutropenia, regenerative nuclear shift to the left and monocytosis ("mononucleosis") were seen on the 3rd and 4th day of illness. From the 5th to the 7th day of illness leucocytosis due to both monocytosis and lymphocytosis was present, they stated, but the duration of leucocytosis was different in each case. As they stated in the defervescent stage, postinfectious lymphocytosis was present and Rieder type of large and small lymphocytes showed slightly an increase in number. This blood picture, they mentioned, was similar to that of lymphatic leukemia. Eosinophile count was normal on the 3rd and

14) H. Lehndorff and E. Schwarz, *Ergebnisse d. inn. Med. u. Kinderheilk.*, 1932, 43, 1.

4th day of illness, and it showed an increase on the 5th~7th day of illness.

In our own case, leucopenia resulting mainly from neutropenia was seen on 10th and 11th day of illness. This agrees with the result of Akashi,⁷⁾ Sakamoto and Kawano,¹⁵⁾ Uchida and Ikawa,¹⁶⁾ Tidy and Morley,¹²⁾ Becker,¹⁷⁾ and Lehndorff and Schwarz.¹⁴⁾

As to the nuclear shift of neutrophiles, in our own case it was strong and regenerative until about the end of the 3rd week, as was experienced also by Takahashi,⁹⁾ Schwarz,¹³⁾ Lehndorff and Schwarz.¹⁴⁾ On the 23rd day of illness, leucocytosis due to lymphocytosis (82.1%) and monocytosis were seen, and neutrophiles still remained below the normal value though they showed a slight increase formerly.

Monocytes, in our own case, showed an increase (above 1,300) from the 23rd to the 30th day of illness. This agrees with what was shown by Akashi,⁷⁾ Sakamoto and Kawano,¹⁵⁾ Tominaga,¹⁰⁾ Takahashi⁹⁾ (maximal count 8.5% on the 14th day of illness), Schwarz¹³⁾ and Lehndorff and Schwarz¹⁴⁾. It is noteworthy that monocyte count increased threefold, and that abnormal forms of monocytes were seen in a large number in our own case. Schwarz¹³⁾ also noticed that monocytes were so injured that the differentiation between this kind of cell and the large atypical lymphocytes was difficult in most cases. Lehndorff and Schwarz¹⁴⁾ were of the same opinion.

Eosinophile count was reduced at the beginning in our own case, slightly increased on the 3rd examination and then showed a remarkable increase from the 39th day of illness, which was probably a post-infectious eosinophilia. Lehndorff and Schwarz¹⁴⁾ observed often an increase of eosinophiles in the convalescence.

Plasma cells showed a slight increase on the 1st and the 6th blood examination, and then were gradually reduced to almost the normal value. According to Majima⁸⁾, Utida and Ikawa¹⁶⁾ and Lehndorff and Schwarz¹⁴⁾ a presence of plasma cells was seen for a long time after the patient recovered from this disease.

As to lymphocytes, in our own case, the count which showed an increase at the beginning of illness kept a high count from the 23rd until the 87th day of illness (on the last blood examination), though it

15) S. Sakamoto and H. Kawano, *Jittli Ika to Rinsho*, 1928, 5, 152.

16) H. Utida and S. Ikawa, *Jikken Iho*, 1932, 18, 1018.

17) H. Becker, *Munch. med. Wschr.*, 1931, 78, 1594.

showed a slight decrease at one time Sato, Otawara, Yamada and Kataoka²⁾ Akashi,⁷⁾ Sakamoto and Kawano,¹⁵⁾ Uchida and Ikawa,¹⁶⁾ Takahashi,⁹⁾ Evans and Roff¹⁸⁾ and Becker¹⁷⁾ stated that also lymphocytosis was present about the 10th day of illness. Among these authors, Uchida and Ikawa,¹⁶⁾ Takahashi,⁹⁾ Tidy and Morley¹²⁾ and Lehndorff and Schwarz¹⁴⁾ the lymphocytosis continued as long as several months, or even a year. In our own case, lymphocytosis was still seen after 3 months, on the 9th examination.

6. Picture of lymphocytes.—We classified the lymphocytic cells in our own case and divided them into 3 groups; Lymphoblasts, large lymphocytes, and mature lymphocytes.*

In our own case, large lymphocytes showed a higher percentage than the mature on the first and second examination. And on the latter, lymphoblasts were seen in 4%. This agrees with the results of Takahashi,⁹⁾ Bloedorn and Houghton⁵⁾ and Evans and Roff¹⁸⁾ and Becker¹⁷⁾.

Lymphoblasts, in our own case, disappeared on the 30th day of illness and large lymphocytes also showed a gradual decrease, while the mature lymphocytes increased steadily, as shown by Takahashi⁹⁾.

In our own case lymphocytes of Rieder type were 13% on the 11th day of illness and showed an increase in the stage of strong lymphocytosis (about the end of the 3rd month of illness), after a temporary decrease in the course. Sato, Otawara, Yamada and Kataoka,²⁾ Uchida and Ikawa¹⁶⁾ and Bloedorn and Houghton⁵⁾ said also that lymphocytes of Rieder type especially showed an increase in the period of lymphocytosis.

There is only one reference concerning azurophile granules. Takahashi⁹⁾ reported that azurophile granules of lymphocytes were 11% on the 6th day of illness. Azurophile granules were in our own case examined repeatedly as long as over 3 months. The percentage of azurophile granules which was 28–33 on admission (the 10 or 11th day of illness), was reduced to 18–19 towards the end of our examination.

Summary.

A case of glandular fever—which seemed to be a possible case of lymphadenosis—was observed by us for about 3 months. Blood was

18) G. Evans and W. A. Roff, Brit. Med. Journ., 1930, 1, 1039.

* The mature lymphocytes, in this paper, means, besides small lymphocytes the mature lymphocytes, however much larger they may be.

examined as often as 9 times, the noticeable hematological findings were as follows: (1) anemia and hypohemoglobinemia; (2) moderate acceleration of hemosedimentation of erythrocytes; (3) slight decrease of blood platelets; (4) lymphocytosis and neutrocytopenia; (5) regenerative nuclear shift to the left; (6) appearance of lymphoblasts and an increase of large lymphocytes.

These changes drew near the normal limits gradually in a month, except for the presence of a remarkable lymphocytosis.

Conclusion.

A case of glandular fever with the hematological findings was reported. The blood picture in this type of case bore a great similarity to that of acute lymphatic leukemia at the beginning of admission. However, the course was a benign one with a recovery.