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Chédiak and Higashi's Disease*. Probable Identity of "A New Leucocytal Anomaly (Chédiak)" and "Congenital Gigantism of Peroxidase Granules (Higashi)"

By

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In the present paper I desire to describe a new blood disease, preliminarily reported a few months ago.[1] How I have come to describe the present blood dyscrasis is rather peculiar as well as accidental.

In Sept. 1953, O. Higashi published a new clinical entity for which he suggested the name of "Congenital Gigantism of Peroxidase Granules".[2] The details of it I refer to his original paper, but I shall relate how he came to find out this new clinical entity.

What surprised him was the peroxidase picture of blood of that case of his. He usually would not use the Giemsa or the Wright stain first, but used to apply the Tohoku Pediatric Method (a modification of Sato and Sekiya's peroxidase reaction)[3-4] on blood smears in every case, because, by that method, he could, however badly a blood film might be prepared, differentiate lymphocytes correctly from (peroxidase-positive) monocytes. He had been using it since 1944. So when he saw in 1950 the peculiar case of his own, he was surprised at the peroxidase picture his case had presented. Abnormity was not the word for it. It was a *monstrous peroxidase picture*, as will be shown below.

Every hematologist with some experience with the peroxidase reaction thinks, I believe, that the peroxidase picture which the neutrophil, a myeloic element, presents is not only general, but even universal (Cf. Fig. 1, a).

In this particular case of his own, he found that neutrophils were peroxidase-stained like the cell (Fig. 1, b), in wihch those small peroxidase granules that would normally have ocurred diffusely scattered all over the cytoplasm did gather in a few or several spots of it to form round clumps or

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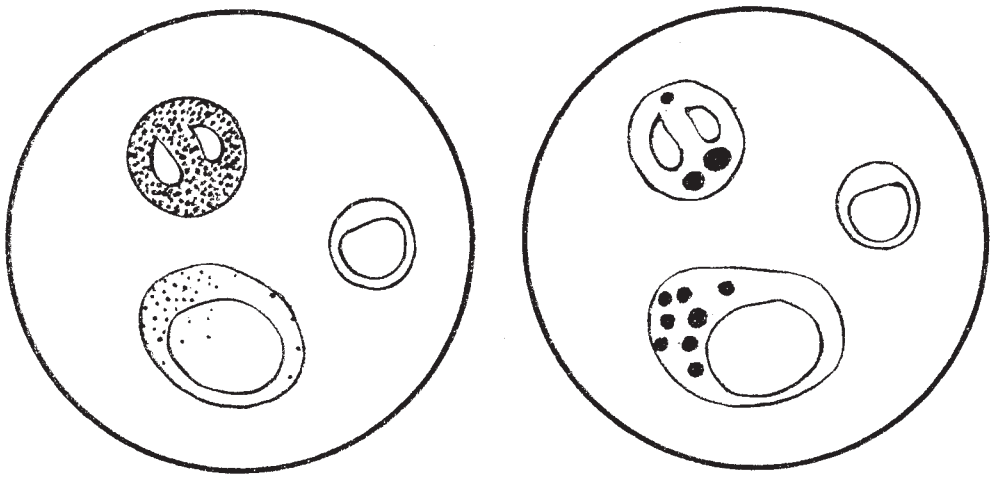
Fig. 1. Peroxidase reaction (Upper : neutrophile. Lower : monocyte. Cell without granules : lymphocyte), diagrammatically drawn.



a. Normal b. Higashi's disease

globes leaving only a few granules scattered in the interspace and in surrounding parts. And attention must be called to the fact that such a monstrous peroxidase picture (Fig. 1, b) was manifested by almost all the *neutrophils* of blood.

Such a gigantism of peroxidase granules is characteristic, not only of the neutrophil, but also of the monocyte. The fact that this gigantism is characteristic of the leucocytes of the myeloic system was still better known when aspirated bone marrow films were peroxidase stained (see below).

Besides the neutrophil and the monocyte, as marrow punctates show, the eosinophil, the myelocyte, eosinophilic as well as neutrophil, and the myeloblast show the giganticism of peroxidase granules. Lymphocytes and megakaryocytes were peroxidase-negative, as had been expected.

On the basis of the above described anomaly of peroxidase granules that affected the entire myeloic system, a new clinical entity was suspected. Now, the mother of the present case was, as she stated, afraid that the child (the present case) might die of the present illness,—rather she *prophesied his death*, because she had, as she stated, already experienced the death of three children who had succumbed to a similar affection. Why this precise prophecy? Because these three children had, as she stated, in common with the present case, albinism with photophobia (with pale color of hair), pigmentation of uncovered parts of skin, frequent occurrence of pustules with generalized lymphadenopathy and marked abdominal distention (due to hepatosplenomomegaly), whereas, as she added, the other three children without these symptoms were well and healthy.

As the present case had xeroderma pigmentosum as one of his diseases or symptoms, it was at first thought that this abnormal pigmentation might

have something to do with the gigantism of peroxidase granules. Higashi then had the opportunity of examining three cases of xeroderma, two cases of retinitis pigmentosa and one case of total albinism, but he found no abnormity of the peroxidase granules of leucocytes in any of these cases.

Though he was thus unable to find the cause for which this monstrosity of peroxidase would occur, yet it seemed highly probable that the present case and his sibs had an inborn error of leucopoiesis in common. And he suggested for this new clinical entitity the name: " Congenital Gigantism of Peroxidase Granules ".

Long, long ago I devised in collaboration with Sekiya a peroxidase reaction.[3] Though I published it in English in 1926. I had been using it since 1920 (up to 1948) on every patient from whom blood was obtained. I have never seen such a peroxidase picture as was presented in this particular case of Higashi's. It is not an abnormity that only a few cells of the same kind present, but one affecting all the cells of the myeloic system.

Such a monstrosity of peroxidase picture was for the first time published. I am quite sure of it. Our peroxidase reaction seems to be fairly widely used under Sato and Sekiya's peroxidase stain[3] in the American continent and under Sato's peroxidase reaction[4] in the European continent. But such a case as the present one has not within my knowledge been published. It is highly probable that Higashi's case is the very first one of this peculiar monstrosity of peroxidase picture.

New Leucocytic Anomaly of Constitutional and Familial Character

Higashi's case was reported in the last autumn in the 51st Meeting of the Miyagi Prefectural Pediatric Society. Soon after it, I came across Moises Chédiak's article.[5] His Fig. 3, which showed Giemsa-stained leucocytes of sternal puncture, attracted my attention first, because in the cytoplasm of some leucocytes in that figure more or less large vacuoles with a large enclosed body, were represented. Then I saw the pictures of the children on the next page and read the word " photophobia ", then saw his conclusions, the digest of which will be something like the following:—' This is a familial anomaly of panleucopoiesis affecting granulocytes, monocytes and lymphocytes. The Giemsa-stained film shows that profound changes and inclusions in the cytoplasm, anomalies of granulations and of nuclear structure occur in these cells. The affected children are albinic or " blond pâle " and photophobic, and show a normal nutritional, somatic and functional development up to 6 years of age, when they succumb to intercurrent infection. Sulfonamides are ineffective.'

In his case *peroxidase was not examined*, so that of course any feature of

the peroxidase reaction cannot be conceived, but there exists a great similarity between his and Higashi's cases, as will be related below.

Comparison between Higashi's and Chédiak's Anomaly

Chédiak's anomaly (reported from Habana)	Higashi's anomaly (reported from Sendai)
A. Familial leucocytal anomaly	A. Familial leucocytal anomaly
B. Patient:—albinic infant with photophobia; non-albinic sibs healthy	B. Patient: albinic infant with photophobia; non-albinic with healthy
C. Fatality: death before 7 years of age	C. Fatality:—death before 3 years of age

These three items of comparison will be discussed below:—

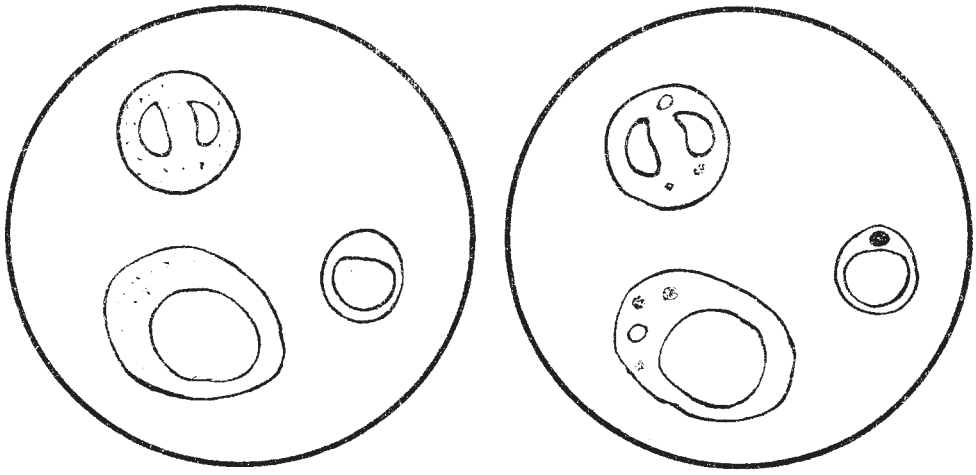
A. Familial leucocytal anomaly

It is evident that the anomaly is familial from both Chédiak's description and the pedigree in Higashi's paper. Consaguinity is common.

The Giemsa stained neutrophils show esp. in the cytoplasm an abnormal arrangement of neutrophil granules; in a word, granules form several clumps instead of being scattered all over the cytoplasm.

The description of the lymphocyte differs according to Chédiak and Higashi. According to the former, in nearly every lymphocyte (Fig. 2) an inclusion body, distinctly stained, is seen, while in Higashi's case such occurred in only 20% of lymphocytes. But the abnormal change that occurred in lymphocytes seems to be the same, so that the difference between Chédiak's and Higashi's cases is only a quantitative one.

Fig. 2. Giemsa stain (Upper: neutrophile. Lower: monocyte. Cell without granulations: lymphocyte), diagrammatically drawn.



a. Normal b. Higashi's disease

The change of the neutrophil seems to be almost the same, as far as the Giemsa stained cytoplam is concerned. The chromatin is abnormal according to Chédiak, while Higashi states that it is now thin, then thick. There is probably no essential difference.

The Giemsa-stained monocytes are probably equal in both cases (Fig. 2).

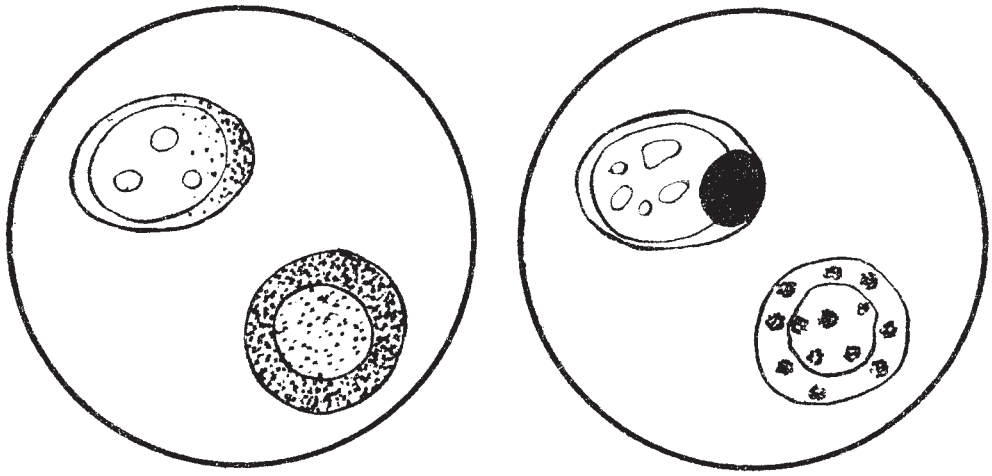
As to the eosinophil leucocyte (in the peripheral blood), there is no description in Higashi's paper, probably because the infant was seen only on the occasion of fatal infection, when all or almost all peripheral eosinophils must have disappeared. So I shall discuss this kind of cells in the following :—

Leucocytes in the marrow punctate :—

a. Eosinophiles : The peripheral eosinophil presents according to Chédiak a very particular aspect showing two types of characteristically large granulations : one type is spheric and unequal, and the othe ellipitic reminding us of horse eosinophil. Higashi describes the marrow eosinophils : The specific granules are large and different in size, and they are mostly spherical, but some of them appear rather polymorphous, presumably showing a coalescence of two or three original less large spherical granules.

b. In Higashi's case (Cf. Fig. 3) marked vacuolization occurs often in myelocytes and myeloblasts, esp. in the latter, in which extraordinally large round vacuoles, each with a round large granule or aggregate of granules, as are seen in Fig. 3. of Chédiak's paper. Inclusion bodies are

Fig. 3. Peroxidase reaction of marrow cells (Upper : myeloblast. Lower : myelocyte), diagrammatically drawn.



a. Normal b. Higashi's disease

frequently seen in Higashi's case as well as in Chédiak's.

c) Other kinds of cells :—

In Higashi's case neither erythroblasts nor megakaryocytes show particular abnormity, while both of them show pathologic regeneration.

In his paper Chédiak states : " One finds nothing abnormal in size, nucleus and cytoplasm of all the elements of the megakaryopoietic system ",

further " All the elements of the erythropoietic series are absolutely normal."

B. Patients

Both Chédiak's and Higashi's cases are albinic infants with photophobia; they were both probably born with these symptoms. But in other respects these cases differ from each other.

Chédiak's case seems to have developed normally with only these two symptoms, but Higashi's case began to show dark pigmentation on uncovered parts of the skin and a more or less darker pigmentation of albinic hair about five months of age. His growth and development were rather retarded. With an expectation that pigmentary abnormity might have something to do with abnormal blood cells, as has been stated already, Higashi examined three cases of xeroderma pigmentosa, two cases of reitnitis pigmentosa and one case of total albinism, but no such abnormity was found.

And it is not excluded that a retardiation of growth and development in Higashi's case would have been be due esp. to avitaminosis D: it will not be difficult to suppose that his mother had been keeping him rather in the dark on account of his photophobia, esp. as skin pigmentation began, as she stated, to occur from the time he was exposed to the sun. It is probable that present blood dyscrasia could occur without such complication as xeroderma pigmentosa.

It is to be emphasized that in both families the sibs not born with albinism are growing normally.

The reaction of both cases to the acute infection was very similar; they presented anemia, leucopenia and thrombopenia. Hepatosplenomegaly occurred in both cases, though in Higashi's case splenomegaly was very remarkable.

Difference of life span: Chédiak's case and her sibs died before attaining full 7 years of age, while Higashi's case and his dead sibs died before attaining full 3 years. This difference of survival might, provided that the underlying disease be one and the same in both instances, be due to the fact that in Higashi's instance the other complication xeroderma pigmentosa or such pigmentation—was concomittant. But it is equally conceivable that Higashi's case and his brethren might have attained the age of Chédiak's patients, if the former had been fed as the latter. In rural villages in our country, nutritional state of affairs is often very poor, esp. in the age of weanling. Higashi's own case—the infant reported in his paper—was esp. shortlived. It is not to be excluded that Higashi's case and his brethren could have attained the age of the cases reported in Chédiak's paper.

C. Fatality

The mother of Chédiak's case prophesied that her child of 6 years

would die of the present affection, because she had already experienced a similar death of her three other children with albinism and photophobia. The mother of Higashi's case prophesied that her infant of 11 months would die of the present affection, because she had already experienced a similar death of her three other infants with albinism, photophobia and pigmentation.

Both cases presented the syndrome of an acute infection, but Chédiak's case did not respond to sulfonamides, blood transfusion etc, though he could not try penicillin, because this antibiotic had not been put on the market yet. In Higashi's case penicillin was tried, but in vain. It is not difficult to suppose that this antibiotic might have been inefficient in Chédiak's case too.

It is highly probable that Chédiak's and Higashi's diseases are only two variations of one and the same disease.

Chédiak and Higashi's Disease

The following is in no way a text book like description of the disease. It is written here for quick orientation and esp. in order that, in case one should come across a similar case, no data important might remain omitted or unexamined.

Etiology. It is a familial and probably congenital disease and affects children of both sexes. The disease is probably transmitted through apparently healthy persons. Consangunity is probably one of the most important factors. The heredity is not sex-linked.

In tracing the pedigree, it is of utmost importance not to omit those who died very young and the symptoms these had manifested.

Symptoms. Infants and children who are the victims of this disease have albinism with albinic hair and photophobia, the latter being noticed soon after birth. But they seem to show a fairly or almost normal growth and development, until they succumb to an infection, from which there can be no recovering.

The question is whether or not the pigmentation which may occur after birth on uncovered parts of albinic skin and in the albinic hair is a facultative symptom. Special attention ought to be paid upon the albinic skin on which some pigmentary anomaly or darkneing of albinic hair may be found. The most important symptoms is the pathognomonic change of blood elements.

Blood picture: The pathognomonic change is seen, if peroxidase reaction is applied to air dried blood films. Instead of the usual peroxidase picture of leucocytes of the myeloic system, a monstrous feature (Cf. Fig. 1) is presented. This feature can be diagnostic by itself.

If the Giemsa stain is applied, some or all lymphocytes are seen to contain each one relatively large round dark stained inclusion body (Fig. 2, b) in the cytoplasm, and a myeloblast in the marrow punctate shows a large vacuole (or vacuole-like structure) with an inclusion body (Fig. 2).

Symptoms of acute infection. If the patient is attacked by acute infection,

he will react with the following symptoms: fever, infection of upper respiratory tract, anemia, leucopenia, thrombopenia, prolonged bleeding time, hepatosplenomegaly, lymphadenopathy and possibly jaundice.

Hepatosplenomegaly:—

The spleen was very large in Higashi's case. As the family of this case live in the country, it was not excluded that they esp. infants were, as is quite often the case in our country, undernourished, so that they used to develop pustules due to which—or due to such recurrent infection—the spleen (and possibly the liver, therefore the abdomen) may have been gradually swollen already before the fatal infection ensued.

Diagnosis: The diagnostic trias may be:—

1) Albinism with photophobia, 2) early death of albinic brethren and 3) gigantism of peroxidase granules of myeloic leucocytes.

In such a case, when no acute infection exists, special attention ought to be paid upon any existence of any pigmentation upon albinic skin or hair, and further upon lymphadenopathy and possibly upon splenohepatomegaly. Ask the mother if the child has had any pustular eruption occasionally.

Prognosis: However healthy—except for photophobia—the albinic in fant or child may appear, death due to acute infection will be inevitable in the 7th year of life at the latest.

Prophylaxis. As the patient will succumb quite easily to acute infection, it may possibly be the only one measure of life-prolonging to keep him from infection.

Treatment: Neither sulfonamides nor penicillin seem to be capable of saving the patient from the fatal infection. The other antibiotics may be tried, but it is a question whether or not these will take effect.

Remarks

1. The name: "Congenital Gigantism of Peroxidase Granules":—

May we use "Congenital Gigantism of *Oxidase* Granules" instead? I was very curious to know the result of oxidase reaction (of Winkler and Schulze), because—perhaps against the expectation of some (or many?) hematologists, I did not expect necessarily that the oxidase reaction would occur in the same way morphologically. (I will explain the "why not?" in another paper of mine—The Quantitative and Qualitative Anomaly of Peroxidase Reaction).

In the actual experiment of Higashi's, however, the oxidase reaction came out exactly as the peroxidase reaction. Then could not the present disease also be called "Congenital Gigantism of Oxidase Granules"? Yes, *it could in all probability.* But Higashi had not been using the oxidase reaction in routine work, while he had been using the peroxidase reaction daily. So it is much safer to use "Congenital Gigantism of Peroxidase Granules" alone for the time being.

2. I desire to ask those interested in hematology to examine blood in

every albinic individium, adult or child, and to ask them, even if myeloic leucocytes on the first few films would not present any peroxidase abnormity, to examine many more to find if there are some cells showing an inclination of the abnormity, further to try *a marrow puncture* to see whether some marrow cells are abnormal or not.

Here for convenience' sake, I shall briefly describe our peroxidase reaction.

Reagents: Solution A. 0.5% copper sulfate ($CuSO_4 \cdot 5OH_2$) solution
Solution B. Benzidine—peroxidase solution.

Rub 0.2 g. benzidine in a mortar with a few drops of water. Add 200 cc. of water and shake well (Filtration is not always necessary.) Then add 4 drops of 3% H_2O_2 (this should be fresh) to it.

Solution B will last a long time if kept in the dark. (It is recommendable to try whether or not Solution B has been well prepared—as is described in Wintrobe's Clinical Hematology, " It may be tested by mixing Solutions A and B in a test tube. If this mixture does not become blue, the reagents are at fault ".

Solution C (Counter strain). 1% aqueous Safranin-O solution.

Technic: Apply Solution A to an air-dried blood film for a short time (10–40 seconds may be sufficient). Then pour off most of it and apply Solution B for two minutes, then wash with water. And apply Solution C for 1–2 minutes.

If all the solutions are well prepared and the technic is right, then the very first trial will succeed in presenting a beautiful peroxidase picture.

3. Fatality and abnormal leucopoiesis :—

Though it is much too premature to discuss the relation between the fatality and the abnormal leucopoiesis in the present disease, it seems to me that the former is closely related to the latter, so much the more, as the patient invariably succumbs to acute infection.

It is also to be considered that there may be a definite relation between the abnormal leucopoiesis in question and the brief span of life.

4. Though this is a mere speculation, it is not excluded that in Chédiak's case the gigantism of peroxidase granules may not be so much pronounced as in Higashi's case, or that in the former case not all the granulocytes show such a gigantism of peroxidase granules, just as in Chédiak's case all lymphocytes showed each an inclusion body, while in Higashi's case only a minority of the cells showed this abnormity. This might be thought of in connection with a longer span of life in Chédiak's disease.

5. Whether or not the red system is utterly normal remains to be solved.

Summary

Higashi published " Congenital Gigantism of Peroxidase Granules " in Sept. 1953, in which I was very much interested, because I had not seen any case of such an abnormity during my own 30 years' experience with the peroxidase reaction.

Then I happened to read an article published in 1952 by Chédiak: Nouvelle anomalie leucocytaire de caractère constitutionnel et familial.

On perusal, I came to consider both diseases as two different manifestations of one and the same clinical entity, though there was no description of peroxidase or oxidase *r*aaction in Chédiak's paper. So I desire to suggest for this new clinical entity the name: Chédiak and Higashi's Disease or Chédiak-Higashi's Leuco-anomaly.

Conclusions

1. The name of " Chédiak and Higashi's Disease " or " Chédiak-Higashi's Leuco-anomaly " is suggested for both " Chédiak's " Nouvelle anomalie leucocytaire de caractère constitutionnel et familial " and Higashi's " Congenital Gigantism of Peroxidase Granules ".

2. The diagnostic trias may be: 1) Albinism with photophobia, 2) early death of albinic sibs and 3) very characteristic (even pathognomonic) blood morphology.

3. The patient seems to enjoy an apparently uneventful growth and development (on a rational regimen) up to a certain age (1–6 years of age), when he or she succumbs *invariably* to acute infection, sulfonamides or penicillin being of no effect.

4. The early death seems to be related to a leucocyte anomaly which is, it seems, transmitted by (either or both of) healthy consanguinous parents to some of their children.

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