Peroxidase-negative Neutrophils in Arakawa-Higashi's Syndrome, in Encephalitis Economo, Further in "Healthy Brethren"

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(Received for publication, June 21, 1965)

The peroxidase reaction of leukocytes is generally considered to be of the same biological significance as the oxidase reaction. The author (1922) is dumbfounded (1922) by the negative peroxidase reaction of all the myeloid leukocytes of blood in acute encephalitis Economo, while they remained normally oxidase-positive. The "Striatal Blood Syndrome" was then suggested by the author.

Now, the name of "Arakawa-Higashi's Syndrome" is suggested (1965) by the author for simplicity's sake for "Uracil-uric Refractory Anemia with Peroxidase Negative Neutrophils" (Arakawa, 1965). In this disease 50 (or larger)% of (ripe) neutrophils are perfectly peroxidase-negative, while the remainings are normally peroxidase-positive. It is to be added that two "healthy" brethren with peroxidase-negative neutrophils were reported by Grignaschi *et al.* in 1963.

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Conclusions.

I. The "Striatal blood syndrome or picture"

"Peroxidase-negative" leukocytes were described by me in 1925.¹ Not only neutrophils, but also all the myeloid leukocytes of peripheral blood were *all* peroxidase-negative, and I doubted the evidence of my own eyes, because these cells were positive in the *normal intensity* to the oxidase stain (of Schultze).

This finding — "oxidase-positive and peroxidase-negative reaction" in all the myeloid cells — was so much the more striking. I used as the peroxidase stain a then newly devised peroxidase reaction (which has later been given the name Sato's or Sato-Sekiya's peroxidase stain in the hematological literature).

I devised this reaction (1922)² as a cheap substitute for the then very high-priced oxidase dye stuff (dimethyl-paraphenylene diamine) of Schultze. I tried my own reaction in many cases and had been convinced of its being a good substitute for the original oxidase stain, when suddenly I came across the above-mentioned strange finding.

Is it possible that all the myeloid leukocytes of the peripheral blood should remain oxidase-positive, while they have become peroxidase-negative? After several years of investigation it was concluded that the complete destruction of the "Peroxidase Centers" — bilateral destruction of certain parts on the bottom of ventriculus III (at first corpus striatum was considered to be the site, hence "Striatal Blood Picture")³ would lead to the above-mentioned strange finding.

This strange blood picture was for the first time seen in an acute case of lethargic encephalitis Economo. In this first case I experienced that the negative peroxidase reaction become positive in all the cells, when the case was recovered, while in a second case I saw that the peroxidase-negative leukocytes remained ever peroxidase-negative until he died within a few days of admission: of course blood smears taken on autopsy were peroxidase-negative, remaining *oxidase-positive*. The "Striatal Blood Syndrome" will thus disappear in reconvalescence, while it will be seen also postmortem in a severe case.

It is to be noted here that encephalitis Economo has never been seen since about 1922, and it should be added that in Japanese encephalitis⁴ which prevails every year in Japan, the "Striatal Blood Syndrome" does not occur at all.

II. "Healthy" brethren with peroxidase-negative neutrophils

The above-mentioned "new peroxidase reaction"² was my first work published as Professor of Pediatrics in the Tohoku University. Our laboratory of hematology had been using this method as one of the routine works until my retirement in 1948. In fact, this state of affairs is still going on in the Pediatric Department (now Prof. Arakawa) of our University. So this peroxidase reaction has been daily tested during these 40 odd years.

There was not a single case, sick or healthy, with peroxidase-negative leukocytes, — of course with the exception of the acute cases of encephalitis Economo.

Now, some Argentine authors⁵ who appear to have had an interest in the "Striatal Blood Picture" and their collaborators came across with a couple of "healthy persons" who showed a very curious blood picture. In these two cases, peroxidase reaction was negative in their neutrophils and monocytes, while *eosinophils* were peroxidase-positive: almost the same finding in the bone marrow. All the peroxidase-negative leukocytes were also negative to oxidase reaction and Sudan black.

These two adult cases were sister and brother, so this hematological abnormality — without any apparently clinical abnormality — is a familial abnormality according

to Grignaschi *et al.*⁵

III. Peroxidase-negative neutrophils in Arakawa and Higashi's syndrome

When I devised my own peroxidase reaction (cf. I of the present paper), I thought that myeloid leukocytes of all the people, old and young, healthy and sick, are oxidase- and peroxidase-positive. So it was my great surprise when I saw the "Striatal Blood Syndrome" for the first time. "How dare one and the same oxidase-positive leukocyte be peroxidase-negative?" I thought that way at that time.

Now I was dumbfounded again by the report of Grignaschi *et al.* (cf. II) that there are "healthy" individuals whose neutrophils are all peroxidase- (and oxidase-) negative.

Now Arakawa *et al.* reported preliminarily in 1965 a case with a very peculiar syndrome — "*Uracil-uric Refractory Anemia with Peroxidase Negative Neutrophils*". Here "peroxidase-negative neutrophils" means that a great many 'ripe' neutrophils are peroxidase-negative; in this case about 50% neutrophils were peroxidase-negative.

Now, anybody who attended the 10th Meeting of the Tohoku Ketsueki Dokokai (held in Morioka) Oct. 12, 1963 and who heard Dr. Higashi⁷ (of Iwate Medical College) read the paper (by Higashi *et al.*) on "A Case of Leukemia?" — discussed by Prof. Kojima (of Fukushima Medical College), Prof. Arakawa (of Tohoku University) and myself — would think, on reading the report of Arakawa *et al.*,⁹ that Higashi's leukemoid case might probably be just another case of Arakawa's anemic disease.

If I dare to describe this disease on the basis of the case of Higashi *et al.* and the case of Arakawa *et al.*, the new syndrome will be like the following: —

Arakawa and Higashi's Syndrome — I should like to suggest this simple name: Arakawa-Higashi's Syndrome for "Uracil-uric Refractory Anemia with Peroxidase Negative Neutrophils."

I shall at first cite verbatim the abstract given by Arakawa *et al.*: A peculiar disorder of a 7-year-4-month-old girl is described which is characterized by 1) a refractory hypochromic anemia with megaloblastic marrow of a slight degree, 2) an occurrence of about half the number of the neutrophils which are negative to all the stains for peroxidase, oxidase, Sudan black B and succinic dehydrogenase, and 3) a urinary output of uracil, UMP and UDP, and 4) fatal outcome due to sepsis with leukemoid blood picture. A term "Uracil-uric Refractory Anemia with Peroxidase Negative Neutrophils" was suggested by Prof. Arakawa for this new disorder.

Here I shall describe the cause, symptoms, diagnosis and prognosis of the new syndrome:

Arakawa-Higashi's Syndrome or Disease

Cause: Though actual cause is unknown, it is probably a congenital dysfunction of bone marrow, characterized by 1) peroxidase-negative neutrophils as a manifestation of defective heme synthesis, and 2) refractory megaloblastic anemia as a manifestation of defective DNA-synthesis.

Symptoms: Both patients were females 7 and 10 years old, complaining of pallor with insidious onset or following a minor infection of upper respiratory tract. There was neither hepatosplenomegaly nor generalized lymphadenopathy.

Diagnosis: 1) Peroxidase-negative neutrophils, amounting to 50–80% of neutrophils in the peripheral blood. 2) Megaloblastic anemia refractory to either vitamin B₁₂ or folic acid therapy. 3) Urinary excretion of large amounts of uracil, UMP and UDP. If I dare propose a very simple method for early orientation, it will be the use of peroxidase stain in each case of infantile anemia. If about half (or more than half) the number of (ripe) neutrophils are peroxidase-negative, then the suspicion of the present disease will be aroused.

Prognosis: Both patients died 5–10 months after the onset. The terminal stage was accompanied with bouts of fever and leukemoid blood picture.

Occurrence: It is a question whether this syndrome is very rare. Higashi *et al.* reported their own case in 1963 and Arakawa *et al.* (who only after a careful study of their own case, came to the conclusion that the leukemic case reported by Higashi *et al.* must be of the same kind of disease) reported their own case of peculiar anemia in 1965; besides, Iwate and Miyagi are neighboring prefectures.

REMARKS

I. Contra-striatal blood picture

Here I desire to describe the “Contra-striatal Blood Picture” which I in collaboration with Kuribayashi⁸ published in 1939, because this picture will further confirm the real existence of the “Striatal Blood Picture” from the other side. The “Contra-striatal Blood Picture” will by far more easily be produced experimentally than the “Striatal Blood Picture”, because the extirpation of bilateral hemispheres of the rabbit brain will produce the “Contra-striatal Blood Picture” (or “Anencephalic Blood Picture”) in a few days of extirpation.

II. Myeloid leukocytes in the mummy

What is related in this paragraph, is of the works of the late Prof. Katsunuma⁹ (of Nagoya), who did much work concerning the oxidase reaction (of Schultze). He died on Jan. 15, 1965, to our great regret.

When I read an invitation address on my peroxidase reaction in the 2nd Meeting of the Japanese Clinical Hematological Society, he was the chairman and spoke, as I had finished my address, about 10 minutes and showed at last a specimen of blood cells in the marrow of a hundred thousand years old mummy. The

stain method was my own peroxidase reaction. The reaction was very distinctly retained.

Later (on that very day) he said to me personally that the oxidase reaction (of that mummy) was negative. Then I remembered that about 1925 (not much later than my publication of the "Striatal Blood Picture") he broadcasted and told about a mummy about ten thousand years old and about the positive peroxidase reaction of the leukocyte. Then he said to me that the oxidase reaction was never positive in any of the three mummies, in either of the two mummies above mentioned. He saw — he further added — that in a two thousand years old mummy the peroxidase reaction was positive and that the oxidase reaction was negative.

Here I have published his own result, because he told me that he had not published it yet in a printed form. It seems that the peroxidase granules of leukocytes will be retained for an exceedingly long time, while the oxidase granules will be lost in a comparatively short time in the mummy within one year at the longest.

In the laboratory oxidase granules of leukocytes of a blood smear will, it seems, last much longer than peroxidase granules. Katsunuma's experience with the mummy will suggest that there is a certain laboratory method to be able to preserve the leukocyte peroxidase for very, very long time — for a practically indefinite length of time.

III. Occurrence of some peroxidase-negative cells in leukemia

After I had published the "Striatal Blood Picture", Katsunuma,¹⁰ who probably believed with most hematologists of the world that the peroxidase method (of Sato and Sekiya) had the same biological significance as the oxidase reaction (Schultze) let some of his scholars study the discrepancy of oxidase and peroxidase granules in the course of acute leukemia. They found that the percentage of peroxidase-positive cells would become smaller than oxidase-positive ones as the disease progressed.

T. Suzuki¹¹ reported that in 5 acute myelogenous leukemia peroxidase-negative neutrophils with segmented nucleus as well as with rod-shaped nucleus would occur in a certain percentage.

IV. Peroxidase-negative cells in the embryo

Tokué¹² must probably be the first investigator of both oxidase and peroxidase reactions of leukocytes in the embryonal (rabbit) blood, because the "Striatal Blood Picture" was published from our Laboratory. Up to that time both reactions had been thought to be of the same biological significance in the hematological world.

I shall not go into details of his study, but peroxidase-negative cells in the embryonal life are generally "peroxidase-negative" cells for that reason because they have not been yet ripe enough.

CONCLUSIONS

"Peroxidase-negative neutrophils" was described.

When I experienced (1922) peroxidase-negative neutrophils in acute encephalitis Economo, I doubted the evidence of my own eyes. In this case, not only the neutrophils, but also all the blood myeloid leukocytes were peroxidase-negative, while all these cells remained oxidase-positive in the normal intensity.

Again I was surprised by negative peroxidase reaction of apparently ripe neutrophils amounting to about 50% of the whole neutrophil population in the case of "Arakawa-Higashi's Syndrome" or "Uracil-uric Refractory Anemia with

Fig. 1. Peroxidase and oxidase stains of neutrophils.

	Oxidase	Peroxidase	Published	Remarks
I Normal			1922 (Sato)	At first I thought that all people would present this picture without exception.
II Encephalitis Economo			1925 (Sato & Yoshimatsu)	Only in acute stage of Economo's disease; in reconvalescence all myeloid cells regain their peroxidase reaction.
III "Striatal blood picture"			1925 (Sato)	Experimental production: the bilateral "peroxidase centres" must be completely destroyed.
IV Chediak-Higashi's disease			1955 (Sato)	Reported from almost all parts of the world.
V Arakawa-Higashi's disease			1966 (Sato)	Of chapter III of the present paper.
VI "healthy" brethren			1968 (Arakawa et al)	Neutrophils and monocytes oxidase- and peroxidase-negative; but monophils are oxidase- and peroxidase-positive.

Fig. 2. Peroxidase and oxidase stains of neutrophils.

Peroxidase Negative Neutrophils" (Arakawa, 1965). In this case these neutrophils were also oxidase-negative.

It was cited that "Healthy" brethren with peroxidase-negative neutrophils and monocytes were reported (1963) by Argentine authors. In this case these cells were also oxidase-negative. Eosinophils were all peroxidase- as well as oxidase-positive.

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