

THE SIGNIFICANCE OF MEGAKARYOCYTES IN THE PERIPHERAL CIRCULATION

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SOME of George Minot's earliest publications were concerned with platelets and megakaryocytes and the significance which should be attached to an increase of the former or the presence of the latter in the circulation. In a paper entitled "Megakaryocytes in the peripheral circulation," Minot (1922) pointed out that an increase in circulating platelets was usual whenever megakaryocytes were present in the peripheral blood, with the exception of myelogenous leukemia in which, despite megakaryocytes, the platelets might still be normal and even decreased. Minot's general observation was that whenever megakaryocytes or fragments were found there was usually other evidence of a grave disturbance of marrow function, as suggested by the simultaneous presence of immature cells of either the white or red cell series, or both. This was an early conception of the phenomenon nowadays known sometimes as leuko-erythroblastic anemia or, sometimes as a leukemoid blood picture caused by a nonleukemic disease.

As to myelogenous leukemia, in which primitive leukocytes (and usually red cells) were already present, Minot suggested that the appearance of megakaryocytes might be a sign of an acute exacerbation of the disease; he observed that when megakaryocytes appeared, the blood picture often changed from myelocytic to the terminal myeloblastic predominance.

Minot's general deductions were that since neither myeloblasts, nor nucleated red cells, nor megakaryocytes are found normally in the blood stream, then the finding of any or all of these cells pointed to a serious alteration in the mechanism regulating the emergence of cells from the bone-marrow into the circulating blood; in such cases, the marrow was subject to great strain; the pathologic process underlying the regulating mechanism was varied, since the immature cells occurred in the blood not only when there were "structural changes in the marrow," as in myelogenous leukemia, but also with other changes, "probably functional, as in pneumonia and sepsis."

Nowadays, one could add a number of other diseases which bring about "structural changes in the marrow," to Minot's example of myelogenous leukemia. An ability to hint at a correct diagnosis in these other diseases, which include carcinomatosis and Hodgkin's disease of bone, myelomatosis, osteosclerosis and myelosclerosis, Cooley's anemia and lipomatosis of the bone marrow (Rosenthal and Erf, 1943) can make or mar a hematologist, who must always be on the alert when he is confronted with a leukemoid blood picture.

Minot's suggestion of the significance of megakaryocytes was, therefore, an observation of fundamental practical value.

In a later publication, Minot and Buckman (1923) drew attention to the fact that megakaryocytes may share in the hyperplastic process of both leukemia and erythremia (polycythemia vera) and that in the former condition, the megakaryo-

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cytes may sometimes appear to be more involved than the leukocytes, so that the blood might indeed be flooded with megakaryocytes and their derivatives, the platelets. For a time, the leukemic process might seem to be almost restricted to the megakaryocytes, even as frank erythremia or leukemia cause varying degrees of pathologic activity of myeloid or erythroid tissue in conformity with a definite type. This paper has sometimes been quoted as suggesting a megakaryocytic type of leukemia, but such is a misrepresentation of Minot and Buckman's views, which go no further than to say that the disease process "appears to be" confined to the megakaryocytes. When taken in conjunction with Minot's (1922) earlier paper the significance of megakaryocytes in erythremia would seem to be a hint that the disease was in process of transition to some complication, possibly to the malignant erythro-leukemic form or to the terminal stage of a "spent" hyperplastic marrow which is becoming sclerosed. This last, as I shall presently show, is the more probable explanation, in view of the frequency with which megakaryocytes and abnormal platelets are found in the blood in myelosclerotic conditions.

Minot and Buckman (1925) followed up their first paper by another on "The Blood-platelets in the Leukemias," in which they concluded that the platelet count yielded useful knowledge for guiding treatment and for appraising the state of the leukemic patient. They observed that the platelets, especially in myelogenous leukemia, might be greatly increased or much reduced, whereas in the acute leukemias and the chronic lymphatic type it was usual to find the platelet count below normal. They noted that petechiae and hemorrhages were often associated with platelet decrease, and that hemorrhages, though not petechiae, might be found in chronic myelogenous leukemia, even when the platelets were greatly increased.

These three of Minot's early papers emphasize four important points, of which some are nowadays accepted as commonplace, though others are not widely known.

1. That megakaryocytes in the circulation are an indication of a serious disturbance of the bone-marrow. The fact must be taken into account when framing a prognosis.
2. That the bone-marrow disturbance is commonly leukemic in origin, but not always so. In the latter case, there is frequently a leuko-erythroblastic anemia, and the causes of such must be considered.
3. That when megakaryocytes appear in the circulation in leukemia or erythremia, they indicate of an impending change in the character of the disease.
4. That the hemorrhagic manifestations of leukemia are not due entirely to reduction in platelets.

MEGAKARYOCYTIC LEUKEMIA

Boros and Korényi (1931) described a case which they designated as megakaryoblastic leukemia. The case was severely anemic and had a leukocyte count of the order of 200,000 cells per cu. mm., among which the most primitive cells were described as large mononuclear leukocytes 10-25 μ in size; megakaryocytes, typical and atypical, complete and fragmented, were numerous in the blood. The clinical course of the disease as well as the postmortem description, suggest a diagnosis of

an acute termination of myeloid leukemia. Indeed, there can be little doubt that Boros and Korényi were observing no more than what Minot had described years before—the appearance of megakaryocytes in the circulation in myelogenous leukemia.

The literature also contains a number of reports under such descriptive names as “chronic nonleukemic myelosis” (Hickling, 1937; Carpenter and Flory, 1941); “aleukemic megakaryocytic myelosis” (Favre et al., 1934) and “myeloid megakaryocytic hepato-splenomegaly” (Downey and Nordland, 1939). Most of the cases described under these various titles have exhibited a leuko-erythroblastic anemia, with megakaryocytes and their fragments in the peripheral blood (as much as 26 per cent of all nucleated cells in Carpenter and Flory’s case). The spleen and liver have been enlarged, but seldom the lymph glands. Sections of the spleen, the bone marrow and even the liver, as well as sites of extramedullary hemopoiesis have shown numerous megakaryocytes. Nearly all such reports concern cases of myelofibrosis, and the frequency with which the megakaryocytic phenomenon is prominent in this condition has been well presented and illustrated in the account given by Rosenthal and Erf (1943) of 17 cases of myelofibrosis and one of osteopetrosis (Albers-Shönberg disease). The megakaryocytic tissue in the spleen and other organs arises from myeloid metaplasia; sometimes the process has been so prominent that authors have put forward the idea of a megakaryocytic leukemia. This cannot be accepted on the evidence presented. It would seem that myelofibrosis is the fundamental factor in producing this megakaryocytic type of metaplasia, whether the underlying cause of the fibrosis be idiopathic, or the “spent” stage of polycythemia, or even myeloid leukemia and other invasive conditions (carcinomatosis, etc.) of the marrow. In practice, whenever megakaryocytes, fragments, giant or bizarre forms of platelets, or even gross platelet increase, are found in the circulation, the question of myelofibrosis should be considered. Other small practical points can each or severally support the diagnosis. These include the evidence afforded by the other features of the blood count, by sternal puncture, and more especially by sternal biopsy, by radiologic examination of the bones with suitable controls of the same age group and, if thought necessary, by splenic puncture.

The result of sternal puncture is usually disappointing on the positive side. This in itself should raise suspicion when the accomplished operator is unable to obtain a satisfactory marrow sample by puncture, and especially if the bone feels gritty on puncture. The sample usually contains few cellular elements derived from the marrow, but either giant platelets or megakaryocytes are highly suggestive. In such cases, sternal biopsy should be performed. With a section, the fibrous nature of the marrow is revealed, and the lack of cellularity often associated with numerous megakaryocytes provides a diagnostic picture. Radiologic examination of the bones occasionally shows mottled rarefactions or irregular condensations in the cortices, which need to be compared with appropriate controls taken at the same time and with the same exposure (Hynes, 1940). Splenic puncture sometimes reveals the characteristic myeloid metaplasia with many megakaryocytes.

The following is a brief summary of a case recently referred to me for adjudication

by The Ministry of Pensions; it illustrates the confusion which may arise in patients who exhibit splenomegaly with leuko-erythroblastic anemia—a confusion which becomes more confounded under service conditions, when the patient moves from one hospital to another.

REPORT OF CASE

Sergeant B. E. P. was examined on re-enlistment in 1940, at the age of 38, and placed in Category A1. He had an uneventful service until, during the campaign in N. W. Europe in 1945, he reported sick with vague pain in the left upper abdomen. He was found to have a spleen enlarged to 2½ fingers' breadth below the costal margin; the liver was not enlarged. The blood count, performed under field conditions, was reported as Hb. 13 Gm. per cent; red cells 4.5 million per cu. mm.; leukocytes 6.5 thousand per cu. mm., with no exact differential, though the report stated that 250 cells were abnormal, including myeloblasts, myelocytes, metamyelocytes and some cells of "unknown origin"; there were also a few early and intermediate normoblasts.

The man was evacuated from Europe and re-investigated in England. The record of the blood count was Hb. 13.8 Gm. per cent; red cells 4.4 million per cu. mm.; leukocytes 6.2 thousand per cu. mm., with 3.6 per cent myelocytes, 0.4 per cent myeloblasts; 0.8 per cent metamyelocytes; 2 megakaryocytes and 0.8 normoblasts per 100 leukocytes. Investigations included the exclusion of syphilis and glandular fever and a diagnosis of aleukemic leukemia was made. A blood count a month later was approximately the same, save that many giant platelets were observed. At the same time, a sternal puncture was performed, which showed essentially the same cell content as the blood, except for a slightly higher proportion of myelocytes and larger numbers of giant platelets and 2 megakaryocytes per 100 nucleated cells.

The patient then had a number of medical boards, where he was labelled ? leukemia; ? Hodgkin's disease; ? Banti's syndrome. At one of the boards, it was noted (without comment) that the patient was high colored and had a blood pressure of 160/90. He was discharged from the Army shortly afterwards. He worked as male nurse for two years, and was then re-examined on account of his pensions appeal. He stated that he had gone down hill a little, but was reasonably well. His blood pressure was 180/110, and there was some left ventricular hypertrophy; the spleen was enlarged to three fingers' breadth below the costal margin, and the liver was easily palpable. The blood showed no increase in the anemia; the leukocyte count was 6.3 thousand per cu. mm., with 8.5 per cent of abnormal cells, of which 0.5 per cent were myeloblasts, 2.5 per cent "unidentified cells," and the remainder either myelocytes or metamyelocytes; there were 3 megakaryocytes and 4 normoblasts per 100 leucocytes.

Thus, during the intervening two years, the character of the leuko-erythroblastic anemia had not altered significantly, nor, indeed, had the clinical state greatly deteriorated. The spleen had become more enlarged, the liver had become palpable and the blood pressure had risen. The true nature of this man's disease, which might have been suspected from the outset by reason of the hematologic findings, is amply confirmed by the subsequent history and later records.

Most of the points relative to the title of this article, which is virtually the title of Minot's original (1922) paper, can be extracted from the above case record, and expressed as a

SUMMARY

1. Leuko-erythroblastic anemia, with leuko-erythroblastosis, rather than anemia, when associated either with the presence of megakaryocytes or giant platelets in the circulation, is very suggestive of the myeloid metaplasia so commonly found with myelofibrosis.

2. Associated splenomegaly with subsequent slow progress to hepatomegaly and a tendency to hypertension are confirmatory clinical features.

3. Sternal puncture may or may not confirm the diagnosis, but if the specimen contains megakaryocytes, the fact is highly significant. Difficulty in piercing the bone or in obtaining a satisfactory marrow sample are points in favor of a myelofibrosis, which should be confirmed by the histologic examination of a trephined specimen.

4. Controlled radiologic examination of the bones is sometimes of value in establishing a diagnosis in the idiopathic disease.

5. A similar blood picture may occur with polycythemia vera, with myeloid leukemia and, occasionally, with other conditions in which invasion of the bone-marrow occurs. In polycythemia vera the finding suggests a terminal phase of exhaustion; in myeloid leukemia, likewise, the megakaryocytic phenomenon is usually an ominous sign of the terminal phase.

6. When megakaryocytes are found in the circulation a diagnosis of myelofibrosis should always be considered.

This short and simple article, which draws attention to some of George Minot's early work, brings with it the greetings of the entire staff of The Cambridge University Medical School to a great physician.

REFERENCES

- BOROS, J., AND KORÉNYI, A.: *Ztschr. f. klin. Med.* 118: 697, 1931.
CARPENTER, G., AND FLORY, C. M.: *Arch. Int. Med.* 67: 489, 1941.
DOWNEY, H., AND NORDLAND, M.: *Folia. haemat. Lpz.* 62: 1, 1939.
FAVRE, M., CROZIER, P., AND GUICHARD, A.: *Ann. de Med.* 35: 5, 1934.
HICKLING, R. A.: *Quart. J. Med.* 6: 253, 1937.
HYNES, M.: *Quart. J. Med.* 9: 177, 1940.
MINOT, G. R.: *J. Exper. Med.* 36: 1, 1922.
—, AND BUCKMAN, T. E.: *Am. J. M. Sc.* 166: 469, 1923.
—, AND —: *Am. J. M. Sc.* 169: 477, 1925.
ROSENTHAL, M., AND ERF, L. A.: *Arch. Int. Med.* 71: 793, 1943.