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Agnogenic myeloid metaplasia

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AGNOGENIC MYELOID METAPLASIA

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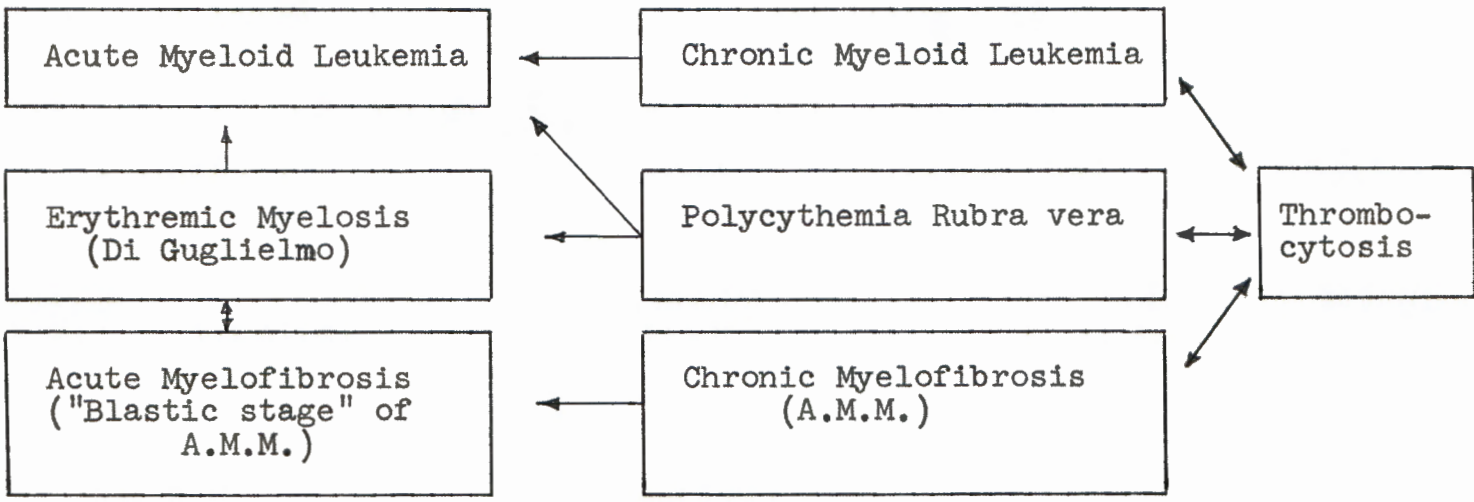
Agnogenic myeloid metaplasia is a disease of the reticuloendothelial system. Its exact morbidity rate is unknown, but it is safe to say it is a rare to infrequently seen malady. Its etiology is yet obscure; its cure is yet wanting; it is an ultimately fatal entity. Its chief symptoms presenting clinically are an enlarged spleen, usually of long duration, and those symptoms related to anemia, i.e. fatigue. Its main histopathologic finding is that of active extramedullary hemogenesis, especially in the spleen and liver. Its relationship to other diseases can be considered in terms of the "myeloproliferative disorders" . . . . . (2), (17)



Etiology:

In the early development of the human embryo, hemopoesis is a function of the connective tissue or mesenchyme. Erythrocytes are first formed in blood islands of the yolk sac; this is followed by later active hemopoesis in the liver, spleen, and lymph nodes; it is not until about the fifth month of gestation that intramedullary blood formation is begun and, in fact, not until the eighth month that the bone marrow is the principle site of erythropoiesis and granulopoesis. From the fifth month the splenic hemopoiesis gradually subsides and, at birth, functional extramedullary blood formation, save for lymphocytes and probably monocytes, no longer exists. However, the multipotential mesenchymal cells persist throughout life, not only in the marrow but in the lymph nodes, liver, and spleen as an integral part of the reticuloendothelial system.(1) These cells normally remain quiescent but they do retain their embryonic potential and under a variety of stimuli are capable of resuming active hemopoiesis.

Varying degrees of extramedullary myelopoiesis may occur in a wide variety of pathologic conditions, viz. carcinoma metastatic to bone, infectious conditions such as scarlet fever and generalized sepsis, and, paramountly,

in granulocytic leukemia.[10] But the etiology differs in the above; extramedullary myelopoiesis as a result of severe sepsis is exactly that; a secondary, induced physiologic phenomenon which is quite reversable. The granulocytic leukemia is a primary type of myelopoiesis, neoplastic if you will, which, except for a few rare occasions, is quite irreversable. Granulocytic leukemia, then, is a "myeloproliferative disorder".

Dameshek observed, some time ago, that the bone marrow elements - erythrocytes, granulocytes, megakaryocytes - often proliferate in masses or as a unit rather than as single cell lines.[5] This observation led him one step farther to suggest that the marrow fibrosis of agnogenic myeloid metaplasia might be explained on the basis of fibroblastic proliferation, similar to the myeloblastic proliferation of leukemia. But since he could demonstrate no correlation between the amount of marrow fibrosis and the amount of extramedullary myelopoiesis, he concluded that they were both independent phenomena of the same disorder. This concept has become generally accepted.

The basic cause of this neoplastic proliferation is, of course, yet unknown. It has been suggested by some

that there may be a chromosomal abnormality[8] similar to the Philadelphia chromosome of acute granulocytic leukemia.[14] This has neither been adequately proven or found widespread acceptance.[19]

Pathology:

The peripheral blood picture may be quite consistant with acute granulocytic leukemia, particularly in the pre or aleukemic stage. In two of ten cases reviewed at the University of Nebraska Hospital a peripheral white count of 5000/mm^3 or less was found. These were both associated with thrombocytopenia of less than 90,000/mm^3 and the existance of nucleated red blood cells peripherally. In neither case were myeloblasts seen, although a marked left shift was found with nearly all other immature forms being present.

The other 80% of the cases had leukocytosis, varying between 15,000 and 35,000 with a marked left shift, blast cells being frequently seen as were peripheral nucleated reds. In only one of these eight cases demonstrating a leukocytosis on first admission was there a thrombocytopenia, the other seven cases having platelet counts ranging from 350,000 to 1,000,000 per mm^3 with the majority at

about 400,000. Incidentally, bleeding tendencies could be demonstrated only in 30% of the cases having a thrombocytopenia.

Two other cell abnormalities have been described and are mentioned more for the sake of completeness than for probable importance. One is a myelocyte containing basophilic, eosinophilic, and neutrophilic granulations.(15) This, reportedly, when seen, is seen in the acute blastic, terminal phase of the disease. The second type is that of giant and atypical platelets; these, however, may be seen in other myeloproliferative disorders.

Basophilia is not uncommon; in nine of the ten cases reviewed there was a consistant basophilia of 1-10% noted.(7)

Anemia, also, is a most constant finding. Studies indicate that eyrthrocyte production may be markedly increased or decreased, irregardless of the degree of splenomegaly. The erythocytes, reportedly, may be produced in the spleen at a rapid rate but fail to be discharged into the peripheral blood, possibly because of some error in their structure. The erythocyte life span also is reportedly diminished; this phenomena being independent of the amount of poikilocytosis of the red cell. Of the University of Nebraska Hospital cases studied, admission

hemoglobins varied from 5.4 to 12.5 gm.%, most consistantly being near a range of 6-10 gm.%. Most were described as being evident of slight to moderate anisocytosis and poikilocytosis.

Of most vital importance in diagnosis is the histopathology of the bone marrow and spleen; of the two, the bone marrow is perhaps most distinguishing.(10) Fibrosis of the marrow is the keynote. This varies in amount, undoubtly, somewhat as an individual difference, but apparently becomes more severe toward the termination of the disease.(1) Because of difficulty in even approximating the date of onset of the disease, evaluation of marrow fibrosis is difficult, to say the least. Of the ten cases reviewed, the 30% showing a marked thrombocytopenia had emphatic descriptions as to the marrow fibrosis; these also showed the most marked degree of anemia.

In 40% of the cases studied there was noted by the pathologist an increase in megakaryocytic elements which were frequently described as larger than usual and with pleomorphic nuclei. No descriptions of the corresponding peripheral platelets could be compiled here, but the frequent presence of giant and atypical platelets has been described.(18)

Splenic biopsy is also of utmost importance in the diagnosis of agnogenic myeloid metaplasia. Descriptions of this microscopic analysis could be found in eight of the ten cases; here were described changes of extramedullary hemopoiesis. Granulocytes in nearly all stages were seen along with frequent nucleated red cells. In many cases the presence of megakaryocytes (morphology not described) and varying degrees of fibrosis, generally of a minimal amount, was described.

The liver, also, is nearly always involved, although possibly not to the marked degree of the spleen.(10) Here can usually be demonstrated evidence of myeloid metaplasia. This has been described as more of a sinusoidal infiltration of granulocytic cells, rather than periportal as in chronic granulocytic leukemia, although one of our cases at the University Hospital was recorded as being periportal in location.

Lymph node involvement is apparently neither as dramatic nor as consistant as the spleen and liver. By physical examination only 60% of our patients were recorded as showing lymphadenopathy. Reportedly, however, evidence of hematopoiesis is nearly always present, showing isolated collections of young granulocytes, nucleated erythrocytes, and megakaryocytes.

Serum uric acid levels are reported to be frequently elevated, although not necessarily corresponding to the blood cell count. These can apparently vary markedly from one patient to another and in one patient from one time to another. For example, in one case history reviewed a patient had a uric acid level of 8.6 mg%. He returned in one year with increased severity of symptoms and a similar blood picture, but a serum uric acid level of 18.5 mg%.

Prothrombin times in the cases reviewed were unanimously slightly, but never markedly, prolonged. Of the two cases which showed any bleeding tendency, platelet counts were depressed into the 80,000 per mm^3 range.

Clinical Manifestations:

It has generally been accepted that agnogenic myeloid metaplasia is a disease of older persons; persons in the 60 to 70 year old age groups. Indeed, the mean age of the cases here reviewed was 73 years old and the median age was 76 years old. However, there has been at least one apparent case reported, having occurred in an infant.(13) That being as it may, it is still safe to presume the disease much more prominent in the social security set than in younger persons.

The one most outstanding clinical entity seen involves the splenomegaly. Reportedly, this has frequently been noticed of the patient by a physician frequently as long as ten years prior to any other symptom of the disease. Although I could find no recording of the splenic histo-anatomy during this period, one might presume the disease process to be actively progressing at this time, and all other symptoms as more near terminal manifestations. But in none of the ten histories reviewed here could mention of the splenomegaly be found in the chief complaint as a fullness or awareness of a LUQ mass. In fact, only one person was at all aware of her splenomegaly, and that was because a physician had brought it to her attention some 13 years prior to her first admission.

Another very consistant complaint is that of weakness.(1) Indeed, this was mentioned in the chief complaint of 80% of the cases reviewed. This symptom is reportedly the result of the progressive anemia and does seem to be related inversely to the hemoglobin concentration. There is no apparent consistant relationship to other physiologic parameters, such as PBI, etc. The typical history seems to relate a progressive weakness whose onset is usually within the year.

There was most consistantly (90%) a history of weight loss in amounts varying from 15-60 lbs. and occurring over a reasonably long period of time, varying from 1-5 years. There was no associated dietetic reason obviating the loss. Reportedly, there is often an elevated BMR associated with the disease, which could account for this weight loss. In only one incidence where this was recorded, the BMR was 110%. In none of the ten cases was there an elevated temperature that was not transient and associated with an obvious infection, however.

Dyspnea reportedly is a frequent complaint and was, in fact, seen in 60% of the cases reviewed. This was reported, typically, as a dyspnea of exertion occasionally with some shortness of breath in the resting state. It typically began within the month prior to first admission. In two of the six cases complaining of dyspnea there was an associated bronchitis diagnosed radiographically; this was clinically observable in only one of the two patients, however. This dyspnea of exertion, when one considers the involved factors of anemia and a seventy-year-old heart, is not surprising nor more than one would expect to see with any anemia of any origin.

Peripheral edema, that is,of the legs, arms, or face, is also a consistant finding. Of the cases reviewed 7 of 10 were reported as having from a moderate to a marked degree of edema most frequently in the ankles and face. This, like the exertional dyspnea, is most likely related to the general consequences of severe anemia and degenerative cardiac disease, rather than being a specific disease manifestation of agnogenic myeloid metaplasia.

In only one of the cases reviewed was there a questionable jaundice; in the other nine there was none. In none of the patients was there any ascites.

Of interest in the cases reviewed was something that I have not seen reported in the literature. Eighty percent or eight of the ten cases were noted to have soft, blowing, grade II to IV of VI systolic murmurs heard primarily in the region of the aortic valve. About half of these were associated with cardiomegally and about half were not. In only three of these cases were autopsy reports available; one showed minimal calcific aortic stenosis with an associated interstitial myocardial fibrosis; one showed minimal arteriosclerotic heart disease and focal areas of myocardial fibrosis; one showed mild arteriosclerotic heart disease with degeneration of cardiac

heart muscle. After all factors are considered one still questions arteriosclerotic heart disease as the major etiologic factor to the murmurs heard.

Although not seen in any of the reviewed cases, there has recently been reported several states of confusion arising from tumor masses, resembling carcinomas or sarcomas, encountered in patients later found to have agnogenic myeloid metaplasia.(11) These tumor masses, upon microscopic examination are found to be composed of cells of the granulocytic and erythrocytic series and giant megakaryocytes. Although these cases appear to represent the exception rather than the rule, they are well documented and do occur.

Diagnosis:

The diagnosis of agnogenic myeloid metaplasia is fraught with variables; the prime factor involved seems to be the stage or chronologic duration of this disease which possibly requires upwards of 20 years before causing the ultimate demise of its victim. It is also probably safe to say that there are a number of individual variances involved in painting the total diagnostic picture.

Anemia, as described previously, is nearly always present. This may be in association with a leukocytosis or a leukopenia and, logically, a normal range between these. The blood picture usually show's a marked left shift involving, infrequently, blasts and, most frequently, immature granulocytic elements somewhere between myeloblasts and myelocytes. Platelets may either be increased or decreased in number, the latter frequently causing purpuric areas and ecchymosis; either situation may show abnormally large platelets.

Splenomegaly is a symptom of prime importance or of even necessary existance in making the diagnosis, provided, of course, that splenectomy has not occurred previously. The splenomegaly is very frequently associated with hepatomegaly, though not necessarily so.

Anemias and hepatosplenomegaly occur in a number of syndromes and diseases; they are most frequently associated symptoms of agnogenic myeloid metaplasia, but from a basis of sheer numbers agnogenic myeloid metaplasia is one of the least common diseases causing these symptoms. Therefore, in order to make a diagnosis of this disease, marrow fibrosis must be present. This usually manifests itself as two or three unsuccessful attempts at aspiration biopsy and an eventual resortment to incisional biopsy.

Also of vital importance, as far as diagnostic criteria is concerned, is the demonstration of evidence of extramedullary hematopoiesis, usually in the spleen, but also the liver and less frequently the lymph nodes.

Treatment:

Treatment, like nearly everything else concerning agnogenic myeloid metaplasia, depends upon the stage or degree of progression in the individual patient. Should the diagnosis be made at an early time when there is little or no splenomegaly and an adequate peripheral blood picture, there is no acceptable treatment and the patient can only be followed.(2)

The impending or existing anemia may be treated in several ways, one of the more conservative being only transfusions with the number being dictated by the severity of the symptoms and degree of anemia. Some have sought to stimulate hematopoiesis and diminish fibrosis by administration of androgens; this has not met with marked success, however.(2) Perhaps a better accepted method of treatment involves the administration of busulfan (myeleran), primarily to diminish the disease process in the spleen; some have even advocated the use of splenic irradiation, although this does not come, apparently, as

highly recommended as the former.[2] In cases where frank hypersplenism has developed, corticosteroids with or without busulfan may be used. Splenectomy has also been advocated.

Although the topic of splenectomy in the treatment of agnogenic myeloid metaplasia has been, and is yet, shrouded in controversy, its use at the correct time in the appropriate patient has been advocated by many.[3] Marked splenomegaly is reportedly complicated in the majority of cases by hypersplenism affecting either RBC, platelets, or both.[1] When platelets are affected, life is threatened by cerebrovascular accident or hemorrhage; when erythrocytes are affected, increased severe anemia with its concurrent fatigue and dyspnea may severely affect the patient. Hypermetabolism from attempted compensation of the above may possibly add to the problem. In such patients, where the red cell or platelet destruction is greater than their formation, splenectomy has resulted in the temporary re-equilibration of the hemopoietic mechanism and a greatly diminished requirement of transfusions for a period of months or years.

The actual finding of a patient meeting these requirements, or predicting the ones that will so benefit from splenectomy is something else, and, indeed, in practice

proves a difficult to nearly impossible task. The post-operative complications in such patients is also frequently severe and very difficult to manage. Three of six patients reported by Jensen as meeting the above requirements for splenectomy died of postoperative complications.(3) Only two of seven reported by Sandusky lived to show even moderate improvement.(4) Treatment of the acute or blastic, terminal phase of agnogenic myeloid metaplasia (vide infra) consists of 6-mercaptopurine.

Irregardless of what treatment is used, and regardless of when it is used, agnogenic myeloid metaplasia is an ultimately fatal disease. Evidence that any more than symptomatic treatment will prolong life or comfort is presently very minimal.

Prognosis:

The greater majority of patients with agnogenic myeloid metaplasia do not die of the disease, they die of intervening difficulties associated with the symptoms of the disease.(2)

In a series of 100 confirmed cases of agnogenic myeloid metaplasia reported by Bouroncle, the following percentages of terminal causes of death were reported:

1. infection, type unspecified - 21.9%
2. cerebrovascular accident or hemorrhage - 18%
3. cardiovascular disease, type unspecified - 11%
4. acute blastic stage - 20%

The so called acute blastic stage is the truly terminal phase of agnogenic myeloid metaplasia.(2) Here the peripheral blood picture resembles that of chronic myeloid leukemia in an acute blastic exacerbation. Here is seen predominately an increase of myeloblasts with an associated increase in basophils, eosinophils and frequently myeloid cells with mixed granulation. The myeloblasts in acute agnogenic myeloid metaplasia have their origin from the reticulum cells of the same organs where the myeloid metaplasia originates, viz. spleen, liver, lymph nodes, long bone marrow. The blastic stage is terminal and irreversible.

Since the ultimate prognosis of agnogenic myeloid metaplasia is death, one might inquire as to how long a survival the patient might expect. In six of our cases where this information was available, an average approximating one year and six months after diagnosis was found; others report similar figures ranging upwards to two years.(2)

There is very good reason to suspect a life expectancy approximating 20 years from the time of onset of the disease, although this is obviously very hard to document. In one of our cases there was a known symptom of splenomegaly for 13 years prior to diagnosis of agnogenic myeloid metaplasia.

Summary:

Agnogenic myeloid metaplasia is a disease associated with the "myeloproliferative disorders". Its etiology consists of neoplastic proliferation of fibroblasts in the bone marrow, yielding osteofibrosis or occasionally osteosclerosis; and neoplastic proliferation of myeloid elements in the spleen, liver,and lymph nodes, yielding splenomegaly, hepatomegaly and occasionally lymphadenopathy. Symptoms of the disease (primarily) consist of the involved anemia which is especially detrimental to the elderly age group associated with agnogenic myeloid metaplasia. Diagnosis rests primarily in the demonstration of a fibrotic bone marrow and demonstration of extramedullary hematopoiesis. Treatment is primarily symptomatic. Prognosis is variable, probably depending more upon when the disease is diagnosed than anything else.

Table of Symptoms

Patient	Weakness	Wt. Loss	Dyspnea	Splenomegaly	Bleeding Tendencies	Fever
1	-	14# in 1yr.	marked	known for 13yrs.	absent	absent
2	present	20# in several yrs.	marked	not noticed	absent	absent
3	chief complaint	53# in 5yrs.	present with exertion	not noticed	present	absent
4	marked for 4 mos.	15# in 8 mos.	none	not noticed	absent	absent
5	marked for 18 mos.	35# in 2 yrs.	present with exertion	known for 1 yr.	present	absent
6	present	-	marked for 2 wks.	-	absent	absent
7	marked for 6 mos.	-	none	known for 6 mos.	absent	absent
8	marked for 2 mos.	20# in 18 mos.	-	not noticed	absent	absent
9	present	30# in 1 yr.	-	not noticed	absent	absent
10	marked for 1 mo.	-	marked for 2 wks.	not noticed	present	absent

Table of Physical Findings

Patient	Splenomegaly	Hepatomegaly	Heart Murmur	Edema	Jaundice
1	++	+	+	+	question-able
2	++	+	0	+	0
3	++	++	+	+	0
4	++	+	0	0	0
5	+	+	+	+	0
6	+	+	+	0	0
7	++	+	+	0	0
8	+	++	+	+	0
9	+	++	+	0	0
10	+	+	+	+	0

++ Marked

\+ Present

0 Absent

Blood Morphology

Patient	Hb	WBC	Blasts	Nuc. Reds	Basophils	Platelets
1	8.9	34,900	0	0	1	411,000
2	13.2	17,800	0	0	5	461,000
3	6.0	4,800	0	0	0	88,000
4	6.0	9,300	0	13/100	1	306,000
5	4.8	13,200	4	4/100	14	83,000
6	10.8	14,100	1	1/100	2	600,000
7	12.5	20,400	0	0	2	350,000
8	6.6	20,100	0	2/100	6	1,000,000
9	9.8	20,000	4	4/100	9	379,000
10	5.4	5,000	0	4/100	1	31,000

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