INFECTIOUS LYMPHADENOSIS ("MONONUCLEOSIS") AND THROMBOCYTOPENIC PURPURA; RECOVERY AFTER SPLENECTOMY.

REPORT OF CASE

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Among the features of infectious lymphadenosis ("mononucleosis") which help to distinguish it from acute lymphatic leukemia is the lack of reduction in both red cells and platelets. Conversely, the association of well-defined anemia and/or thrombocytopenia with a marked degree of lymphocytosis in which abnormal lymphocytes are conspicuous, almost certainly indicates acute leukemia. The present case report deals with an exception to this rule. A young woman with severe purpura hemorrhagica was found to have generalized lymphadenopathy and a marked lymphocytosis. Although the clinical picture appeared to be that of acute lymphatic leukemia, the character of the lymphocytes suggested infectious mononucleosis; this was confirmed by a strongly positive heterophile agglutination. When the patient's bleeding became uncontrollable, splenectomy was performed and was followed by prompt recovery. The splenic histology was that of a reactive hyperplasia and that of adjacent lymph nodes was characteristic of infectious mononucleosis.

This case is of interest not only because of its rarity, but because it brings up anew the diagnostic features of infectious mononucleosis, the question of "hyper-splenism" and its relationship to thrombocytopenia, and the lymphocytosis observed in a number of cases of idiopathic thrombocytopenic purpura.

REPORT OF CASE

Doris P., a married woman aged 23, first seen on September 28, 1944, complained of profuse catamenia of two weeks' duration. One week prior to the onset of this period, she had noticed profuse bleeding from the gums and small "blood spots" over the chest and arms. These increased in number. The menstrual bleeding was so profuse as to cause alarm. Further questioning revealed that in the past two years she had noted vaginal bleeding between periods, an increased tendency to bleed from cuts, and bleeding following a dental extraction. An occasional sore throat and a few swollen and tender glands in the neck had recently been noted. In 1940, a miscarriage of approximately two months' gestation had occurred, requiring hospitalization; the leukocyte count at this time was 16,500 with 80 per cent polymorphonuclears; no note regarding the platelets was made.

Examination revealed a pale, sick-looking young woman. Numerous petechiae in the conjunctivae and the buccal mucosae were present. The cervical and axillary lymph nodes were readily palpable as bean-sized, nontender glands. The edge of the spleen was felt two fingers' breadth below the left costal margin. Over the skin of the trunk and extremities were numerous petechiae and small ecchymoses. Profuse vaginal bleeding was present.

Blood studies at this time showed the following: Hemoglobin 80 per cent (Tallqvist); R.B.C. 4.40 M.; W.B.C. 15,000; polymorphonuclears 14 per cent (band forms 14); lymphocytes 73 per cent (mature 61, young 12); monocytes 3 per cent. The red cells appeared normal, but only a rare platelet was seen. The coagulation time was 6 minutes (normal); the tourniquet test strongly positive; and the bleeding...
time more than 120 minutes (greatly increased). A tentative diagnosis of thrombocytopenic purpura was made and hospitalization advised; this the patient at first refused. However, with continued very severe menorrhagia, her condition became critical and she was admitted to the Hale Hospital of Haverhill, Massachusetts, on October 2. At this time, the hemoglobin was 60 per cent, R.B.C. 3.19 M.; W.B.C. 12,800; polymorphonuclears 34; lymphocytes 64 per cent; platelets less than 10,000 per cu. mm., and there was no clot retraction.

Therapy included a transfusion of 500 cc. of citrated blood, ascorbic acid 300 mg. daily, ferrous sulfate 1.0 Gm. daily, and menadione (vitamin K) 5 mg. daily. Since there was no improvement with these measures, she was seen in consultation by one of us (W. D.), at which time the generalized lymphadenopathy, the well-defined splenomegaly, and the great variability in lymphocyte morphology were pointed out as indicative of infectious mononucleosis. A sternal puncture showed an essentially normal marrow picture with islands of nucleated red cells and granulocytes, together with a slight increase in lymphocytes. There was no effacement of marrow architecture as seen in acute leukemia; the megakaryocytes, although increased in number, showed a greatly diminished platelet production. The heterophile agglutination test was positive in a dilution of 1:640. The diagnosis of infectious mononucleosis in association with thrombocytopenic purpura was made, and the patient given a good prognosis.

It was believed that the bleeding would probably diminish with subsidence of the infectious state.

However, vaginal bleeding continued unabated and the patient's condition grew rapidly worse. Despite another transfusion of 500 cc. of citrated blood, the hemoglobin on October 5 was 36 per cent and the red cell count 1.91 M. Since further transfusions seemed inadvisable, splenectomy was decided upon and performed under spinal anesthesia by Dr. Joseph Tartakoff. A transfusion of 500 cc. of blood was given 10 hours preoperatively. The spleen was found enlarged to about three times its normal size. There was a dramatic postoperative response, with a rapid rise in platelets and a quick cessation in vaginal bleeding. The platelet count became increased immediately after operation, and 36 hours later was 114,000 per cu. mm. There was a reversal in the leukocytic formula, which now became neutrophilic rather than lymphocytic. On the fifth postoperative day, lymph nodes were barely palpable. The heterophile agglutination test was positive in a dilution of 1:320. The peak platelet count was reached on the eighth postoperative day and was 600,000 per cu. mm. There was a gradual increase in hemoglobin and red cell count, which on October 18 showed the following: Hemoglobin 65 per cent; R.B.C. 3.31 M. During this 12 day postoperative period, an irregular fever of 98 to 103.2° F. was present, but there was no evidence of pulmonary or other complications.

On October 19, the patient was allowed out of bed. Tablets of ferrous sulfate (1.0 Gm. daily) were again given. On October 31, the patient was discharged from the hospital feeling well and with the following blood counts: Hemoglobin 71 per cent; R.B.C. 3.94 M.; W.B.C. 10,400; platelets 240,000; polymorphonuclears 51; lymphocytes 40 per cent, eosinophiles 6 per cent, basophiles 1 per cent; the heterophile agglutination test on October 16 was 1:40.

The spleen, which weighed 3.4 grams, was unfortunately placed in strong (100 per cent) formalin, and then brought to Dr. H. Edward MacMahon for examination. Grossly, nothing abnormal was discerned. Histologically, the follicles were found enlarged, some with very large reactive centers showing extensive cellular necrosis and reticulum cell hyperplasia. The intersinusoidal pulp cells were increased in number. Slight subendothelial lymphocytic infiltration of the veins was present. Several moderately enlarged lymph nodes were present in the splenic hilus and were examined. The capsule and general architecture were well preserved. The cords were packed with unusually large numbers of lymphocytes. There was patchy and atypical hyperplasia of lymphoblast-like cells, among which mitoses were very numerous. These encroached upon the cords and the sinuses and at one point spread out and blocked the peripheral sinus. The findings in the lymph nodes were characteristic of infectious "mononucleosis"; in the spleen with a simple reactive hyperplasia.

**Comment:** Infectious mononucleosis is a generalized infection of lymphoid tissue which is characterized by a benign, self-limited course, a characteristic blood picture, and the presence of a heterophile agglutinin in the blood serum. The blood picture presents a well-defined lymphocytosis, in which all types of lymphocytes are seen, including rare lymphoblasts, frequent very large lymphocytes with thick
glassy cytoplasms, and ordinary large lymphocytes, plasma cells, and mature lymphocytes. The term ‘mononucleosis,’’ suggesting as it does an increase in monocytes, is a misnomer, ‘‘infectious lymphadenosis’’ being preferable. An outstanding feature of the disease is the lack of associated anemia and of hemorrhagic phenomena. In fact, if anemia or thrombocytopenia is present, the diagnosis of acute leukemia rather than of an infectious condition is usually justified. However, a few cases have now been observed in which a well-defined thrombocytopenic purpura was present. We first observed it in a case subsequently reported by Tager. The patient was a young female law student who was thought to have acute leukemia because of a severe hemorrhagic state in association with a high leukocyte count and the presence of numerous abnormal cells variously interpreted as myeloblasts, lymphoblasts, or monoblasts. The true nature of the process became apparent when the great variability in lymphocyte morphology characteristic of infectious lymphadenosis was pointed out. Other cases have been reported by Minot, Magner and Brooks, and by Lloyd. In none of these cases was splenectomy required, complete improvement of the hemorrhagic disturbance occurring with subsidence of the infection.

In the present case, the history of a mild hemorrhagic condition of about 2 years’ duration was present. However, a very marked accentuation in vaginal bleeding had occurred in the three weeks previous to her first visit, and spontaneously occurring hemorrhagic spots had developed during a two weeks’ period. Thus, at least an acceleration in the bleeding disturbance had taken place simultaneously with the development of infectious mononucleosis.

The cause of this acceleration may be speculated upon. The spleen was considerably enlarged. ‘‘Idiopathic’’ thrombocytopenic purpura may well be of splenic origin and possibly in the nature of a form of ‘‘hypersplenism.’’ Studies by various investigators, including Frank, Limarzi, and Dameshek and Miller have indicated that the bone-marrow megakaryocytes, although increased in number, are deficient in platelet production. That this may be due to an inhibitory mechanism by an abnormal spleen acting upon the marrow is indicated by the greatly increased production of platelets by megakaryocytes which takes place very soon after splenectomy. Extracts of the spleen from cases of the disease have, in the hands of a number of investigators, including recently Dameshek and Denakes, resulted in the production of thrombocytopenic purpura in animals.

Splenomegaly from many sources is often associated with leukopenia and thrombocytopenia. Thus in chronic infectious splenomegaly (malaria, syphilis, tuberculosis, Felty’s syndrome), in portal hypertension, splenic vein thrombosis, Gaucher’s disease, etc., pancytopenia—anemia, leukopenia, or thrombocytopenia—is often present. Acute or subacute infections which involve the reticulo-endothelial system of cells and result in splenomegaly—typhoid fever, brucellosis, malaria, subacute bacterial endocarditis, kala-azar, etc.—are usually associated with leukopenia and thrombocytopenia. In the presence of well-defined splenomegaly in infectious mononucleosis, a similar state of hypersplenism might conceivably result, with the production of megakaryocytic inhibition and thus thrombocytopenia. In the present case, a possible mild thrombocytopenia had previously been
present, and the coincidental occurrence of infectious mononucleosis with consider-
sable splenic enlargement might conceivably have aggravated the process.
In any event, the development of severe bleeding jeopardized the patient's life
and led to the operation of splenectomy, which was dramatically successful.

Of interest in connection with the present case is the occurrence in some cases of
idiopathic thrombocytopenic purpura of a well-defined lymphocytosis. This has been
pointed out by a few observers, notably by Minot, who suggested the possibility
of an altered endocrinial function. Another possible mechanism for the reversed
granulocyte-lymphocyte proportion is hypersplenism. That is, the spleen might
not only depress the formation and delivery of megakaryocytes and platelets, but
cause a reduced delivery of neutrophiles from the bone marrow and thus result in
lymphocytosis. The whole subject of spleen-bone marrow relationships under
normal and pathological conditions has only recently come to the forefront, and
many questions relating to the possibly increased activity of the spleen must await
further investigation.

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