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MYELOMATOSIS


In the hematologic clinic of the Central Institute of Hematology and Transfusion of Blood, we have had an opportunity in the last two years to observe three patients with myeloma without any typical x-ray or anatomical picture of an affection of the skeleton. In all three cases the bone marrow aspirate revealed a large number of plasma cells (from 28-58 per cent), and among the reticulum cells there were many forms representing transitions to the plasma cells.

Among the characteristics of the first two patients we should list the pronounced hepatosplenomegaly, hyperchromic “pernicious-like” type of anemia at the beginning of the disease, and also the relatively long duration of the disease (3/2 years and 7 years). In both patients the myeloma ran its course without any focal changes in the skeleton, that is, it was chiefly the diffuse type. The patholo-go-anatomical investigation showed a picture of considerable devastation of bone marrow. In the sections of bone marrow the tissue was represented by nondifferentiated reticular cells and accumulations of plasmatic cells. The bone tissue proper was not disturbed; on the contrary, we observed the phenomenon of osteosclerosis. In the internal organs there were centers of extramedullary hematopoiesis and foci of reticular plasma cells. In the third patient myeloma ran its course more acutely (1 year). A peculiarity of this observation was the sharply pronounced involvement of the internal organs – the liver, spleen, pancreas, kidneys, and also, in contrast to the first two patients, a normal content of albumin and globulin being replaced in the terminal period even by a hypoproteinemic condition.

Our observations confirm the various quantitative and qualitative changes in the albumin turnover in myeloma. For example, the total content of albumin in the patients observed by us with different forms of myeloma fluctuated from 5.25 to 14.5 per cent. The three cases observed by us of diffused myelomatosis help to confirm the existence of this clinical variety of myeloma.

Apart from the absence of x-ray signs of focal involvement of the skeleton, this variant can still be characterized by the involvement of the internal organs, which is clinically shown by the hepatosplenomegaly, and also by the comparatively long course with gradual development of the separate symptoms. In addition to this, in the terminal period of two patients, we observed pronounced phenomena of hemorrhagic diathesis, not characteristic of the usual course of myeloma.
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A detailed study of diffused myelomatosis, so it seems to us, helps to determine precisely the place of myeloma in the systematization in hematologic diseases. The diffused character of the affection of the bone marrow with the peculiar dissociation between the myelogram and the hemogram, and also the affection of the extramedullary hemopoietic organ, bring diffused myelomatosis very close to the variety of leukosis which was described by Kh. Vlados and N. A. Kravitsky under the name of reticulosis.—A. A. B.


Previous studies utilizing C-14-labelled or N-13-labelled amino acid have shown that there is no relationship between any abnormal serum proteins in myeloma and Bence-Jones protein in the urine, but that the urinary protein is formed de novo from free amino acids and is excreted rapidly after formation. In the present article, C-14-labelled lysine was injected intravenously into a patient with multiple myeloma in order to study the rate of synthesis and excretion of a Bence-Jones protein. It was found that no radioactivity appeared in the first specimen of urine, which was collected 30 minutes after injection. After 30 minutes, however, there was a progressive rise in urinary radioactivity which reached a maximum at 10 hours after injection, and then fell off abruptly in a non-logarithmic fashion. The previous results were thus confirmed: Bence-Jones protein was formed de novo from free amino acids, was formed and excreted rapidly, and any Bence-Jones protein formed in a given interval appeared in the urine within the next 12 hours.—S. E.

Myeloma Cryoglobulin. Morphologic, Electrophoretic, and Immunologic Studies. W. G. Rice. From the Department of Pathology, St. Louis University School of Medicine, St. Louis, Missouri. Lab. Invest. 5:410-421, 1956.

A cryoglobulin was consistently found in the plasma and joint effusions of a patient with plasma cell myeloma. The abnormal protein was subjected to special studies: 1) Phase microscopy revealed that the cryoglobulin consisted of irregular, flakelike clear crystals, which were insoluble in distilled water but dissolved easily in physiological saline at 37 C. The appearance was different from that of a cryoglobulin described in the literature in a patient with periarteritis nodosa. 2) Paper electrophoresis showed that this cryoglobulin was a gamma globulin. 3) Immunologic studies by Ouchterlony's agar gel technic showed that the cryoglobulin had three antigens in common with normal serum and a fourth abnormal antigen. The author speculates that such abnormal proteins may thus evoke an antibody reaction, and that, perhaps, the resulting conjugates of myeloma protein and antibody are precipitated in the patient as perivascular amyloid.—S. E.


In six cases of beta and gamma plasmocytoma a spontaneous erythrocytic autoaggregation was observed. It was interpreted as a physico-chemical phenomenon without any connection with immunohematologic alterations. Particularly, the phenomenon was observed immediately after the collection of blood; it was not affected by the temperature, was constantly reversed by the addition of saline or of magnesium sulfate, but not by PVP. Heparin did not modify the phenomenon. Washed erythrocytes of the patients did not exhibit autoaggregation, while normal erythrocytes suspended in the patients' plasma gave autoaggregation. Mercuric solutions (Hayem's fluid) added to oxalated or citrated blood caused reversal of the autoaggregation.—P. d. N.

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In eight cases of plasmocytoma, intravascular erythrocytic aggregation was studied by means of microscopic observation in vivo of the conjunctival and nail bed microvascular areas. Clumps of aggregated red cells were observed, particularly in the venous limbs. No modifications were observed following the action of cold. This finding was considered to be constant, although aspecific, in plasmocytoma.—P. d. N.

PLASMA PROTEINS


This paper presents a case of macroglobulinemia and reviews the clinical, laboratory, and physicochemical finding of 25 cases in the literature. The case report presented is that of a man, aged 50 years. His chief clinical features were weakness, dyspnea, bleeding manifestations, lymph gland enlargement, hepatosplenomegaly, and bone marrow infiltration with small lymphocytic cells of a malignant type. An electrophoretically homogenous globulin component was present in serum; the sedimentation coefficient, by ultracentrifugal analysis, was that of an abnormally high molecular weight globulin or "macroglobulin." Evidence is provided for the concept that macroglobulinemia is a disease entity, which resembles, but is not a variant of, multiple myeloma, chronic lymphatic leukemia, and lymphosarcoma. The synthesis of macroglobulins by malignant lymphocytic cells is considered to be a result of a somatic mutation in the same cell line as that from which these cells have originated; this provides strong evidence for the correctness of the somatic mutation hypothesis of cancer.—G. C. de G.


Macroglobulins are globulins of molecular weight exceeding one million. For conclusive diagnosis of macroglobulinemia, ultracentrifugal analysis of the serum is required. It occurs in elderly people and the main symptoms are lethargy and a bleeding tendency. There may be recurrent infections, often of the respiratory tract. Slight painless enlargement may be found in the liver, spleen, and lymph glands. There is anemia and usually pancytopenia. No consistent coagulation defect is observed. There is rouleaux formation, a high E.S.R., a positive formol-gel test, and a myeloma-like protein component is found on filter paper electrophoresis of the serum. The marrow is invaded by "lymphocytoid" cells. A highly raised serum glucosamine may be found. A description is given of four cases seen in Melbourne in eight months. Macroglobulin synthesis may be the result of a somatic mutation in malignant lymphocytic tissue, which may occur independently or be induced by x-rays or cytotoxic drugs.—R. H. G.


Cytological investigations of the bone marrow in patients with macroglobulinemia Waldenström were carried out and the results are discussed. It is emphasized that the pathologic cells resemble lymphoid reticulocytes. As well as the latter, the pathologic cells are able to form a fibrous reticulum, which was demonstrated by silver staining.
of the smear in three cases. The morphologic substrate, at least in these cases, could be characterized as a lymphoid reticulosis.—M. H. H.


The characteristic morphologic picture of macroglobulinemia of Waldenström consists of a cellular proliferation which, according to presently available reports, is composed of several elements: 1) small cells resembling lymphocytes, 2) somewhat larger cells with one to two nucleoli, frequently arranged in a syncytium designated as lymphoid reticulum cells, 3) atypical and typical plasma cells, 4) tissue mast cells, 5) large mononuclear cells with plump nuclei containing one or several nucleoli, a delicate chromatin structure, and usually a narrow, strongly basophilic cytoplasm, 6) multinucleated giant cells. The relative proportions of the individual cell types participating in the proliferative process vary from case to case; so does the amount of fibrillar reticulum. In cases of hemorrhagic diathesis, fresh foci of hemorrhage and hemosiderin deposits are observed. The bone marrow shows extensive depletion of fat tissue with focal cellular infiltrations frequently showing a hemorrhagic marginal zone and hemosiderin deposits. The distribution of the infiltrates in lymph nodes, spleen, and liver are described in detail. The intravascular and extravascular deposition of a protein-rich fluid is emphasized. The biologic significance of the cellular proliferation is discussed, and on the basis of their findings the authors regard macroglobulinemia of Waldenström as a disease of the reticuloendothelial system and designate it as a reticulosis. They propose that some of the cases have all the earmarks of an autonomous neoplasia, but in other instances it is not possible to exclude a reactive process on the basis of the histiologic observations.—H. R.


A so-called prealbumin, a protein fraction of the normal human serum which migrates electrophoretically in front of the albumin fraction, was isolated and investigated by different means. In the ultracentrifuge this fraction shows a sedimentation constant of \( S_{20,w} = 4.2 \), differing from that of the albumin. Its electrophoretic mobility is 50 percent greater than that of the albumin. It has a molecular weight of 61,000 and a photometric density 2.5 times higher than albumin at 280 nm and pH 7.0. Chemically, there are further differences between the two fractions, shown by analysis of their carbohydrate and amino-acid content. The purity of the new fraction was examined by means of immune electrophoresis and the agar diffusion test. The different methods are described and graphs are added.—M. H. H.


The authors give a report of their electrophoretic and microchemical studies of the serum carbohydrate fractions. They were able to demonstrate carbohydrate complexes in all the serum protein fractions, the highest percentage of them being located in the alpha and beta globulin fractions.—M. H. H.


The serum globulins in the blood serum from siblings who suffered from the rare
anomaly of analbuminemia were investigated. Electrophoretic studies (Tiselius' method, and electrophoresis in starch, Kunkel) not only showed the absence of the albumin fraction but also an increase in the serum globulin fractions. No pathologic proteins were observed. The bulk of the test dyes which are normally exclusively bound to the serum albumin remained free; only traces could be detected in the V'-fraction, while colloid-disperse dyes were found in high concentrations in the alpha-2-fraction. The colloid-osmotic pressure of the pathologic serum was diminished. It appeared that the albumin defect was compensated to a certain degree by an increase in the globulin fractions. A complete functional replacement did not occur, but the clinical importance of the deficiency seems to be small.—M. H. H.

BONE MARROW


In aplastic pancytopenia, transfusions remain the method of choice. Splenectomy leads relatively rarely to a restoration of the bone marrow activity; more often it leads to a decrease of hemorrhagic manifestations even without causing an increase in the number of platelets. As consequence of splenectomy, the intervals between the blood transfusions may be lengthened. ACTH and cortisone do not really improve bone marrow activity, but they may alleviate hemorrhagic manifestations by increasing capillary resistance, and they may lessen the severity of reactions following repeated transfusions.

In agranulocytosis, antibiotics take the first place; in more serious cases, ACTH and cortisone may prove to be of value.

In idiopathic thrombocytopenic purpura, ACTH and cortisone are valuable as a control of sudden severe attacks of bleeding and as a preparation for splenectomy. This procedure is indicated in cases of severe repeated hemorrhages and if hormonal therapy has not lead to durable remissions.

In splenopathic inhibitions of the bone marrow function, the severity of the clinical symptoms must be the main consideration in our decision for or against splenectomy. —M. N.


Congenital absence of erythroid precursors is discussed and a clinical presentation is incorporated into this interesting article. Imperical use of ACTH and cortisone in infants with congenital hypoplastic anemia has demonstrated the effectiveness of these agents in maintaining normal hemoglobin levels. In the case reported here, the authors describe a schedule of intermittent therapy which produced normal hemoglobin levels in the patient without the undesirable side effects of continuous steroid therapy. Cortisone therapy did not appear to decrease anthrionic acid excretion in this patient.—N. J. S.