PLASMACYTOSIS IN DISEASES OTHER THAN THE PRIMARY PLASMACYTIC DISEASES

A Report of Six Cases

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During the examination of one hundred routine bone marrow preparations performed, on the Medical Service of Mercy Hospital, San Diego, California, 6 cases of unusual interest were observed. These cases, (1) a Hodgkin's sarcoma, (2) a lymphosarcoma, (3) an acute monocytic leukemia, (4) a primary "refractory" anemia, (5) a hiatal hernia, and (6) a papilloma of the bladder, are of interest because each demonstrated: (a) a significant increase of plasmacytic elements in the bone marrow above that considered diagnostic of primary plasmacytic disease,* and (b) a predominance of mature plasmacytic elements associated with an increase of reticulum cells. It is the purpose of this report to describe these cases.

Method of Preparing Bone Marrow for Examination

Bone marrow was obtained by sternal aspiration by a modified Arinkin and Schleicher method: A 14 gage Türkel needle with stilet was introduced 1 to 3 mm. beneath the inner table of the cortex of the sternum at a level convenient for aspiration and at least 2 cm. distant from previous puncture sites. The stilet was removed; 0.1 to 0.3 cu. cm. of bone marrow aspirated into a dry sterile syringe; the aspirated material placed on a clean glass slide; small "units" of marrow transferred to coverglasses; and coverglass smears drawn.

The coverglass smears were fixed for two minutes with Wright's stain. Buffered distilled water was added to the fixed smears, and the preparations were stained for 1, 5, 9, and 12 minutes. The smears were dried and mounted in balsam on clean glass slides.

Classification of Plasmacytic Elements in Wright's Stained Bone Marrow Preparations

The classification and terminology of plasmacytic elements in this report conform to the recommendations of "The Committee for Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood-Forming Organs"7:

A. Plasmablast. The plasmablast varies in size from 25 to 40 micron in diameter. The nucleus is large, measuring 20 to 30 micron in diameter and is surrounded by a thin rim of cytoplasm. Its nuclear chromatin is fine and reticular, and there may be none to three pale, blue staining nucleoli distributed irregularly in the nucleus. There is no nuclear membrane, but the chromatin fibrillae are distributed radially at the periphery of the nucleus. The cytoplasm occasionally contains irregularly sized, round, nonstaining vacuoles.

B. Proplasmacyte. The proplasmacyte varies in size from 15 to 30 micron in diameter. Its nucleus may be centrally or eccentrically placed within the cell. The nuclear chromatin is coarsely reticular and is irregularly clumped. A nuclear membrane is suggested at this stage by clumping of the chromatin at the periphery of the nucleus. Nucleoli are absent. The cytoplasm is more abundant in relation to the size of the nucleus than that of the plasmablast. The cytoplasm is basophilic and stains with different intensities.

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* By primary plasmacytic diseases the authors refer to multiple myeloma, diffuse plasma cell myelosis, and plasma cell leukemia.
of blue from light to dark. Nonstaining, irregularly sized, round vacuoles are frequently found in the cytoplasm.

C. **Plasmacyte.** The plasmacyte has been adequately described by others. It is a cell 8 to 25 micron in diameter that has a relatively large amount of cytoplasm in relation to the size of the nucleus. The nucleus is usually in an eccentric position within the cell, and nuclear chromatin is clumped in an irregular pattern that often resembles a "spoke-wheel" or "Radkern." A definite nuclear membrane is present that appears to be the result of heavy clumping of the chromatin at the periphery of the nucleus. Binucleated and trinucleated plasmacytes are observed. The cytoplasm is diffusely basophilic and stains a light to medium blue. Frequently a perinuclear clear, nonstaining zone in the cytoplasm is present that has previously been referred to as a "Hof." Irregularly sized, round, nonstaining vacuoles are frequently found in the cytoplasm and are most abundant at the periphery of the cell.

D. **Degenerative Plasmacytes.** Degeneration has been considered the ultimate fate of the plasmacyte. The process of uneven, light, or nonstaining of the cytoplasm while the nucleus remains intact in its staining characteristics has been referred to as homogenous degeneration. Associated degenerative changes in the nucleus have been described as pyknosis and fragmentation. Occasionally acidophilic, violet-red staining, intracytoplasmic bodies are seen which have been referred to as Russell bodies. These Russell bodies are thought to be the result of hyaline degeneration or of pathologic secretions within the cytoplasm.

Plasmablasts and proplasmacytes are considered immature varieties and plasmacytes and degenerative plasmacytes mature varieties of the plasmacytic elements.

The series is referred to as the plasmacytic series; the cells, as the plasmacytic elements.

**INTRODUCTION**

The observed plasmacytosis of multiple myeloma, diffuse plasma cell myelosis and plasma cell leukemia has been described many times. In the recent literature, several authors have drawn attention to the increased numbers of plasmacytic elements in the bone marrow in diseases other than the primary plasmacytic diseases. This increase has been considered a response to the underlying disease process.

Bing in 1940 and Bayrd in 1948 stated that there is an increase of plasma cells in and out of the bone marrow in certain diseases other than the primary plasmacytic diseases. They included such conditions as chronic infections, granulomas, measles, roesella infantum, carcinoma, aplastic anemia, infectious mononucleosis, Boeck's sarcoïd, cirrhosis of the liver, lymphogranuloma inguinale, monocytic leukemia, polyarteritis nodosa, kala-azar, and certain acute infections. Finch in 1948 when discussing an article by Kolff and Dhont on plasmacytoma stated that a diffuse increase in plasma cells is found not infrequently in other diseases. Falconer and Leonard in 1948 stated that there is a marked increase of plasma cells in the bone marrow in Hodgkin's disease.

Even though there has been frequent mention of plasmacytic responses in diseases other than the primary plasmacytic diseases, there have been no data presented indicating the degree of plasmacytosis nor any description of the varieties of plasmacytic elements observed in these responses.

**CASE REPORTS**

**Case 1.** W. T., a 34 year old white male, was found to have Hodgkin's disease following a cervical lymph node biopsy at the Toronto General Hospital in 1943. Deep x-ray therapy instituted at that time was followed by a regression of the lymphadenopathy. The patient remained under the care of a radio-
logist for the next five years and received local x-ray therapy to recurrent enlarged lymph nodes. He responded satisfactorily until September, 1948, at which time x-ray therapy to enlarged inguinal and femoral nodes did not affect their enlargement.

The patient was admitted to Mercy Hospital on November 8, 1948, for nitrogen mustard therapy. A femoral lymph node biopsy performed on November 11, 1948, revealed Hodgkin's sarcoma which was indistinguishable from reticulum cell sarcoma. He was treated with two courses of nitrogen mustard for a total dose of 1.2 mg. per kilogram of body weight. Following this therapy his lymph nodes became smaller in size, and his general condition improved. He was discharged from the hospital on December 8, 1948.

Several bone marrow aspirations performed during his admission revealed a marked plasmacytosis. Certain areas of bone marrow showed total replacement of the normal architecture with plasmacytic elements. His serum proteins were normal with an A/G ratio of 1.4:1. There was no Bence-Jones protein demonstrated in ten urine specimens. A complete skeletal roentgenographic survey revealed no local or diffuse bone lesion.

Case 2. H. S., a 65 year old white female, was found to have lymphosarcoma in 1947 following an inguinal lymph node biopsy performed because of a generalized lymphadenopathy. During the following year she remained comfortable with periodic deep x-ray therapy to enlarged nodes. In September, 1948, she began to suffer severe headaches and abdominal pain. Infiltrative lymphosarcoma was demonstrated in a biopsy of the scalp overlying the left parietal bone. X-ray therapy to the head and abdomen gave her temporary relief until November, 1948, when her headaches and abdominal pain became associated with temperature elevations to 101 and 104 degrees F.

She was admitted to Mercy Hospital on November 10, 1948, for treatment with nitrogen mustard. A review of the previous biopsies confirmed the diagnosis of lymphosarcoma, and she was treated with one course of nitrogen mustard for a total dose of 0.6 mg. per kilogram of body weight. Following treatment there was a marked reduction in her temperature to normal and relief of her complaints. She was discharged in an improved condition on December 3, 1948.

Two bone marrow aspirations performed during her admission revealed increased numbers of plasmacytic elements. Her serum proteins were normal with an A/G ratio of 1.8:1. There was no Bence-Jones protein demonstrated in nine urine specimens. A complete skeletal roentgenographic survey on November 13, 1948, revealed a single large, irregular area of rarefaction in the left parietal bone.

Skull x-rays on February 16, 1949, revealed complete recalcification of the previously demonstrable lesion in the left parietal bone.

The patient was admitted to another hospital on three occasions during January and February 1949, for blood transfusions because of a persistent anemia and leukopenia. Her family refused further transfusions in March, 1949, and the patient died on April 12, 1949.

Postmortem studies confirmed the diagnosis of systemic lymphosarcoma. Bone marrow studies revealed a generalized increase of plasmacytic elements, but no local or diffuse bone lesion could be demonstrated. Examination of the calvarium revealed a normal left parietal bone except for smoothness of the inner and outer cortices in the area in which a bone lesion had previously been demonstrated on skull x-rays.

Case 3. L. P., a 39 year old white female, was admitted to Mercy Hospital for observation on January 15, 1949, because of an elevation in temperature of 103 and 105 degrees F. of two days' duration. A peripheral blood study revealed a white blood count of 49,000 per cu. mm. with many "primitive" blast cells, promonocytes, monocytes, and an occasional plasmacyte. A bone marrow aspiration was performed on January 16, 1949, which substantiated the diagnosis of acute monocytic leukemia of the "primitive" or reticulum cell type. The bone marrow also revealed an associated plasmacytosis.

Aminopterin therapy was instituted on January 20, 1949. She developed a hemorrhagic pulmonary consolidation on January 24, 1949, became progressively worse, and died on January 25, 1949.

Postmortem studies confirmed the clinical diagnosis. Autopsy findings revealed complete replacement of the normal bone marrow elements with reticulum cells ('primitive' blast cells), promonocytes, monocytes, and plasma cells. The normal architecture of the lymph nodes was disrupted by infiltrations.
of large mononuclear cells. Bilateral polycystic kidneys were present. There was no local or diffuse bone lesion due to proliferation of plasmacytic elements.
FIGS. 5-10. Photomicrographs of Wright's Stained Bone Marrow Preparations X900. PP. = proplasmacyte, P. = plasmacyte, DP. = degenerative plasmacyte.

Fig. 5. Typical plasmacyte from bone marrow of Case 4. Fig. 6. Proplasmacyte with fine nuclear chromatin resembling that of reticulum cells and a binucleated plasmacyte from bone marrow of Case 5. Fig. 7. Proplasmacyte with cytoplasm resembling that of reticulum cells and a typical plasmacyte from bone marrow of Case 6. Fig. 8. Binucleated plasmacyte with central "Hof" from bone marrow of Case 1. Fig. 9. Binucleated proplasmacyte from bone marrow of Case 5. Fig. 10. Degenerative plasmacyte from bone marrow of Case 1, showing light staining of the cytoplasm.
Case 2. L.M., a 55 year old white female, had been under the care of her family physician for two years because of persistent anemia, leukopenia, and thrombocytopenia. Her complaints were weakness and fatigue and easy susceptibility to infections. She was treated with adequate doses of liver and iron on three occasions with no improvement. Blood transfusions were necessary to maintain her red blood cell count at near normal levels.

The patient was admitted to Mercy Hospital on February 11, 1949, with an admission diagnosis of primary refractory anemia. At that time physical examination revealed a pale white female who was otherwise normal. A thorough study failed to reveal a cause for the anemia, leukopenia, and thrombocytopenia. A sternal marrow aspiration performed on February 16, 1949, revealed a normally cellular bone marrow with an increase of plasmacytic elements and reticulum cells. This was interpreted as being consistent with the diagnosis of primary refractory anemia. The patient was transfused with 2500 cc. of whole blood and was discharged with a near normal red cell count on February 23, 1949.

Admission studies revealed reduced serum proteins with an A/G ratio of 2:1. No Bence-Jones protein was demonstrated in three urine specimens. A complete skeletal roentgenographic survey revealed no local or diffuse bone lesion.
Case 5. P.Y., a 43 year old white female, was admitted to Mercy Hospital for the second time on December 10, 1948, because of epigastric pain and persistent nausea and vomiting. A gastrointestinal series revealed a hiatal hernia and the patient was transferred to the surgical service on January 16, 1949.

Because of a red blood cell count on admission of 3.6 million per cu. mm., a bone marrow aspiration was performed which revealed an essentially normal marrow except for an increase of plasmacytic elements. Serum proteins were normal with an A/G ratio of 1.7:1. There was no Bence-Jones protein demonstrated in four urine specimens. A complete skeletal roentgenographic survey revealed no local or diffuse bone lesion.

Case 6. W.B., a 64 year old white male was admitted to Mercy Hospital on February 5, 1949, for fulguration of a papilloma of the bladder performed on February 10, 1949. The patient’s postoperative course was uneventful and he was discharged February 14, 1949.

Because of an admission red blood count of 6.0 million per cu. mm., a bone marrow aspiration was performed on February 12, 1949. The red cell elements were normal. The differential revealed an increase of plasmacytic elements and reticulum cells. Serum proteins were normal with an A/G ratio of 2.6:1. There was no Bence-Jones protein demonstrated in three urine specimens. A complete skeletal roentgenographic survey revealed no local or diffuse bone lesion.

Comment

From the laboratory data summarized in tables 1 and 2 it is apparent that:

1. Each of these cases demonstrated a significant increase of plasmacytic elements in the bone marrow varying from 5.4 per cent to 23.6 per cent.
2. The plasmacytic elements observed were predominantly mature varieties consisting of plasmacytes and degenerative plasmacytes.
3. With the exception of Case 3, in which these studies were not performed, none of these cases demonstrated hyperproteinemia, Bence-Jones proteinuria, or roentgenographic evidence of local or diffuse bone lesions of primary plasmacytic disease.
4. Each case was characterized by an increased number of reticulum cells in the bone marrow.

Discussion

The degrees of bone marrow plasmacytosis demonstrated in these 6 cases, varying from 5.4 per cent to 23.6 per cent, are well above the 3 per cent level described by Waldenström as diagnostic of primary plasmacytic disease. The marked degree of plasmacytosis that we have described in Case 1 might be considered by many as pathognomonic of primary plasma cell disease. However, since none of these cases demonstrated other evidence of primary plasmacytic disease, and because in each a definite diagnosis had been established, we must recognize that plasmacytosis may occur in response to other disease processes.

It may be significant that careful analysis of the varieties of plasmacytic elements observed in these cases revealed that they were predominantly mature forms consisting of plasmacytes and degenerative plasmacytes. Immature plasmacytic elements, plasmablasts and proplasmacytes, were present in small numbers. The greater number of the degenerative plasmacytes were undergoing homogenous degeneration, and Russell body degeneration was rare. Plasmacytes with eccentric nuclei and typical "spoke-wheel" chromatin configurations were present in large numbers. Multinucleated plasmacytes were rare. Vacuolization of the cytoplasm was observed in many of the proplasmacytes and in most of the plasmacytes.
Increased numbers of reticulum cells were observed in the bone marrow of each of these cases. This increase of reticulum cells deserves further comment because many cells of the plasmacytic series were observed with nuclear or cytoplasmic characteristics of reticulum cells. Such cells have previously been described by Bayrd.2 We have observed such cells that appear to be intermediates between the reticulum cell and the plasmablast and the proplasmacyte. Even though such morphologic evidence is of limited value in proving or disproving the origin of cells, it lends some support to the suggested reticulum cell origin2 of the plasmacytic series. Such an origin would explain the coexistence of increased numbers of reticulum cells with increased numbers of plasmacytic elements.

Several other cells of the plasmacytic series were observed that resembled lymphocytes, lymphoblasts, myeloblasts, and erythroblasts. While many of these cells were difficult to classify, it was our feeling that many of them represented other intermediates between plasmablasts and proplasmacytes and between proplasmacytes and plasmacytes.

**SUMMARY AND CONCLUSION**

1. This limited study has revealed plasmacytosis of 5.4 per cent to 23.6 per cent in the bone marrow of six diseases other than the primary plasmacytic diseases.
2. The plasmacytic elements observed in these responses were predominantly mature varieties consisting of plasmacytes and degenerative plasmacytes.
3. In each of the cases described a coexisting increase of reticulum cells was observed in the bone marrow.
4. Plasmacytic elements with nuclear and cytoplasmic characteristics of reticulum cells were described and lend additional morphologic evidence to the suggested reticulum cell origin of the plasmacytic series.
5. Even though a morphologic analysis of these cells has revealed a predominance of plasmacytes and degenerative plasmacytes it has not been suggested that plasmacytic responses can be distinguished from the primary plasmacytic diseases on the morphologic appearance of the plasmacytic elements in the bone marrow. Rather, the demonstration of bone marrow plasmacytosis should be subjected to careful evaluation with consideration of other diagnostic criteria before a diagnosis of primary plasmacytic disease is made.

**REFERENCES**

6. CAPPSELL, E. F.: Two cases of myelomatosis; Diffuse plasma celled, with tumor-like nodules and visceral lesions. J. Path. & Bact. 32: 293, 1929.
NEWS AND VIEWS: CONDENSATION OF THE FIRST TWO REPORTS OF THE COMMITTEE FOR CLARIFICATION OF THE NOMEN


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38 ———: Das Menschliche Knochenmark. Leipzig, George Thieme, 1940.
43 TURKEL, H. AND BETHELL, F. H.: A new and simple instrument for administration of fluids through the bone marrow. War Med. 5: 222, 1944.
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