Bone Marrow Plasmocytosis
A Review of Sixty Cases

By Herman Klein, M.D., and Matthew Block, Ph.D., M.D.

Increased numbers of bone marrow plasma cells have been reported in a wide variety of clinical disorders. Plasma cell proliferation has also been correlated with protein synthesis. The purpose of this study is to review the relationship between marrow plasmocytosis, level of plasma globulins, and the clinical conditions with which they are associated, employing a different and more reliable method of evaluating the number and distribution of plasma cells in the marrow. Cytologic studies were done using bone marrow sections rather than the conventional smear.

Historical

In 1875, Waldeyer, being impressed with the disproportionate amount of cytoplasm in a group of cells, labeled them "plasma cells," although it is apparent from his description that this was a heterogeneous group. Marschalko, in 1895, accurately identified and described the plasma cell. In 1913, Hubsehman postulated that plasma cells produced antibodies and suggested that this probably could be proven by abstracting the protein granules from the cell. This theory, that plasma cells were involved in protein synthesis, gained major support in 1937 when Bing and Plum wrote that "a comparison of the various affections in which hyperglobulinemia is found, shows as a common feature, an augmentation of plasma cells and other cells of the reticuloendothelial system within and outside the bone marrow." Subsequently, numerous investigators, including Fagraeus, Gormsen, and Bjorneboe, have contributed evidence in support of this thesis.

Method

Sternal biopsies of sixty cases previously reported as containing increased plasma cells were reviewed as unknowns with a randomly selected control series of slides. All specimens were bone marrow sections rather than the conventional smears. The method of preparation of marrow sections is briefly as follows: The sternum is penetrated with an 8 gauge needle and clumps of the aspirate are fixed in Zenker's solution. The marrow is embedded in nitrocellulose, sectioned, and stained with hematoxylin and eosin azure. An estimate of the total number of plasma cells in each section was interpreted as normal, moderate increase, marked increase, very marked plasmacytosis, or solid replacement of marrow with plasma cells, respectively. These data were correlated with the patient's clinical diagnosis and plasma globulin level. Plasma proteins were determined by the macro-Kjeldahl method with separation of the albumin-globulin fractions in the manner described by Campbell and Hanna. These values were not considered acceptable unless the determinations were done in close proximity to the time of sternal biopsy. Any form of therapy which might influence the ratio of plasma cells to the remainder of marrow elements, e.g., nitrogen mustard, irradiation to the mediastinum, or P32 was accordingly noted. In this respect, the plasma cell appears to be more resistant to the depressant effect of these agents than most of the other cells of marrow (fig. 1).

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RESULTS

The section technic has numerous advantages as compared to marrow smears, one being that traumatization to cells is minimal. The main advantage, however, is that the cells are fixed in their normal relationship as they appear in the
Bone marrow plasmocytosis

Fig. 3.—Clump of mature plasma cells in an otherwise normal marrow. X 1430.

Fig. 4.—Diffuse sprinkling of plasma cells in the marrow of a patient with periarteritis nodosa. X 1430.

In this respect it is of interest to note that plasma cells are most frequently seen sheathing the arterial capillaries (fig. 2), although they may also be seen in clumps (fig. 3), spread diffusely throughout the section (fig. 4), or solidly packed in the marrow (fig. 5).
The distribution of cases in which bone marrow plasmocytosis occurred is represented in table 1. The disorders in our series which were most frequently associated with plasma cell proliferation were multiple myeloma, rheumatoid arthritis, hepatic cirrhosis, Hodgkin's disease, and granulomatous and collagen diseases. However, increased numbers of bone marrow plasma cells are not limited to this group of disorders.

No single disease predisposed to a greater degree of plasmocytosis than another, with the possible exception of multiple myeloma. This disease is frequently manifested cytologically by complete marrow replacement with immature or mature plasma cells (figs. 5, 6). However, this is not invariably true, since our cases were categorized with every gradation of plasma cell proliferation.

Figure 7 demonstrates the relationship between the degree of plasma cell proliferation and the level of plasma globulin. Although the normal range for plasma globulins by our method is 2 to 2.5 Gm. per cent, the value for significant hyperglobulinemia was arbitrarily set at 3 Gm. per cent to eliminate borderline elevations. Significant hyperglobulinemia was present in 80 per cent of sixty cases with increased plasma cells in contrast to a randomly selected control group of fourteen cases in which there were two instances of hyperglobulinemia. There appeared to be a direct relationship between the more pronounced degrees of plasma cell proliferation and the higher globulin levels, although this correlation was not striking.

**Discussion**

Plasma cell data have been presented in this paper with particular emphasis on the following topics: (1) the characteristic distribution of plasma cells in
human bone marrow; (2) the pathologic conditions with which bone marrow plasmacytosis is associated; and (3) the relationship between plasma cell proliferation and hyperglobulinemia.

When bone marrow containing increased numbers of plasma cells is examined, utilizing the section technic, the plasma cells are most frequently seen sheathing the arterial capillaries, although clumping, random scattering, or complete marrow replacement may occur. The peculiar property of the plasma cell to sheath small blood vessels of human bone marrow had been previously reported by Block. Plasma cell perivascular sheathing is seen as commonly in marrows with slight plasmacytosis as in marrows with very marked plasma cell proliferation.

Diseases associated with increased numbers of bone marrow plasma cells have been listed in table 1. Bone marrow plasmacytosis has also been reported as occurring in asthma, hay fever, and cutaneous and febrile reactions to transfusions and drugs, including sulfadiazine sensitivity, acute infection, and rheumatic fever. It is probably true that there are other disorders associated with

Table 1.—Demonstration of the Distribution of Cases with Increased Marrow Plasma Cells in a Series of Sixty Cases

<table>
<thead>
<tr>
<th>Disease</th>
<th>+</th>
<th>++</th>
<th>+++</th>
<th>++++</th>
<th>Total</th>
</tr>
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<tr>
<td>Multiple myeloma</td>
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<td>2</td>
<td>2</td>
<td>6</td>
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<td>Rheumatoid arthritis</td>
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<td>5</td>
<td>1</td>
<td></td>
<td>8</td>
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<tr>
<td>Hepatic cirrhosis</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
<td>6</td>
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<tr>
<td>Hodgkin's disease</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Granulomas</td>
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<td>4</td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Sarcoid</td>
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<td>1</td>
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<td></td>
<td>2</td>
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<tr>
<td>Collagen diseases</td>
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<td></td>
<td></td>
<td>2</td>
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<tr>
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<tr>
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<tr>
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<td>2</td>
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<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
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<tr>
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<td>Chronic brucellosis</td>
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<tr>
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<tr>
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</tr>
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<td>1</td>
<td>4</td>
<td></td>
<td>60</td>
</tr>
</tbody>
</table>

This data does not necessarily represent the occurrence rate of marrow plasmacytosis associated with these diseases.
Fig. 6.—Complete marrow replacement with anaplastic plasma cells in a patient with multiple myeloma. × 1430.

Fig. 7.—Scattergram relating the degree of marrow plasmacytosis to plasma globulin levels. The marrows influenced by therapy and the cases of multiple myeloma are specifically labeled.
plasma cell proliferation which go unrecognized because sternal puncture is not done. The apparent nonspecific nature of plasma cell response is evidenced by the fact that it occurs in neoplastic, granulomatous, infectious, and allergic disorders. Perhaps a common factor, such as a hypersensitive state, exists in these broad groups of diseases. Rich demonstrated in rabbits that periarteritis nodosa was a “manifestation of the anaphylactic type of hypersensitivity,” and stated that this disease had developed in patients following hypersensitive reactions. Teilum described the morphologic reactions in Boeck’s sarcoid and disseminated lupus erythematosis as allergic immunity reactions and suggested that the various forms of hyalin and paramyeloid found in the reticuloendothelial system, and especially in the periartrital zones, must be “considered products of plasma cells.”

These observations, aside from supporting the theory of hypersensitivity as a factor in initiating plasmocytosis and hyperglobulinemia, suggest a relationship between the phenomenon of plasma cell perivascular sheathing, described above, and the typical vascular lesions seen in sarcoid, periarteritis nodosa, and disseminated lupus erythematosis.

Although there is still no uniformity of opinion concerning the function of plasma cells, there can be little remaining doubt that plasma cell proliferation is usually associated with elevated plasma globulin levels. The inference that proteins, in particular antibodies, are produced by plasma cells has been substantiated by other investigators. Fagraeus noted marked plasmacytosis in rabbits after injecting antigens; this effect being distinctly accentuated in animals which had been previously sensitized. Plasma cell proliferation was directly correlated with a measurable rise in specific antibodies. Gormsen and Bjorneboe injected rabbits with polyvalent pneumococcus vaccine which resulted in pronounced plasma cell proliferation. The renal sinus fat tissue contained an almost pure plasma cell infiltration with a high antibody content.

Thus the assumption can logically be made that the hyperglobulinemia associated with plasma cell proliferation is a product of these cells.

Conclusions

1. Sternal marrow sections of sixty patients with bone marrow plasmocytosis were reviewed as unknowns with a control series of slides. The degree of plasma cell proliferation was correlated with the clinical diagnosis and plasma globulin level.

2. The diseases most frequently associated with marrow plasmocytosis in our series were multiple myeloma, rheumatoid arthritis, hepatic cirrhosis, Hodgkin’s disease, and granulomatous and collagen diseases.

3. Significant elevation of the plasma globulin occurred in 80 per cent of the cases with increased plasma cells.

4. Plasma cells are characteristically seen sheathing the arterial capillaries, but may also be found in clumps, spread diffusely throughout the section, or solidly packed in the marrow.

References

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