MULTIPLE MYELOMA AS A FORM OF LEUKEMIA

By Michael A. Rubinstein, M.D.

The first case of multiple myeloma was reported as "mollities ossium" by Dalrymple, McIntyre, Bence-Jones and Watson in 1848, following closely the first description of leukemia as a disease entity published independently by Craigie, Bennett, and Virchow (1845). The important pathologic studies of Rustizky (1873) and Kahler (1899) established multiple myeloma as a malignant infiltrative disease of the bone marrow of unknown origin, characterized by multiple tumor involvement of the skeleton. Almost at the same time Neumann's description of the myelogenous form of leukemia (1870) and Ehrlich's discovery of blood staining methods led to the recognition of leukemia as a primary proliferative disease of hematopoietic tissues, medullary and extramedullary. Extension of leukemic lesions from the bone marrow to the bone itself was also recorded in early observations.

Since then, as both multiple myeloma and leukemia were recognized as 'primary' infiltrative diseases of bone marrow, their relationship has been the subject of continued discussion. Rustizky was first to classify multiple myeloma as a systemic disease of the hematopoietic tissues related to leukemia, a view taken later by Lubarsch. However, most authors have made a sharp distinction between multiple myeloma and leukemia. The following points have been stressed in the literature and have been conventionally held to distinguish multiple myeloma from leukemia.

Conventional Points of Distinction between Myeloma and Leukemia

1. Type of infiltration (whether circumscribed or diffuse). It has been maintained that whereas multiple myeloma produces circumscribed tumor masses, leukemia is characterized by generalized diffuse infiltration of marrow.

2. Bone destruction. The distinction made here is that multiple myeloma is characterized by the presence of multiple punched out areas of bone destruction, while in leukemia the infiltrative process in the bone marrow does not as a rule erode the bone cortex.

3. Visceral involvement. It has been contended that in contradistinction to the myelomatous proliferation which was held to be typically limited to the osseous system, the leukemic infiltration exceeds as a rule the boundaries of bone marrow and is found in visceral organs as well.

4. Invasion of peripheral blood. While leukemia is manifested, at least at some stage of its evolution, by massive invasion of the peripheral blood by the leukemic cells of the bone marrow, the myeloma cells, it has been maintained, do not pass into circulation.

5. Biochemical characteristics. Multiple myeloma is associated with abnormalities in protein metabolism manifested in Bence-Jones proteinuria and hyperprotein-
emia with hyperglobulinemia. On the other hand, abnormal chemical metabolism in leukemia is manifested mainly in increased basal metabolic rate and elevated uric acid of the blood.

6. Age incidence. It has been pointed out that while leukemia has been observed at all ages, including infancy, multiple myeloma is a disease of the middle and older age groups.

7. Symptomatology. Bone lesions are the main basis of the clinical picture in multiple myeloma, while symptoms in leukemia are mainly due to involvement of hematopoietic and visceral organs.

Each of these points in the differential diagnosis between multiple myeloma and leukemia will be discussed. Evidence will be brought to show that the listed points of distinction between multiple myeloma and leukemia cannot be regarded as being of fundamental nature; i.e., there is no sharp demarcation line between the two diseases. Instances are abstracted where cases of multiple myeloma show the various characteristics of leukemia and vice versa.

Features of Leukemia in Multiple Myeloma

1. Diffuse infiltration in multiple myeloma, without circumscribed tumor formation

It has been shown by many observers that in addition to the well known circumscribed tumor formation, diffuse infiltration of the bone marrow also exists in multiple myeloma. Such cases of diffuse infiltration without any evidence of circumscribed tumor formation are known.

Occasionally cases of multiple myeloma have been observed where the bones appear normal. The spongy trabeculae are numerous and the cortices are not noticeably thinned. The skeletal roentgenograms taken during life in such cases may show at most some diffuse osteoporosis, and do not reveal anything even remotely suggestive of the picture which is accepted as being typical of multiple myeloma. In these cases, only the marrow is modified and replaced diffusely by a tissue which on histologic examination of aspiration material is proved to be myelomatous tissue.

Other cases show some thinning of the cortices as well as great reduction of the spongy trabeculae, but they still may have smooth and undistended bone contour. The roentgenograms show vague mottled rarefaction and thinned cortices. These cases are transitional to the full-fledged picture with multiple areas of bone destruction in typical cases of exuberant growth of myelomatous tissue.

Lack of circumscribed tumor formation does not rule out the possibility of multiple myeloma.

The case reported below is an instance of such diffuse infiltration of bone marrow without apparent evidence of bone destruction. It emphasizes the importance of bone marrow studies in any case of atypical amyloidosis, with or without evidence of bone lesions.

Case 1. M. S. 3846, white female, admitted with signs of renal insufficiency. In 1944, bone marrow aspiration repeatedly revealed from 12 to 27 per cent plasma cells. Soon Bence-Jones proteinuria was also noticed.
Blood examination showed moderate normocytic anemia, and occasional plasma cells in the smear. Later a leukemoid picture developed: white blood count 25,000; myelocytes 5 per cent; nonsegmented neutrophil 35 per cent; segmented neutrophil 25 per cent; lymphocytes 3 per cent; plasma cells 1 per cent. Terminally plasma cells increased to 20 per cent. The plasma cells in the blood were morphologically of the same type as those in the bone marrow.

The diagnosis of multiple myeloma was suggested. However, repeated x-ray examinations of the skeleton showed no abnormalities at any time, and the serum proteins were low (albumin 3.4 Gm. per cent to 4.2 Gm. per cent; globulin 1.0 Gm. per cent to 2.2 Gm. per cent). The Congo red test showed 45 per cent retention. The patient’s course was one of rapid deterioration marked by progressive azotemia (B.U.N. up to 150 mg. per cent). She died in March 1945.

Autopsy revealed no gross lesions in the skeleton.* Microscopic examination of sections of ribs, sternum, vertebrae showed marrow largely replaced by plasma cells, trabeculae thin and amyloid deposition in walls of the vessels. Amyloidosis was the most important extraskeletal finding. It was most generalized, involving all blood vessels, connective tissue in lungs, ovaries, kidneys, thymus, smooth muscles of most viscera, and the cardiac muscle.

The pathologic diagnosis was plasma cell myeloma, diffuse type; atypical amyloidosis.

2. **Extraskeletal Visceral Involvement in Multiple Myeloma**

Extraskeletal myelomatous infiltrations have been reported in various organs. It is possible that in some cases what may appear to be independent extraskeletal foci might actually have been direct outgrowth of tumor from nearby bones. However, there can be no doubt that in some cases of visceral involvement the infiltrations are of extramedullary origin. Less unusual than grossly discernible foci are microscopic infiltrations in the spleen, kidneys, lungs, lymph nodes.

* Autopsy performed by Dr. D. Unterman.
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Up to 1936, there were 21 cases of myelomatous visceral involvement recorded in the literature (Blumenfeld). Since that time many other instances have been added. Infiltration of practically every organ in the body has been noted (lungs, heart, spleen, liver, lymph nodes, pancreas, kidneys, adrenals, tonsils, skin, etc.). Extraosseous infiltrations are more commonly seen when plasma cells are also found in the blood. Of interest is a case of plasma cell involvement of the tonsils (Jackson et al.) which preceded generalized involvement of bones by many years.

In a recent report, visceral involvement in multiple myeloma is presented as a rather common finding in the disease, if carefully looked for in microscopic studies.

Fig. 2. Bone marrow aspiration in the case of M. S., showing myeloma cell infiltration (diffuse myeloma without bone destruction).

Three of our own cases showed foci of extramedullary myelomatous spread. Two instances with involvement of the tongue (R. S. #362373),12 and buccal mucosa (M. K. #43608)13 respectively are reported elsewhere. A third case with extensive extramedullary involvement is presented here.

Case 2. A. W., #10534, a 15 year old boy, in 1941 gave a three year history of pain in the left hip and fracture of left thigh. X-ray studies early in the disease revealed areas of bone destruction in the skull, femur, and ribs. Bone marrow aspiration revealed in 1943 the presence of myeloma cells. Bené-Jones proteinuria was also discovered. There was no hypoproteinemia. Moderate hypochromic anemia was found.

In the course of a few months new lesions in different bones were discovered, and several palpable tumors appeared over the clavicles, sternum, ribs. There were pathological fractures of humerus and lumbar vertebrae. However, the patient's course was marked by spontaneous remissions with healing of
fractures and periods of improved anemia and general condition. Radiotherapy was applied at different sites of the skeleton. Also a course of antimony was given. Treatment was rather difficult to evaluate in view of spontaneous remissions. In 1945 patient developed inability to urinate, necessitating an indwelling catheter, and ascending urinary infection followed. Terminally there was profuse rectal hemorrhage.

At autopsy* multiple myeloma was found to involve not only the skeleton, but showed also two extensive extraskeletal infiltrations: (1) One tumor mass (800 Gm.) involving the pelvic space so as almost to obliterate it with compression and infiltration of nearly all pelvic organs (ureters, bladder, prostate, seminal vesicles). (2) Another extraosseous accumulation of myeloma tissue was found to invade and partially to replace the left kidney which weighed 350 Gm. (right kidney weighed 160 Gm.).

Microscopically, the extraosseous infiltrations presented the same picture as the myeloma tissue seen in the skeletal lesions. This extraosseous involvement explained the clinical course marked by renal insufficiency and recurrent pyelonephritis with urinary obstruction. The terminal hemorrhage was due to erosion of the pelvic tumor mass through the perianal structures.

* Autopsy was performed by Dr. R. Lubliner.
3. Invasion of Peripheral Blood in Multiple Myeloma

It has been shown that not only visceral organs, but blood itself may be invaded by myeloma cells. Although massive invasion of peripheral blood, so as to produce
the picture of plasma cell leukemia, occurs rarely (except terminally), occasional myeloma cells may be found quite often (Morissette and Watkins, and others).

In our experience, study of smears made from the white cell layer of packed blood cells facilitates the discovery of occasional myeloma cells, and thus may become an important aid in the diagnosis. We have applied this procedure in multiple myeloma as it is used when looking for occasional abnormal cells in aleukemic forms of leukemia.

The case of M. S. #38462, abstracted previously in this paper as an instance of diffuse myeloma, showed a few myeloma cells in the blood smear. This patient may be designated as "aleukemic plasma cell leukemia"—by analogy to the conventional leukemia terminology. Another case with massive invasion of the blood, one of "plasma cell leukemia," will be briefly abstracted.

**Case 3, R. S. #36257:** in this 58 year old woman the disease was ushered in by a profuse rectal hemorrhage, followed by back pain, weakness and soreness of the tongue. On admission there was generalized moderate lymphadenopathy, and several red nodules, measuring from 1 mm to 1 cm in diameter, scattered over the margin of the tongue. There was severe anemia (hemoglobin 31 per cent; red blood count 1,900,000; white blood count 6,100).

Studies of the peripheral blood smear showed 5 per cent plasma cells in an otherwise normal differential count, and were the first to suggest multiple myeloma. This diagnosis was confirmed by sternal marrow aspiration, which revealed 65 per cent plasma cells. Also aspiration biopsy of the lesions in the tongue showed infiltration by myeloma cells, i.e., extramedullary myelomatous spread.

X-ray studies showed multiple punched-out areas in skull, ribs, long bones. Bence-Jones proteinuria was also noticed, first intermittently and later constantly. Serum albumin was 2.9 Gm. per cent, globulin 4.4 Gm. per cent.

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**Fig. 6. Section of myeloma tumor of the kidney in the case of A. W. (high power)**
During eight months observation there was progressive increase of white blood count with simultaneous rise of the number of plasma cells in the peripheral blood. The highest values were: white blood count 26,000 with 38 per cent plasma cells, 10 per cent myelocytes. Patient died in renal failure.

4. Biochemical Characteristics of Leukemia Seen in Myeloma

The main biochemical findings in leukemia concern the uric acid metabolism and the basal metabolic rate. The uric acid of the blood and the endogenous uric acid elimination are greatly increased in leukemia. Also the basal metabolic rate is increased in the great majority of cases of myelogenous leukemia and in more advanced instances of lymphocytic leukemia, and less frequently in aleukemic forms of leukemia.

These changes are ascribed to the elevated protein catabolism in leukemia.

As may be seen from various reports in the literature, increased uric acid content of blood is a rather common finding in multiple myeloma, probably as frequently seen in this disease as in leukemia. In three of our own cases where uric acid studies were made, it was found to be 5 mg. per cent, 3.5 mg. per cent and 7.5 mg. per cent. As in the case of leukemia, the elevated blood uric content in multiple myeloma is thought to result from the catabolism of the proliferating cells in the bone marrow.

There are also indications of increased basal metabolic rate in multiple myeloma. This appears from some references in the literature, as well as from our own observations. Of 7 cases of multiple myeloma without complications (fever, frac-
5. Age Incidence: Multiple Myeloma in Youth

The accepted textbook view is that multiple myeloma is a disease of older age. However, review of recent literature will show isolated instances of myeloma in younger age groups, including infants. Also, some older records of bone diseases in youth, originally reported under various descriptions—such as "lymphadenia osseum" described by Nothnagel—must be recognized as true myeloma in the light of new knowledge. Especially noteworthy are the cases of myeloma reported by Zach and by Gordon and Schneider in children under 10 years of age.

We have observed a case of multiple myeloma in a child, aged 12, at the onset of disease, in whom the diagnosis was not considered for three years, mainly because of his age. This case (A. W., case 2) showed extensive extraosseous involvement
and has previously been abstracted in this paper as an example of visceral involvement in myeloma. Bone marrow studies were first to suggest the diagnosis of multiple myeloma. Before these studies were done, diagnoses were entertained of osteosarcoma, Schiller-Christian's disease, etc. This case, as well as those reported in the literature, prove that youth should not rule out the possibility of multiple myeloma.

6. Symptomatology: Symptoms of Multiple Myeloma not Referable to Osseous System

While in the majority of cases, the symptomatology of multiple myeloma is due to tumor involvement of bones with resulting complications (pathologic fractures, deformities, with ensuing pain and neurologic signs, etc.), in a number of patients the complaints are not referable to osseous system, \(^22\) and may be similar to those ordinarily found in leukemia.

In cases of unexplained anemia and cachexia, multiple myeloma is occasionally discovered as the underlying disease. In other instances hemorrhagic manifestations constituted the presenting signs (hematemesis, melena). Epistaxis, ecchymosis, petechiae, and bleeding from gums first suggested leukemia in patients who were proven to have myeloma. Among our own patients, in one instance (A.R. \(^{114881}\)) the clinical picture was dominated by uncontrollable nose bleeds; in another patient (R.S. \(^{362573}\)) the disease was ushered in by profuse rectal hemorrhage.

In other cases, thrombosis was reported as the presenting sign, for example, when failing vision or complete blindness due to thrombosis of central artery of the retina ushered in the clinical picture of multiple myeloma. Gastro-intestinal symptoms (diarrhea, colicky attacks, nausea and vomiting) may dominate the picture. They may be due sometimes to thrombosis of mesenteric vessels. Thrombosis may be due to the increased viscosity of the blood. The latter and the tendency of red cells to clump may give rise to peripheral vascular disturbances not unlike those seen in Raynaud’s disease.

Occasionally patients in chronic renal failure diagnosed as "nephritis" turned out to have multiple myeloma, with the clinical picture dominated by the "myeloma kidney."

Very occasionally hepato-splenomegaly was observed in multiple myeloma, and very exceptionally lymphadenopathy. This extraskeletal symptomatology in multiple myeloma may be seen not only in the diffuse type of myelomatous infiltrations, but also in cases with circumscribed tumor formation and bone destruction which may remain symptomless for some time. Bone marrow examination will reveal the true nature of the disease in the absence of any symptoms referable to the osseous system.

Features of Myeloma in Leukemia

1. Medullary Forms of Leukemia; Skeletal Involvement

Very rare cases of leukemia have been reported (Storti, Klima and Syfried, etc.) where only the bone marrow was involved. \(^23\) No visceral infiltration was found
even on thorough autopsy examination. In these cases the diagnosis could be made only on the basis of bone marrow studies. These rare forms of leukemia would correspond to the usual forms of multiple myeloma limited to the bone marrow and without visceral involvement.

Less uncommon is involvement of different bones in leukemia. It has been well known ever since Heschl in 1847 described osteolytic lesions in leukemia patients. Bone lesions are more common in acute leukemia, especially in children in whom x-ray examination of the skeleton proved to be an aid in the diagnosis of leukemia. The lesions may take form of tumors, destruction and absorption of bone leading to fractures, periosteal elevations and arthritis; the latter is produced by leukemic proliferation in juxta-articular portions of the bone. Chloroma refers to localized tumors associated especially with the acute forms of leukemia. However, the finding of bone tumors in cases of classic chronic myelogenous leukemia has also been reported.

X-ray studies have shown that in some instances leukemia may lead to generalized decalcification of the skeleton (osteomalacic forms of leukemia). However, occasionally the x-ray pictures of bone infiltration in leukemia may resemble closely those seen in multiple myeloma (Mandl and Saxle).

As an example, the following case is of interest.

Case 4. F. G. #112875, white female, age 30: in 1946 generalized lymphadenopathy and splenomegaly were found. Biopsy of a lymph node as well as peripheral blood and bone marrow studies (90 per cent lymphocytes) were typical of chronic lymphatic leukemia. Patient developed extremely severe pain in left thigh and toes and required increasing doses of opiates. X-ray examination showed areas of translucence in the femur and also several areas of bone destruction in the distal phalanges of the foot. Relief of pain followed x-ray therapy to the affected bones.

2. Biochemistry of Leukemia

Bence-Jones proteinuria and hyperproteinemia, admittedly typical of multiple myeloma, have also been occasionally observed in leukemia. These observations were made more frequently in the lymphatic than in the myeloid variety. Magnus-Levy in 1932 collected 11 cases of lymphatic and 5 cases of myeloid leukemia showing Bence-Jones proteinuria. Although only two cases have been reported of leukemia associated with hyperglobulinemia, the actual number is probably much larger, as appears from the literature on occurrence of hyperproteinemia in general. Bence-Jones proteins in the plasma have also been observed in leukemia.

From our own observations, 2 cases of leukemia will be abstracted, where Bence-Jones proteinuria and hyperproteinemia were seen. These will be briefly abstracted. Similar instances were observed by Dr. N. Rosenthal (personal communication to the author).

Case 5. Bence-Jones proteinuria in leukemia.

The diagnosis of lymphatic leukemia in the case of R. K. (case observed on the outside and at Mount Sinai Hospital), a 72 year old male, was made in 1940. At that time generalized lymphadenopathy and hepatosplenomegaly were noticed. Blood examination showed moderate anemia. White blood count was 50,000 with 89 per cent lymphocytes of mature type. Also bone marrow (90 per cent lymphocytes) and biopsy of a lymph node were typical of lymphatic leukemia.
In March 1944, Bence-Jones proteinuria was discovered. At that time the hepato-splenomegaly and lymphadenopathy had considerably increased, and white blood count rose to 140,000 with 97 per cent lymphocytes. On admission to the Mount Sinai Hospital in March 1944, x-ray examination of the bones showed no abnormalities, and the serum proteins were normal or low.

At first Bence-Jones proteinuria was found only intermittently, but after November 1944 it was present constantly in large amounts. During his hospitalization repeated roentgenographic examinations were made of the skull, ribs, and long bones, but no evidence of bone lesions was ever found. In spite of treatment (radiotherapy, transfusions) the patient's course was progressively downhill and he died as the anemia became very severe with very high white blood count (up to 500,000) almost entirely composed of lymphocytes.


H. L. #38595, 65 year old white male, admitted because of weakness, frequent nosebleeds, hepatosplenomegaly and general lymphadenopathy. Studies of peripheral blood revealed a picture of lymphatic leukemia: hemoglobin 6 Gm.; red blood count 2,300,000; white blood count 60,000; lymphocytes 80 per
This diagnosis was confirmed by sternal marrow examination (90 per cent lymphocytes out of a total nucleated cell count 110,000), and by biopsy of a cervical lymph node.

A most striking finding was very marked hyperproteinemia due to hyperglobulinemia, consistently seen on repeated examination.

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The formol gel test was immediately positive. There was excessive rouleaux formation and a rapid sedimentation rate of red cell (80mm./hr.). The urine was positive for albumin but negative for Bence-Jones protein. The basal metabolic rate was plus 21 per cent.

X-ray examination of the skeleton failed to reveal any destructive lesion or even osteoporosis.

At autopsy the diagnosis of lymphatic leukemia was confirmed.

3. Symptomatology of Leukemia Referable to Osseous System.

It has been mentioned in a previous chapter that bone lesions may be found in leukemia, especially in acute forms in children. Sometimes symptoms referable to the bones and joints may dominate the clinical picture. Pain, limitation of movement and other symptoms which suggest various bone and joint diseases (such as rheumatic fever, Still's disease, caries of the spine, osteomyelitis, etc.) may occur in leukemia.

Symptoms may arise as the result of compression by bone tumors on nerves. Bone tenderness is not infrequent and may be elicited usually in the lower portion of the sternum. The following case illustrated the domination of the clinical picture by bone and joint pains.

Case 7. N. G. # 39335, boy of 18, was diagnosed in the beginning as a case of acute rheumatic fever, because of migrating pains in the joints of all extremities. Later the pain became more localized in the left knee which was swollen and stiff. The diagnosis of osteomyelitis was then suggested. However, blood and bone marrow studies revealed a picture characteristic of chronic myeloid leukemia. Also splenomegaly was soon noticed. Throughout the disease, pain in the bones especially in the elbows and knees remained a prominent feature. X-ray studies revealed generalized decalcification of long bones.

Coexistence of Multiple Myeloma and Leukemia

The literature contains a number of reports indicating the coexistence of leukemia and multiple myeloma. Apart from plasma cell leukemia, clinical multiple myeloma was found in combination with lymphatic leukemia and more rarely with myeloid leukemia.

Also, experimental evidence suggests a connection between multiple myeloma and leukemia. Successive inoculations of transplantable leukemia in mice may give rise to multiple myelomatous infiltrations, instead of true leukemia (Furth). The result obtained, whether multiple myeloma or leukemia, seemed to depend on the dosage of inoculated tissue, and on the state of the recipient animal (whether
previously irradiated or not). In connection with these observations and experiments, our case of extensive combined lymphocytic and plasma cell infiltration is of interest.

**Case 8.** Combined lymphocytic and plasma cell infiltration.

R. K. # 372229, age 50, white female, was admitted with a diagnosis of lymphatic leukemia because of marked generalized lymphadenopathy, and typical blood findings: hemoglobin 6 Gm. per 100 cu. cm.; red blood count 2,000,000 per cu. mm; white blood count 18,000 per cu. mm; the differential count showed 80 per cent lymphocytes of the mature type; 1 per cent plasma cells, 19 per cent neutrophiles. Biopsy of a lymph node performed at another hospital was reported as typical of lymphatic leukemia.

At the Montefiore Hospital, bone marrow aspiration showed mixed lymphocytic (38 per cent) and plasma cell (2.1 per cent) infiltration. The rest of the bone marrow cells of the white and red cell series were crowded out, but showed the normal myeloid-erythroid ratio. The mixed lymphocytic and plasma cell infiltration was found on both sternal and iliac bone marrow aspirations. The peripheral blood studies showed: white blood count 20,000; lymphocytes 80 per cent; plasma cells 2 per cent. The lymphocytes in the blood and bone marrow were of the small cell type, as seen in chronic lymphocytic leukemia, but the plasma cells, often showing multiple nuclei with nucleoli, were suggestive of myeloma cells.

There was hyperglobulinemia (albumin 3.9 mg. per cent; globulin 4.1 Gm. per cent), excessive rouleaux formation, rapid sedimentation of red blood cells, and positive formal gel test of the serum. No Bence-Jones proteinuria was seen.

The possibility of multiple myeloma was suggested. However, x-ray studies showed no evidence of bone destruction. The patient died four years after onset of disease. Autopsy findings were described as follows:
Malignant mixed lymphocytic and plasma cell lymphoma involving peripheral, intrathoracic and intra-abdominal lymph nodes, spleen and bone marrow with infiltration of most organs (liver, lungs, heart, stomach, kidneys, adrenals, pancreas). There were both focal and diffuse infiltrations of these organs.

The infiltrations, whenever seen, were composed of lymphocytes and plasma cells in varying proportions, in many places the latter cells being by far predominant and occurring in clumps. These plasma cells were described as being identical in cytology and staining reactions (Pappenheim stain, etc.) with those seen in plasma cell tumors.

The pathologic diagnosis was malignant mixed lymphocytic and plasma cell lymphoma, showing both diffuse infiltration and circumscribed tumor formation.

**Discussion**

The conventional points in differential diagnosis between myeloma and leukemia have been discussed. The following points have been held to distinguish the two diseases: (1) Type of infiltration, whether diffuse or circumscribed. (2) Bone destruction. (3) Extraskeletal visceral involvement. (4) Invasion of peripheral blood. (5) Biochemical characteristics. (6) Age incidence, clinical manifestations.

It has been shown, by assembling different data from the literature and on the basis of our own observations, that the difference between myeloma and leukemia, as far as these characteristics are concerned, is merely one of incidence; what is rare in one disease is common in the other. Instances of myeloma may show all the characteristics of leukemia, and vice versa, but not with the same frequency.
MULTIPLE MYELOMA AS FORM OF LEUKEMIA

The following table summarizes the discussion:

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<td>Circumscribed tumors</td>
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<td>Bone symptoms</td>
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It is known that there is a difference in incidence of various leukemic characteristics depending upon the cell type of leukemia (myelogenous, lymphatic, etc.). Certain features (such as splenomegaly, lymphadenopathy, skin or skeletal involvement, etc.) are more common in one variety than in the other. All the features of leukemia may be found in all leukemic varieties, but not with the same frequency. It has been demonstrated in our discussion that myeloma may show all the characteristics of leukemia, and vice versa, but not with the same frequency. This is however merely a quantitative difference. As far as the listed characteristics are concerned, there is no qualitative difference between myeloma and leukemia. Myeloma is, then, merely a leukemia of plasma cells. This variety of leukemia is ordinarily of aleukemic type. Moreover, as compared to other leukemias, it is characterized by very common occurrence of bone destruction, by relatively infrequent visceral involvement, and by frequent and characteristic biochemical abnormalities in protein metabolism. It has a definite predilection for older age groups and its clinical picture is usually dominated by bone pathology. In this light, viewing myeloma as another member of the "leukemia family," it is more plausible to understand the coexistence of myeloma and leukemia as something more than accidental.

SUMMARY

The conventional points in the differential diagnosis between myeloma and leukemia have been discussed. Evidence has been brought to show that these points of distinction cannot be regarded as being of fundamental nature. Instances are abstracted where cases of multiple myeloma show the various characteristics of leukemia and vice versa.

1. Leukemic features in myeloma have been shown in:
   a. diffuse infiltration in multiple myeloma without circumscribed tumor formation and without any gross bone destruction;
   b. extraskeletal visceral myelomatous spread involving the kidney, spleen, lymph nodes, etc.;
   c. invasion of peripheral blood in myeloma—occasional myeloma cells (corresponding to the aleukemic forms of leukemia) may frequently be found in concen-
trated smears, even though they may be missed on routine examination; however, massive invasion of peripheral blood is rare;

d. increased uric acid content of the blood and elevated basal metabolism, characteristic of leukemia, frequently seen also in myeloma;
e. occurrence of myeloma in youth;
f. symptomatology of multiple myeloma at times not referable to the osseous system.

2. Myeloma features in leukemia have been shown in:
a. skeletal involvement in leukemia;
b. very rare medullary forms of leukemia (without visceral involvement);
c. occurrence of Bence-Jones proteinuria or hyperproteinemia with hyperglobulinemia in rare cases of leukemia;
d. instances when the symptomatology of leukemia was referable to the osseous system.

3. Coexistence of multiple myeloma and leukemia is reviewed from the literature, and a case is reported of extensive mixed lymphocytic and plasma cell infiltration.

In conclusion, the difference between myeloma and leukemia, as far as the listed conventional distinguishing features are concerned, is merely one of incidence: what is rare in one disease, is common in the other, and vice versa. Multiple myeloma is in all probability a leukemia of plasma cells.

REFERENCES


4 Craigie, D.: Case of disease of the spleen, in which death took place in consequence of the presence of purulent matter in the blood, Edinburgh M. & S. J. 64: 400, 1845.

5 Bennett, J. H.: Case of hypertrophy of the spleen and liver in which death took place from suppuration of the blood; Edinburgh M. & S. J. 64: 413, 1845.


MATERIALS AND METHODS

Monoclonal antibodies were used to immunostain paraffin-embedded tumors for B7-H3 (clone 9.11, Santa Cruz Biotechnology, Santa Cruz, CA), CD20 (clone L26, DakoCytomation, Carpinteria, CA), CD3 (clone C11, DakoCytomation), CD4 (clone 5G11, DakoCytomation), CD8 (clone 53-6.7, DakoCytomation), and Ki67 (clone MIB-1, DakoCytomation). Immunohistochemical staining was performed using the Envision+ System (DakoCytomation). Briefly, tissue sections were dewaxed in xylene, rehydrated, and unmasked in protease solution (PAP-Kit, DakoCytomation). Antigen retrieval was performed in citrate buffer (pH 6.0) in a microwave oven for 5 minutes. Endogenous peroxidase was blocked with 3% hydrogen peroxide in methanol. The slides were incubated with monoclonal antibodies for 30 minutes, and the immunodetection was performed using the Envision+ System according to the manufacturer's instructions.Sections were counterstained with hematoxylin.

Staining was evaluated at the level of the individual cases, and for each of the antibodies, the percentage of positive cells was estimated in the tumor tissue. The intensity of staining was scored on a scale of 0 (no staining), 1 (weak staining), 2 (moderate staining), or 3 (strong staining) for each case. The final score was calculated by multiplying the percentage of positive cells by the intensity of staining, resulting in a score ranging from 0 to 300.

For statistical analysis, the Mann-Whitney U test and the chi-square test were used to compare the staining results between the two groups. A p-value of less than 0.05 was considered statistically significant.


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MICHAEL A. RUBINSTEIN