1960

Multiple myeloma : a review of twenty cases

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MULTIPLE MYELOMA: A REVIEW OF TWENTY CASES

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Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

April 1, 1960

Omaha, Nebraska

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In 1845 Sir James Watson saw a man who had been "out of health for thirteen months." Because of a substance which solidified on cooling of the urine, he called Dr. MacIntyre for consultation. They sent samples of the patient's urine to Henry Bence-Jones. The latter found a substance in the urine which precipated on heating, liquified on boiling and solidified on cooling. At necropsy he found that the ribs and bodies of the vertebrae were easily cut with a knife. He concluded that the substance in the urine was a protein and suggested that it should be looked for in further cases of "mollities ossium."[5]

Dalrymple[10] in 1846 described the bone pathology of an affected patient and suggested the malignant nature of the disease be called mollities ossium.

In 1850 MacIntyre[23] contributed a quite accurate description of the case he had seen with Watson and Bence-Jones.

Von Rustizky[38] in 1873 was the first to describe the condition under the name of "Multiples Myelom." In 1889 Kahler[19] gave the four cardinal finding of this disease. These are bone pain, deformation and abnormal fragility of bone, cachexia, and the presence of Bence-Jones proteinuria.

The interrelationship of multiple tumors of bone and hyperproteinemia was first reported by Ellinger[13] in 1899 and received support by Jacobson[17] in 1917 and many investigators since then.

Electrophoretic studies were first made and the existence of

unusual patterns pointed out in 1939 by Longsworth, Shedlovsky, and MacInnes.[22]

Review of Cases

This series consists of twenty patients which have been seen at University Hospital and Immanuel Hospital. These were seen over a period of ten years and information for this discussion has been taken from these patients' charts.

The most common complaint in these patients was of pain. Eighteen of the patients complained of pain. This was usually pain in the skeletal system, most often involving the vertebral column. Pain was the first symptom to occur in fifteen of the eighteen cases. In two cases it was the second symptom and in one case the third symptom to occur.

The second most common symptom was unexplained weight loss. This occurred as a presenting complaint in twelve cases and in at least two more cases subsequent to the diagnosis.

Anorexia or nausea and vomiting was a complaint in five cases, and in three of these cases to be discussed later there were stomach lesions. Six patients complained of "arthritis." This was usually stiffness in joints of the extremities. Three patients complained of fatigue and weakness. Seven patients had complaints referable to gross bleeding. Two patients had had persistant hoarseness, and at least three had had infections along with their other symptoms.

There were two patients who complained of painful masses. Three had CNS symptoms, but these could not be proved to be caused by multiple myeloma. One patient had herpes zoster with a nerve root distribution near an affected vertebra.

It is interesting to note the symptom or sign leading to initial hospitalization and/or diagnosis. In ten of the cases pain lead to their diagnosis. Pathological fractures were the reason for diagnosis in two cases. Persistant recurrent infections lead to the diagnosis in two. Also leading to the diagnosis in two cases each were masses and a generalized weakness which was probably due to anemia. Only one case was diagnosed because of the frequent complaint of weight loss. One other patient entered the hospital because of angina pectoris but was diagnosed as having multiple myeloma before he died of a myocardial infarct seven days after admission.

Ten of the patients had had symptoms one to six months before the diagnosis was made. Usually this was the time elapsed between onset of symptoms and the seeking of medical advice. Five cases had had symptoms for six to twelve months. Two had symptoms for one to two years before diagnosis, and two had had symptoms for over two years. One patient had had a plasmocytoma removed two years before the diagnosis of multiple myeloma was made. At the time of the diagnosis she stated that she had had painful spots during the two years since the removal of the plasmocytoma. The

average duration of symptoms before diagnosis in the twenty patients was eight months.

Table I

Symptom or Sign	Number of Patients Found in	Percentage
Pain	18	90
Weight loss	14	70
Anorexia, nausea, vomiting	5	25
Arthritic complaints	6	30
Weakness and fatigue	3	15
Palpable masses	4	20
Painful masses	2	10
Palpable liver	6	30
Palpable spleen	1	5
Pathological fractures	2	10
Bleeding phenomena	7	35
Hoarseness	2	10
Neurological changes	4	20
Infections	3	15

Symptoms and signs in a series of twenty cases of multiple myeloma.

The age of the patients varied from forty-six to seventy-eight. The mean and median age was sixty-three. The greatest

number (eleven) were in the age range of sixty to seventy. There were only two patients less than fifty years old and four in the age range of fifty to sixty. There were three patients seventy years or over. There were fifteen men and five women in this series.

Physical examination seldom revealed anything specific. Six patients had a palpable liver. Four had palpable masses. One had splenomegaly clinically. One patient had many small bruised areas and also signs of epistaxis.

Eighteen of the patients had normochromic normocytic anemia with a hemoglobin level below twelve grams at the time of their diagnosis. Eleven of these eighteen had hemoglobin levels below nine grams. Of the seventeen patients on whom the erythrocyte sedimentation rate was done it was abnormal. Serum protein determinations were done on eighteen patients. Fifteen of these patients had increased serum globulins and decreased serum albumin. Serum protein electrophoresis was done in five cases and abnormalities were found in all cases. Cryoglobulins were tested for in eight cases, but none were found to be present. Rouleaux formation of the erythrocytes on peripheral smear was reported for ten of the twenty cases. Nucleated erythrocytes were reported in the peripheral blood smears of six of the twenty patients. The reticulocyte count was greater than one per cent in the eleven patients in which it was done. The leukocyte count was normal in

fifteen of the patients. Four patients had leukocyte counts in the range of three thousand to five thousand per cubic millimeter. One patient had a leukocyte count greater than ten thousand per cubic millimeter prior to his diagnosis. Toxic granules were reported from peripheral smears in the granulocytes of seven patients. Myeloid immaturity was reported from the peripheral smears of three patients. Plasma cells were found in the peripheral blood of four patients. Platelets were found to be below 200,000 per cubic millimeter in nine patients. In the four other patients in whom platelet counts were done they were in the normal range.

The serum inorganic phosphorus levels were determined in ten of the patients. These were reported as seven increased above normal, two below normal and one in the normal range. The serum alkaline phosphatase was done in twelve patients with only one reported as being increased. Serum calcium levels were done on eleven patients. They were reported as increased in three patients, below normal in one patient and in the normal range in seven patients. The serum uric acid level was only determined in three patients. Two of these had an increased serum uric acid level. The NPN or BUN was increased in ten of fifteen patients in which one of the tests was done.

Seventeen of the patients had proteinuria. Of these seventeen there were eight cases in which only a trace of protein was reported. The Bence-Jones test was done on the urine of seventeen

patients. Seven patients had Bence-Jones protein present in their urine. All seven of these patients had increased serum globulins.

Skeletal X-ray survey revealed osteolytic areas in eighteen of these patients. Osteolysis was not reported in the other two cases. Osteoporosis, other than osteolytic lesions, was reported in nine cases. Pathological fractures were reported in twelve cases. Many of these pathological fractures were vertebral body compression fractures, but some involved the long bones. In the remaining eight cases no pathological fractures were reported. Three patients were suspected of gastric malignancies because of finding on X-rays of the upper gastrointestinal tract.

In eighteen of these patients the marrow was diagnostic of multiple myeloma. In one case in which there were other positive findings, it was reported as compatible with multiple myeloma. In one case the diagnosis of multiple myeloma was not made until necropsy.

Table II

Laboratory Findings	Number of Patients with Abnormal Results	Number of Patients Test Done on
Anemia		
Below 12 grams	18	20
Below 9 grams	11	20
ESR	17	17
Increased serum globulins	15	18
Decreased serum albumin	15	18
Serum electrophoresis	5	5
Cryoglobulins	0	8
Rouleaux formation on blood smear	10	20
Nucleated rbc	6	20
Reticulocyte count	11	11
WBC	5	20
Plasma cells on blood smear	4	20
Platelets	9	13
Serum inorganic phosphorus	9	10
Alkaline phosphatase	1	12
Serum calcium	3	8
Serum uric acid	2	3
NPN or BUN	10	15
Proteinuria	17	20

Table II Continued

Laboratory Findings	Number of Patients with Abnormal Results	Number of Patients Test Done on
Bence-Jones proteinuria	7	17
Bone marrow biopsy	19	19

Laboratory findings in twenty patients with multiple myeloma.

We have the reports of only five autopsies. Two of these confirmed the original diagnosis made by marrow examination. One patient, as mentioned above, was not diagnosed until autopsy. In two cases multiple myeloma could not be diagnosed at autopsy even though the marrow biopsies had been positive. One of these latter patients had changes consistant with, but not diagnostic of, multiple myeloma in his kidneys. He had hepatic and splenic enlargement at necropsy. He died of a myocardial infarct.

The second case not confirmed to have multiple myeloma on necropsy had what appeared to be a primary type of amyloidosis. This patient had complaints of anorexia, nausea, and vomiting and had X-ray signs of gastric malignancy. Two other patients were suspected of gastric malignancies because of X-ray findings, but they had no gastric lesions at the time of autopsy.

In two cases the patients survived less than one month after the diagnosis. There were six patients who survived one to six months. There were three patients who lived from six to twelve

months after the diagnosis. There are two patients known to be still alive. One of these has lived two years and ten months since her diagnosis. The second one has lived six months since her diagnosis. The length of survival is unknown in six patients. One patient was diagnosed at autopsy.

The following picture emerges if one adds together the length of symptoms before diagnosis and the length of survival after diagnosis. There were four patients who lived from one to six months after the onset of their symptoms. There were four who lived six to twelve months. Two patients lived one to two years after onset of the symptoms. There were two patients who lived two to three years after the onset of their symptoms. Of the two patients still alive, one has had symptoms for three years, and the second has had symptoms for eighteen months. Including these last two cases who are still alive the average length of survival after onset of symptoms was thirteen months.

Review of the Literature

Skeletal pain has been reported to occur in sixty-eight to eighty-six per cent of the cases.[3,7,20] The incidence of weight loss varied widely in the reported cases from thirty-four to sixty-eight per cent of the cases.[1,3,7,8,14,20,28] Carson et al.[8] state that weakness with fatigue and/or weight loss was the primary reason for admission to the hospital in thirteen per cent of his series

of ninety cases.

A palpable liver was reported by Kenny and Moloney[20] as occuring in nineteen per cent of their cases. Adams et al.[1] reported this in twenty-six per cent of their cases. A palpable spleen was reported as occuring in nine to twenty-one per cent of the cases. Palpable masses or tumors were reported as occuring in twelve to twenty-two per cent of the cases. Most of these were not tender or painful and were rarely presenting complaint.[1,3,7]

Glenchur et al.[15] report an incidence of fifty-five per cent of patients with one or more episodes of pneumonia. This does not include terminal pneumonia. They also reported that fifty-seven per cent of their patients had other infections, primarily urinary tract infections. Thoracic deformity associated with bronchitis and emphysema was reported by Geschickter and Copeland[14] in two-thirds of their reported series.

In much of the literature the presenting symptom leading to the diagnosis was not tabulated. Usually the percentage of occurrence of symptoms was reported as those present at the time of diagnosis and no attempt made to try to pick out the first symptom. Carson et al.[8] did report on the initial symptom in a series of seventy-eight patients. In their report skeletal pain was the complaint leading to the diagnosis in sixty-nine per cent of the cases. This was the initial complaint in seventy-nine per cent of cases reported by Brownell[7] and sixty-seven per cent of cases

reported by Glenchur et al.[15] As stated earlier this was the presenting complaint in one-half of our series.

In a review of the reports on multiple myeloma the duration of symptoms before diagnosis was not often found. Two groups reported the average duration before diagnosis as nine months. These were Adams et al.[1] and Lichtenstein and Jaffe.[21] Carson et al.[8] reported on a group of patients with primary skeletal involvement. Considering the complaint of skeletal pain, the length of time of symptoms before diagnosis varied from one week to twenty-four months. In their group sixty-four per cent had symptoms for less than six months. As stated earlier, the average duration of symptoms in our group was eight months.

In the 425 cases they reviewed in 1928, Geschichter and Copeland[14] found eighty per cent of the cases in people between forty and seventy years of age. The peak incidence was at fifty-five years. Lichtenstein and Jaffe[21] reported three-fourths of their thirty-five patients between the ages of forty and sixty. Bayrd and Heck[3] reported the average and median age in their series of eighty-three cases as being fifty-seven years. Carson et al.[8] reported a series of ninety cases with the commonest age between fifty and seventy. They had only six cases less than forty years of age. Adams et al.[1] reported sixty-one cases with an average age of fifty-eight. Eighty-nine per cent of the series was over fifty years.

Geschickter and Copeland[14] stated that seventy per cent of the cases were males. Osserman[28] recently cited two series of 279 and 575 cases in which the incidence of males was fifty-four per cent and sixty per cent respectively. This might tend to suggest failure to make the diagnosis in women in the past or a change in the pattern of the disease in the recent past.

The incidence of anemia occurring with multiple myeloma has been reported variously in fifty-three per cent to ninety-one per cent of the cases. The range reported is wide because in some reports the patients were said to have anemia if anemic at the time of diagnosis. In other series the patients were reported as being anemic if anemia occurred at any time in the course of the disease.[1,3,7,8,14,20,21,35]

Several factors are thought to participate in the production of the anemia in multiple myeloma. Among these are bone marrow replacement, increased erythrocyte destruction, blood loss, renal insufficiency, associated infections, and nutritional factors. After treatment is begun, chemotherapy or radiotherapy may participate in the production of the anemia.[28]

Uniformly there is reported in the literature an elevated erythrocyte sedimentation rate. This is said to occur in sixty-seven to eighty-two per cent of the cases. Very common also is rouleaux formation on the blood smear. The incidence of the rouleaux formation is reported to be from thirty-one to sixty

per cent. Both of these changes are said to be due to the abnormal serum proteins found in multiple myeloma.[1,3,7,8,14,20,21,35]

Hyperproteinemia has been reported to occur in fifty to seventy-three per cent of the cases. Hyperglobulinemia has been found in fifty-two to eighty per cent of the cases.[3,7,14,16,21] The probable reason for the larger number of cases with hyperglobulinemia than of hyperproteinemia is the frquency of hypoalbuminemia. The latter has been reported in one series to occur in eighty-four per cent of the cases.[1] The incidence of Bence-Jones proteinuria varies extremely in reports from eight to eighty-seven per cent.[2,21] One reason for this may be the intermittent occurrence of Bence-Jones protein early in the disease with more constant occurrence late in the disease.[21] Proteinuria often occurs even though the urine is negative for Bence-Jones protein. In one series there was a sixteen per cent incidence of Bence-Jones protein with an eighty per cent incidence of proteinuria.[7]

It was stated by Cross[9] that approximately ninety-seven per cent of patients with multiple myeloma have an abnormal protein in the plasma and/or urine. He also stated that these proteins could be identified by electrophoresis. Adams et al.[1] stated that there were electrophoretic abnormalities in one hundred per cent of sixty-one cases. Putnam[33] feels that in no case of myeloma does the serum yield a normal electrophoretic pattern. He states that the filter paper method is well adapted for diagnostic survey

but that the free solution (Tiselius method) technic has to be used for detection of minor irregularities and for characterization by means of mobilities. In the five cases in our series in which serum electrophoretic patterns were done, there were abnormal patterns.

Frequent mention is made in reports of the presence of serum cryoglobulins in myeloma. Osserman[28] stated that five per cent of myeloma globulins are cryoglobulins. In a series of fifty-seven cases Kenny and Moloney[20] had a nine per cent incidence of cryoglobulins. They felt that cryoglobulin would be found more often if more careful technic were used. Cryoglobulins are found in many chronic pathologic states associated with hypergammaglobulinemia but generally are not found in large quantities. Cryoglobulin in excess of one hundred milligrams per one hundred milliliters usually indicates a primary plasma-cell dyscrasia or a related lymphoid proliferative state.[28]

Adams et al.[1] reported the incidence of leukopenia in myeloma before initiation of treatment as eleven per cent. Osserman[28] reports that in about a third of the cases there is moderate to severe leukopenia or thrombocytopenia or both. Generally it is thought that if a leukopenia exists in this disease that it is due to bone marrow replacement. James and Monto[18] report that the myelophthisis may occasionally be so severe clinically it is indistinguishable from aplastic anemia. Osserman[28] suggests that

there may also be humoral factors responsible for the leukopenia or thrombocytopenia. He calls these factors "leukoagglutinins" and "platelet agglutinins". In our series there were four patients who had a leukocyte count in the range of three thousand to five thousand. Of the thirteen patients who had platelet counts done, there were nine whose counts were below 200,000.

The finding of meyloma cells in the peripheral blood is repeatedly mentioned as a diagnostic aid. The incidence of atypical plasma cells varies in reports from ten to seventy-three per cent.[7,14,24] Plasma cells are more easily found if the buffy coat is examined.[34] If plasma cells are found in large numbers peripherally, it is called plasma cell leukemia.[8] Carson et al.[8] believe that this is a phase or variant of multiple myeloma which is often terminal. Plasma cells in the peripheral blood are not pathognomonic for multiple myeloma and have been found in cases of rubella, rubeola,[27] leukemia, metastatic carcinoma to the bone, Hodgkins disease,[31] cirrhosis, aganulocytosis, tuberculosis,[26] and hypersensitive states.[32,39] In our series there were only four cases in which plasma cells were reported in the peripheral blood.

Myeloid immaturity on the peripheral blood smear is often noted. This is thought to be due to marrow replacement and depletion. This is demonstrated by the appearance of myelocytes, myeloblasts, or stem cell on blood smear. These immature leukocytes may be present in such large numbers as to show a leukemoid

picture. This is reported to occur in twenty-six to forty-one per cent of the cases.[3,7] The latter figure was reported by Bayrd and Heck in a series of sixty-three cases. In this forty-one per cent there was myeloid immaturity to the myelocyte at least. In twenty per cent of cases they saw stem cells.

Hypercalcemia has been often noted in multiple myeloma and is reported to occur in ten to fifty per cent of the cases.[3,7,8,35] The increased serum calcium is thought to be due to the lytic resorption of bone. It may also be related to the tendency toward renal failure found in many patients.[21] The serum phosphorus is normal in most cases but may be elevated if there is renal impairment. The alkaline phosphatase is usually normal but may be slightly elevated shortly after a pathological fracture. These tests, while not diagnostic of myeloma, all tend to help differentiate it from hyperparathyroidism, Paget's disease, and metastatic carcinoma.[1,25]

Hyperuricemia was noted by Carson et al.[8] as being "not uncommon" in multiple myeloma. This has also been reported by Stewart and Weber[37] who thought the cause of the elevated uric acid was the breakdown of nucleoproteins derived from the myeloma cells as well as the apparent part played by decreased renal function. The elevation of the uric acid may occur in leukemias and other conditions.[8] Bronsky and Bernstein[6] reported a case of acute gout secondary to multiple myeloma. This is an infrequent occurrence.

The serum uric acid was elevated in two of the three patients in which it was determined in our series.

Renal insufficiency is a frequently reported complication. It is thought to be due to tubular degeneration and atrophy caused by plugs or casts of abnormal globulins in the renal tubules as well as the presence of droplets of these proteins in the renal epithelial cells.[4,36] In the papers reviewed an increase in NPN or BUN was reported in thirty-four to forty-six per cent of the cases.[3,8,14,20,21] It is thought, generally, that these kidney changes are responsible for the proteinuria although not necessarily the Bence-Jones proteinuria.[8] The NPN or BUN was abnormal in ten of the fifteen patients on whom the tests were done in our series. Seventeen of these twenty patients had proteinuria.

The classical roentgengraphic description is of clearcut punched-out osteolytic defects in many bones including the calvarium. The general consensus is that the classical description is the exception rather than the rule.[12,21] There is no roentgenographic picture which is pathognomonic for multiple myeloma.[12] Hyperparathyroidism, metastatic cancer, or other tumors may simulate the osteolytic lesions of myeloma. Diffuse osteoporosis and pathological fractures are frequent findings also. The osteoporosis must be differentiated from post menopausal and senile osteoporosis.[1,12] Pathological fractures are serious manifestations of this disease and are responsible for many of the neurological

complications.[29] Pathological fractures may also have other etiologies. Compression fractures of the vertebrae are very frequent and often cause symptoms leading to the diagnosis of multiple myeloma. The frequency of occurrence of these roentgenographic changes varies widely in case reports. In one series[20] osteolytic lesions occurred in sixty-eight per cent and pathological fractures in forty-eight per cent of cases. Rarely a patient may not have any bony abnormalities on X-ray.[20]

The abnormal appearance of the bone marrow biopsy has long been the absolute diagnostic criterion. The diagnosis of multiple myeloma is rarely made without a positive bone marrow examination. Schwartz and Cataldo[35] reported that the bone marrow was diagnostic in seventy-four of seventy-five cases in their series.

Lichtenstein and Jaffe[21] report the incidence of amyloidosis complication myeloma as six[2] to ten per cent. Osserman[9] stated that the majority of cases of so-called primary amyloidosis are on a plasma cell basis. The etiology of the amyloid has not been determined. It is thought that the amyloid is due to the hyperglobulinemia which, in turn, is thought to be produced by the abnormal plasma cells.[21,29] Davis et al. have reported cases of multiple myeloma associated with rheumatoid arthritis in which postmortem studies revealed amyloid deposits in and about the joints. In their series of twenty-six cases of multiple myeloma,

arthrities of some type was the primary diagnosis in sixteen.

Much is written about extra-medullary infiltrations of plasma cells in diffuse myeloma. The most commonly involved tissues are the spleen, liver, lymph nodes, and kidneys. Clinically this is reflected by palpable lymph nodes, splenomegaly, hepatomegaly or even by liver dysfunction.[8,21]

Almost in all cases multiple bone marrow and extramedullary plasma cell infiltrations are found at the time of necropsy. The occurrence of large casts involving a large portion of the renal tubules is a fairly frequent finding in diffuse myeloma.[8]

Summary and Conclusions

The diagnosis of multiple myeloma can be suggested but not established clinically. The presence of myeloma cells in the bone marrow and the presence of abnormalities in the serum or urine electrophoretic patterns are pathognomonic. Other laboratory tests are highly suggestive and of help in the diagnosis. These are anemia, rapid sedimentation rate, rouleaux formation, plasma cells peripherally, elevated serum globulin and Bence-Jones Proteinuria. Other nonspecific tests are hypercalcemia, hyperuricemia, elevated NPN, moderate leukopenia, thrombocytopenia, and proteinuria. X-ray changes of the skeleton may be of the typical osteolytic type but more often are of the nonspecific type. The osteolytic lesions cannot be differentiated on X-ray from those of

hyperparathyroidism and metastatic tumors. The nonspecific X-ray changes are osteoporosis and pathological fractures. The latter occur as vertebral body compression fractures and as fractures of the long bones and ribs. The review of these cases would seem to indicate that many interesting tests are often not done because the diagnosis is established by bone marrow biopsy. Most recent reports indicate that there are almost always abnormalities of the serum or urine electrophoretic patterns. This was one of the tests frequently not done in this series of patients. In this series electrophoresis was done and was positive in five cases. Cryoglobulins were tested for and were negative in eight cases. It would seem that the former test would be of more value in diagnosis of this disease.

The presence of plasma cells in the peripheral blood was seldom reported in this series. In the literature this is reported in a much higher incidence because a buffy coat examination is usually done.

The average duration of symptoms before diagnosis was eight months in this series. This is about the average reported in the literature. It might be suggested that should the diagnosis be thought of more often it could be made earlier in the course of the disease.

In this series and in other small series there seems to be a much greater incidence of men with myeloma. In the recent

large series there is reported only a slightly greater incidence in men. This would suggest that myeloma may not be suspected often enough in women. It might be well to go over cases of postmenopausal osteoporosis more closely to rule out multiple myeloma.

Amyloidosis has often been reported as being associated with multiple myeloma. In this series amyloidosis was diagnosed clinically in one patient. Two other patients showed amyloidosis on autopsy. Two of the three patients who had amyloidosis had complained of hoarseness. The cause of the hoarseness was not determined. It may have been a result of the amyloidosis or it may have been a neurological complication. One of the cases showing amyloidosis on autopsy had had symptoms of a gastric lesion before his death. There were two other cases in which gastric malignancy was suspected because of X-ray findings. Necropsy revealed no lesions. This makes one wonder if these two patients might not have had amyloidosis involving the stomach.

Multiple myeloma is not often diagnosed early in the course of the disease because it has no characteristic symptoms or physical findings. One should consider the diagnosis in patients with skeletal pain, weight loss, recurrent infections, anemia, pathological fractures, and osteolytic or osteoporotic lesions. One should suspect multiple myeloma if hyperglobulinemia, hypercalcemia, hyperuricemia or Bence-Jones protein is found. Positive

diagnosis is made by bone marrow examination and by serum and urine electrophoresis.

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