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Multiple myeloma

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MULTIPLE MYELOMA

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In 1848, a grocer, who was forty-seven years of age, and who had not been in good health for thirteen months, consulted Dr. Watson and Dr. MacIntyre. The doctors noted that their patient had extremely fragile bones and an unusual "animal substance" in his urine. They sent separate specimens of the urine to Henry Bence Jones who described the protein substance which was later given his name. Dalrymple published the post mortum findings of the case and MacIntyre described the caseas "Mollities et Fragilitas Ossium" in 1850. These are the three reports of the original work in the disease now known as multiple myeloma.

Rustizky wrote the first definitive pathologic description of the disease in 1873 and proposed the name myeloma for this condition. Forty years after the original paper Kahler published an article which associated the deformity and abnormal fragility of the bones, bone pain, cachexia, and the presence of Bence Jones proteinuria under the heading of multiple myeloma. Today multiple myeloma is often referred to as Kahler's disease in recognition of his work.

This paper shall consider the following aspects of multiple myeloma: etiology, clinical picture, X-ray manifestations, pathology, treatment and prognosis.

GENERAL

In general, multiple myeloma is an ultimately fatal disease common in the fifth to seventh decades of life and more common in men than in women. Classically, the disease is characterized by punched-out lesions in the entire axial skeleton. The lesions are completely osteolytic in character showing no osteoblastic qualities. Also, there is a proliferation of immature plasma cells of the bone marrow that are thought to be derived from the reticulum cells. The entire bone marrow is usually involved.

As to etiology, it was originally thought that the disease was, as its name implies, a myeloma, i. e., a neoplasm composed of plasma cells derived from the bone marrow. Presently, some clinicians consider it to be the aleukemic phase of plasma cell leukemia, as there are many clinical observations linking it with leukemia and other diseases of the reticuloendothelial system. For example, often the peripheral blood smear in multiple myeloma will have many abnormal cells in it presenting a picture similar to a plasma cell leukemia. In addition, both meyloid and lymphatic leukemia, tumor formations are known to occur. Further, as is the rule in leukemia, certain cases of myeloma exhibit diffuse proliferation of the abnormal cells of the bone marrow without localized tumor formation. Thus, regardless of its generalized skeletal or localized onset, there is much to be said for including multiple myeloma among the generalized proliferative disorders of the reticuloendothelial system.

The incidence of multiple myeloma is higher in men than in women and highest in the Caucasian than in the Negro. The majority of cases are seen between the ages of fifty and seventy years, but cases in patients below twenty and over ninety years of age have been reported. The average length of life following the onset of symptoms is twenty months, while the majority of patients live about sixteen months. The disease is uniformly fatal despite all theraputic efforts.

CLINICAL PICTURE

The description of the clinical picture of multiple myeloma as redefined from MacIntyre by Kahler is still applicable today, namely:

(1) bone pain

(2) deformity and pathological bone fragility

(3) cachexia

(4) Bence Jones proteinuria

Geschickter and Copeland in reviewing the cases of multiple myeloma reported in the literature up until 1928 and reporting their own experience noted that the extreme variability of symptoms with which this disease can present itself. They expounded on Kahler's criteria and submitted the following symtoms:

(1) Multiple tumorus involvement of the skeletal system

(2) Pathological fractures--usually of ribs

(3) Exeretion of Bence Jones protein in urine

(4) Characteristic backpain and signs of paraplegia

(5) unexplained anemia

(6) Chronic nephritis with nitrogen retention, low to normal blood pressure, high serum proteins with reversal of the albumin-globulin ratio

In contrast to other malignant neoplasma. The onset of multiple myeloma is insidious with no characteristic early symptoms. Commonly, vague back or bone pain, swelling or signs of local pressure and pathological fracture are the presenting complaints. The average patient will seek medical advice after three months of symptoms referable to the disease. The patient may present himself with symptoms of progressively increasing bone pain, progressive fatigue, progressive anorexia, nausea and vomiting, progressive weight loss or recurrent pulmonary infections with many febrile episodes. To elucidate the clinical picture hemorrhagic tendencies, neurological problems, and symptoms simulating rheumatoid arthritis must be ferreted out in order that the final diagnosis can be made and therapy instituted.

Pain is the most outstanding and consistent presenting complaint in patients with multiple myeloma, being seen in 80-90% (9) of patients on the first visit. Pain is usually

gradual in onset may be fleeting, migratory, or abrupt when associated with a pathological fracture. The pain may be localized, commonly in the low back, thoracic spine or rib area; or it may be generalized skeletal pain. The pain is usually progressive, may be mild or severe, may increase with coughing or sneezing, and usually decreases at night in association with a decrease in the patient's activities.

Neuretic pain may be seen with compression fractures of vertebrae. This of course is sudden in onset and may be relieved by traction or laminectomy. The pain of multiple myeloma is usually associated with acutely exquisite superficial tenderness. Pain may be of a characteristic cyclic nature as described by Copeland and Geschickter. Terminal patients usually require round the clock sedation for relief of their pain symptoms. The clinical picture of pain may suggest the diagnosis but is usually considered nonspecific.

Pathological fractures are seen in about 60% (12) of multiple myeloma patients. They are associated with minor trauma and are quite painful. A lump at the fracture sight may be noted by the patient. The most common sight of pathological fracture is compression of a vertebral body in the area of greatest spinal mobility, the lower thoracic and lumbar regions. Fractures may also be noted in the cervical area. The next most common sites are rib, proximal one third of femur, pelvis,

sternum and clavicle. Many times the most severe fracture is that of the sternum as this may eventually embarrass respiration. Many of these patients are in the older age groups, are males, with or without some degree of kyphosis due either to compression of a vertebral body or other causes; and thus already have limited pulmonary function due to emphysema, chronic bronchitis and recurrent episodes of bronchopneumonia. The onset of paradoxical respiratory motion by the sternum following fracture may seriously impair ventilatory capacity and may lead to death. Therefore it may be wise to use the iliac crest to take diagnostic bone marrow specimans. Fractures usually heal rapidly, as associated with this disease there ia an elevated serum calcium allowing rapid callus formation. Multiple deformities are common due to many partial and complete fractures. Deformities seen commonly are kyphosis, shortening of the spinal column, rib cage touching the pelvis, severe kyphosis and scoleosis and often a disappearance of the normal lumbar lordosis.

Severe renal impairment is not uncommon. Reportedly, kidney function is impaired to some degree in about 70% (6) of patients with multiple myeloma. In 1908 Von Decastello described the "myeloma kidney" which had three definite characteristics: (1) large hyaline droplets in the lumen of the tubules, (2) crystalline material in tubule lumen and (3) amorphous precipitates or casts high in the renal

tubules. These obstructive casts are thought to be made up to some degree of Bence-Jones protein. Due to the intra-tubular obstruction the terms "nephrohydrosis" and "intranephric hydronephrosis" have been coined to describe this phenomenon. The casts act as a foreign body causing obstruction, glomerular atrophy, contraction of renal parenchyma and severe renal insufficiency. Uremia, often being the terminal event, is not associated with hypertension, edema or retinitis. Thus in a pt. with uremia and a normal blood pressure the diagnosis of multiple myeloma is eminent.

Bence-Jones proteinuria is seen in 50-60% (12) of pt. with multiple myeloma and is considered pathognemonic of this disease. The protein is of low molecular weight, 35,000-40,000, and thus passes through the glomeruli quite easily and enhances the renal insufficiency. There is a very high correlation between patients presenting with Bence-Jones proteinuria or albuminuria and those who eventually go on into renal failure. Though Bence-Jones proteinuria is absent in about one half the cases, the diagnosis can be made because this half will usually show typical changes in the serum proteins diagnostic of multiple myeloma, namely, hypergamma-globulinemia or paramyloidosis.

Anemia and fatigue, so common a complaint in the older age group, may point to the diagnosis of multiple myeloma. The anemia is usually due to marrow replacement but may be

due to anorexia or hemorrhagic tendencies as noted by a history of epistaxis or bleeding from the gums. Other causes of anemia are the toxic effects on the bone marrow by the proliferating plasma cells and azotemia noted in uremia. The anemia is usually a normocytic normochromic type as would be expected in the myelophthisic disease, but it may be machrocytic similar to pernicious anemia if marked anorexia and cachexia are evident. These anemias are notably resistant to iron, Vit B12 and folic acid therapy.

Another clinical manifestation of the disease is the finding of a palpable tumor which can be expected in about 25% (12) of patients. Common sites of palpable tumors are the ribs, skull, femur, humerus, sternum, and the sacrum. The tumor, composed of sheets of plasma cells may range in size from a pea to a grapefruit. The tumor may appear to be firm and boney or rubbery in consistancy, depending on whether or not the cortex of the bone underlying the tumor has been completely eroded away or not. The exquisite tenderness of the lump may be the first attraction to the involved area. The tumor may involve adjacent structures by direct extension causing localized symptoms and additional pain.

Some patients may be noted to have a continuous fever of unknown origin. This fever, though low grade, is thought to reflect chronic or subacute pulmonary infections or perhaps a chronic nephritis. Pulmonary infections are common in multiple

myeloma because of the high incidence of deformity in the thoracic region, disability and pain on movement, all of which retard ventilation. An other contributing factor is hyperglobulinemia causing increased blood viscosity. Thus, with sluggish circulation and decreased aeration, small pulmonary infarcts are produced. Also seen with hyperglobulinemia is a depression of antibody levels in the blood, weakening the body's defences. Tumors eroding through bone into the lung are common. These suprapleural tumors, while they may or may not enhance infection, are very difficult to differentiate from metastic carcinoma on x-ray and physical examination.

Patients with neurological symptoms comprise 40% of Snapper's series of 97 patients. Symptoms may arise from direct extension of the tumor through bone and compression of adjacent nervous elements; by compression of the spinal cord following fracture and collapse of a vertebral body resulting in paraplegia, bladder and bowel paralysis, etc; or from a peripheral neuritis not directly associated with tumor involvement. Myelomatous tumors in the calvarium may cause brain involve-ment resulting in ptosis (unilateral usually), crainal palsy, thrombosis of an artery or even coma. Many of these patients show nerve root involvement following collapse of a vertebral body; hyperesthesias, paraesthesias, foot drop and loss of proproception are not uncommon. Others showed herpes zoster, hemiplegia, convulsive seizures, degenerative cord diseases, various carinal nerve problems and Horner's syndrome.

Lymphadenopathy and hepatosplenomegaly due to marked plasma cell infiltrate or amyloidosis was found in 75% of cases coming to autopsy, while clinically it could be found in only 10% of cases on careful physical examination (12).

Another manifestation of multiple myeloma is that of simulating rheumatic arthritis in cases of long duration. Pain on movement and swelling of joints caused by deposition of amyloid in the synovial membrane make the clinical differentiation difficult.

Though the above mentioned clinical manifestations may seem quite vague and nonspecific, when the clinical picture is allied with the proper laboratory and x-ray data the diagnosis of multiple myeloma often becomes quite clear cut. Unfortunately, however, the laboratory and x-ray findings may also be inconclusive, making the diagnosis uncertain, which is undesirable in this rapidly fatal disease.

In the search for an accurate diagnostic tool with which to cinch the clinical impression it was found that bone marrow aspirations were most reliable, proving to be 90% accurate. The indication for bone marrow examination is anemia. Most hematologists agree that no anemia should be treated blindly, i.e. without first making the etiology of anemia known so that proper therapy can be instituted. The diffuse involvement of the bone marrow throughout the body makes it immaterial from

where the aspirate is obtained. On microscopic examination the marrow will show a dense over growth of the plasmocytes with concomitant suppression of the erythroid elements.

Presumptive evidence of multiple myeloma based on the peripheral smear are the following:

1. Anemia - thought to be due to (a) bone marrow replacement (b) toxic inhibition of bone marrow (c) renal failure. Though none of these seems to completely explain the anemia, about 50% (12) of patients being seen for the first time will have less than 11gm% and RBC less than 4 million. Anemia is the most consistent finding among these patients. It is usually of the normocytic normochromic type and responds poorly to iron, folic acid and Vitamin B12 therapy.
2. Excessive rouleaux formation - this is consistently found in patients with hyperglobulinemia with a reversed albumin-globulin ratio. It is also suspected that there is a hydrophilic colloid present. This finding is also well correlated with elevated sed rates. Increased rouleaux is reported in about 60% (12) of cases.
3. Leukocyte count - 40% of patients have leukopenia while 20% (12) have a leukocytosis. Many times the differential is unremarkable, but it may reflect an increase in the plasmocytes and an increase in younger myelocytes.

It is though that there is an acute "plasma cell leukemia" phase of this disease in which the plasma cell count in the peripheral blood may go as high as 50% (12). There is at present no concrete link between the two diseases as the patient who has an increase in the plasma cells in the peripheral blood shows no boney lesions characteristic of multiple myeloma nor does the patient have Bence Jones proteinuria. An increase in plasma cells in the peripheral blood may be seen in 25% (12) of patients.

4. Eosinophilia - a totally unexplained eosinophilia occurs not uncommonly with multiple myeloma. The eosinophil count may reach as high as 45% and is not associated with overt evidence of an allergic state or infestations with parasites.

In about 35% (12) of cases an unusual propensity to bleed may be noted. A history of epistaxis, bleeding from the gums, hemoptysis, retinal hemorrhages, petechial and ecchymosis is significant. These hemorrhagic tendencies are hard to explain strictly on the basis of a thrombocytopenia alone. It is thought that hyperglobulinemia and deficient clotting factors may play an unknown role here, as there is an increase in fibrinogen and plasma viscosity.

X-RAY MANIFESTATIONS:

Although the typical case of multiple myeloma presents an obvious picture the variants are difficult to diagnose. In this connection Geschickter has stated that in the x-ray diagnosis

of this disease it may be practically impossible to distinguish it from diffuse metastatic carcinoma. Camp has stated that he knows of no characteristic roentgenographic picture which will permit the unquestionable diagnosis of multiple myeloma. Though the presence of "punched out" lesions of bone is indeed the classical x-ray manifestation of the disease, it cannot be con-sidered as a sine qua non as no lesions of this nature can be demonstrated in 10% (12) of cases which were later proven by necropsy. Thus, there is an increased appreciation for the diffi-culties in establishing the diagnosis of multiple myeloma on the appearance of x-rays structures.

The lesions of multiple myeloma are malignant osteolytic tumors arising from cells in the red bone marrow. They have no relation to osteogenic cells and hence, they produce no new bone. The lesions are thought to be independent of one another rather than metastasis, however, metastic lesions can be found in soft tissues such as lymph nodes, spleen and liver.

It is generally accepted that the x-ray picture varies a great deal from patient to patient and that is has a very poor correlation with the pathological findings at necropsy. It is useless in "staging" the disease. A patient with profuse lytic lesions and marked osteoporosis on x-ray may have few if any lab or clinical findings with as many as 10% (12) of patients succumbing of multiple myeloma will have no positive x-ray findings.

Heiser and Schwartzman have attempted to classify multiple myeloma on the basis of x-ray and histological findings.

I NORMAL - The absence of radiographically demonstrable abnormalities in osseous structures. This could mean that the bone is uninvolved, that the myelomatous infiltration of marrow is without alteration of trabecular or that trabecular destruction is present but not microscopically. Adran showed that a lesion 1 cm in diameter could be missed in the spine.

II OSTEOPOROSIS - Thinning of the trabeculae with increased radiolucency is not pathognonomic of multiple myeloma. This picture may be seen in senile osteoporosis, hyperparathyroidism, hyperthyroidism, and atrophy of disuse. In osteomalacia of the vertebral bodies the intervertebral discs expand in direct proportion to the amount of halisteresis.

III INTERMEDIATE GROUP - OSTEOPOROSIS VS. OSTEOLYSIS - This group appears to be the transition between marked osteo-porosis and those cases presenting definite destruction of a poorly defined type. The x-ray picture is one of spotty osteoporosis in which diffuse demineralization is overlaid by focal, well demarcated radiolucencies. There is trabecular thinning of varying degrees and some trabecular dissolution. In this group it is hard to differentiate between severe osteoporosis and malignant disease.

IV SHARPLEY CIRCUMSCRIBED DESTRUCTION - In this group is seen the so called "classical lesion" i.e. a punched-out area of about 1-2 cm with a slightly thickened border. This lesion is rarely seen in the spine, and is usually seen in completely normal bone. The site of origin of this lesion is in the medulla of calcenous bones; and with progression there may be encroachment on the cortex which may cause cortical expansion, followed by invasion of the periosteum and adjacent soft tissue.

V POORLY CIRCUMSCRIBED BONE DESTRUCTION - The margins of the osteolytic lesions are not sharply demarcated and there is a subtle merging of the lesion with the surrounding normal or osteoporotic bone. These lesions imulate metastatic carcinoma from the thyroid, breast, prostate, lung, kidney, and in the extremities may appear to be rheumatoid arthritis.

VI SEVERE BONE DESTRUCTION - THREE TYPES

A. Complete replacement by tumor - this is the most common type. The medulla is completely eroded away along with most of the cortex so that only a paper thin cortex remains.

B. Radiolucent areas marginated by surviving trabeculae presenting a bizarre reticular pattern, termed a "honey comb" pattern.

C. Involved areas are crisscrossed by large condensed trabeculae resulting in a soap bubbling appearance similar to a giant cell tumor.

Suggestive x-ray findings may not be present on the first patient visit as severe back pain, anemia and fatigue may cause the patient to seek medical advice before the skeletal system becomes sufficiently involved. Osteolytic punched-out lesions are most often seen in the skull, ribs, pelvis and bones of the extremities, while the spine may show only diffuse osteoporosis.

In the skull the punched-out lesions are most common. This may be accounted for on the basis that the calvarium is thin and there is an absence of overlying tissue, making lesions of smaller dimensions more easily discernable. The lesions are most frequently seen in the frontal and parietal areas, and in more advanced cases may coalesce to form diffuse mattling of the skull. The differentiation from pacchionion ' ody dehiscences or diploic venous lakes may be difficult. There is no thickening of the tabes and no large areas of destruction as seen in Hands-Schuller-Christian disease. As the lesions expand they may be hard to differentiate from metastatic carcinoma. Though they are not as irregular and infiltrative, nor do they cause any reaction in the surrounding bone as carcinoma or syphilis does. The skull is often not examined because the patient presents with few or no symptoms referable to the skull. When the skull is examined by x-ray, there may be no involvement, while the re-maining skeletal system shows marked tissue changes. In the skull there are few if any fractures noted, and soft tissue masses are rare.

The predominent x-ray finding in the spine is osteoporosis varying in degree from thinning of the trabeculae to complete effacement of the medullary architecture leaving only a thin cortex. Often there is softening and swelling of the intervertebral discs. Seventy-five per cent (5) of cases show collapse of one or more vertebrae during the course of the disease. Rarely are contiguous structures involved though extension around and across joint spaces is noted, and soft tissue masses are seen. The findings in the spine are indefinite and are thus hard to differentiate from other problems of the spinal column.

Fifty per cent of patients in Smith's series were hospitalized complaining of severe low back pain. Of these patients, x-ray of the spine showed either normal structures with no osteoporosis or a mild degree of osteoporosis. He concludes then that there are three classes of spinal findings by x-ray:

1. Normal structures without osteoporosis
2. Normal structures with mild osteoporosis
3. Compression fracture or lytic lesion with osteoporosis.

Smith maintains that osteoporosis is the most consistent x-ray finding in multiple myeloma. Lesions of the spine may be obscured by poor positioning and a poorly aerated lung clouding the bony changes. Therefore, examinations of the skull, pelvis, chest and femuri are more accurate.

In the ribs the most frequent finding is diffuse motling and demineralization of bone progressing to discrete and destructive osteolytic lesions. There may be many areas of cyst-like

expansion with palpable tumors (usually near the anterior axillary line) or complete destruction of portions of the ribs. Fractures of the ribs are very common, occuring usually in the lateral rib cage. Frequent and multiple rib fracture in the 50-70 year age group should suggest the diagnosis. Rarely, lesion of multiple myeloma may perforate the ribs and present themselves on x-ray examination as soft tissue tumors of the lung. An important diagnostic point in this regard is that multiple myeloma has never been known to metastize to the lung fields, virtually excluding it then from the differential diagnosis of lung infiltrates. Fracture of a rib can cause a subpleural hematoma, with development of pleural effusion and empyema which further confuse the exam-iner.

X-rays of the pelvis reveals all forms of involvement rang-ing from small classical punched-out lesions to large wholesale destruction of boney structures simulating giant-cell tumors. Soft tissue masses are infrequent and pathological fractures are rarely if ever encountered.

At the ends of long bones the lesions may fuse into large cyst-like areas which may simulate cystic osteitis. These les-ions may lead to marked bone atrophy, and the cortex becomes paper thin, predisposing it to pathological fracture. Occasionally the lesions at the ends of long bones may exactly simulate osteoclastic lesions of metastatic carcinoma, but the typical lesions here as elsewhere are punched-out areas. Other than

the above mentioned bones the proximal femur, scapula, humerus and clavicle are frequent sites of radiographically demonstrable involvement. However, the entire skeleton may be riddled with lesions, as seen by x-rays in about 13% (5) of cases.

In general, the presence of the typical sharply etched destructive lesions in otherwise normal bone will point to the diagnosis of multiple myeloma. Although the x-ray findings from patient to patient are highly variable, common combinations of x-ray pictures are noted. These are :

1. Discrete punched-out lesions of the skull with osteoporosis of ribs, severe osteoporosis and partial collapse of vertebrae.
2. Normal skull, borderline destruction in ribs, circumscribed destructive lesions in the pelvis and mild osteoporosis of the spine.

The typical intramedullary, circular lesion showing osteolytic changes with no osteoblastic component is not as pathogonomonic as was once thought. These lesions must be differentiated from metastatic carcinoma, parathyroid disease, and other osteo-malacia discussed in the differential diagnosis. On x-ray exam-ination, then, having demonstrated the geography of a punched-out lesion, a definite effort should be made to ascertain the char-acter of the lesion. To demonstrate a punched-out lesion with an osteoblastic component and new bone formation or a reactive osteitis will militate against the diagnosis of multiple myeloma.

A diffuse osteoporosis may be accounted for on the basis of faulty calcium metabolism or hormonal deficiency. Thus the final diagnosis may require biopsy and microscopic examination of suspected boney lesions.

METABOLIC ALTERATIONS IN MULTIPLE MYELOMA

A disease that is radiographically evident is usually a disease that has already progressed to an advanced stage, and the diagnosis of multiple myeloma as a proliferative disorder of plasma cell origin is frequently possible by biochemical technique before x-ray changes are demonstrable.

Historically, Bence Jones proteinuria is the most significant laboratory test for multiple myeloma, although it is known to occur in only 65% (9) of cases. This abnormal protein is known to be excreted in the urine of patients with metastatic carcinoma of bone, multiple sarcoma of bone, senile osteomalacia, fibrocystic disease, myelogenous leukemia and polycythemia. The protein is a low molecular weight albumin (35,000-40,000), therefore, is filtered through the glomeruli very easily. It is thought to be formed by the plasma cells in the bone marrow and in the normal state is made in such small quanitities that it is inperceptible in the normal urine. When, as in multiple myeloma, the plasmocytes proliferate rapidly, the serum content of this albumin increases and is filtered out by the glomerulus in measurable quantities. There is an inverse relationship between the degree of serum hyperproteinemia and the quantilative

excretion of Bence Jones protein in the urine. This relationship is as yet unexplained and bears only practical diagnostic importance.

The elevated serum proteins in multiple myeloma have been known and studied for many years. Solesnick has concluded that hyperproteinemia is present in 50-60% of patients with multiple myeloma. Both the bone marrow reticulum cells and faulty liver metabolism have been implicated in the elevation of serum proteins. In many patients an early rise in the serum globulins and later a marked depression of the albumin fraction will be noted long before x-ray manifestations of the disease are noted. The increase in serum globulins is largely due to an elevation in the gamma globulin fraction; elevations in the beta and alpha fractions are also seen, though rarely.

Recent studies have sought to link antibody and antigen reactions to the increase in gamma globulins in multiple myeloma. Antibodies migrate with the gamma globulins on electorphoretic analysis. Associated with an increased antibody production is an increase in the plasma cell count in the bone marrow, lymph nodes and spleen.

In patients with congenital agammaglobulinemia there is a lack of plasma cells in the hemopoetic systems. Conversely, in diseases associated with increases in gamma globulin production, namely cirrhosis, lymphogranuloma, sarcoidosis, kalaazar, systemic lupus erythematosis, and other collegan diseases, there is an increase in the number of plasma cells in the bone marrow and lymphoid tissues. The plasmocytosis in these

cases is thought to be secondary to some unknown primary stimulus as opposed to multiple myeloma, where plasma cell proliferation is thought to be the primary factor.

Electrophoretic studies show that it is not the quantity or mobility of the globulin, but the discreteness of the globulin migration, that is diagnostic of multiple myeloma. In multiple myeloma or "primary hypergammaglobulinemia" the electrophoretic pattern shows a very discrete fraction varying in quantity and motility from patient to patient, while in the collegan diseases and other "secondary hypergammaglobulinemias" there is a diffuse increase in the globulin area. Similarly, the urinary proteins of the Bence Jones type seem to be very discrete and homogenious and with variable motility. Electro-phoresis and ultracentrifugation have proven to be valuable tools in the diagnosis and follow-up of patients with multiple myeloma, but the accuracy of these tools is grossly decreased when the serum levels of the abnormal proteins falls below 200-300 mgm %. Many patients who show abnormal serum proteins long before x-ray findings are evident die of paramyloidosis or cardiovascular disease before diagnostic x-rays become available.

Amyloidosis and paramyloidosis are seen in about 10% (12) of patients with multiple myeloma. Some authors believe that this complication is due directly to the deposition of Bence Jones protein in the body tissues, while others think that it is a tissue reaction to the hyperglobulinemia. Paramyloidosis

in multiple myeloma must be identified with primary amyloidosis, according to Snapper. In the secondary amyloidosis, which follows prolonged suppuration, the localization of the amyloid is predominently in the liver, spleen, kidneys, adrenals and blood vessel walls. In primary amyloidosis or paramyloidosis the deposition occurs in atypical locations, mainly in the mesodermal tissues of the heart, blood vessels and G.I. tract. The involvement of blood vessels is common to both but only paramyloidosis forms the amyloid tumors. The most common site of involvement by amyloid is its deposition in the gastrointestinal tract. The heart and blood vessel walls are also frequently involved which may contribute to some patients congestive failure. An interesting feature of multiple myeloma with paramyloidosis is that the patients rarely develop bone lesions demonstrable by x-ray. This emphasizes again the difficulty of diagnosing this condition. In patients with amyloidosis many do not have hyperglobulinemia. To explain this, it has been suggested that instead of abnormal proteins circulating in the blood, they are deposited in the mesenchymal tissues.

Probably as a result of the rapid demineralization of bones, the findings of hypercalcemia and hypercalcinuria are characteristic of multiple myeloma. This situation may be noted is as many as 50% (11) of cases. The calcium serum levels are increased out of proportion to the protein bound calcium increases due to the hyperglobulinemia. The serum phosphorus

levels are increased only in the face of kidney failure and uremia. The serum alkaline phosphatase may be normal or slightly increased and acid phosphatase levels may be increased when pathologic fractures are present. The triad of hyper-calcemia, hyperphosphatemia and elevated serum alkaline phosphatase militates against the diagnosis of hyperparathyroidism, thus narrowing down the differential diagnosis.

There is a significant elevation of the serum uric acid level even in the absence of renal insufficiency. This is evidently due to the increased catabolism of nucleoproteins derived from the nuclei of myeloma cells.

SOLITARY MYELOMA

Paul and Pohle have reviewed 45 cases of solitary myeloma arising from the mucous membranes of the antrum. These tumors were not unequivocally solitary, but it was doubtful that they were multiple. These tumors comprise 10% of myelomas and seem to carry a better prognosis, even though 30% of them become generalized. To separate these into a category by themselves is artificial, as they are probably all a phase of the same disease of which plasma cell leukemia is the more malignant end of the spectrum. It is apparent that the benignancy of the solitary myeloma is only relative, that they are associated with what is customary to refer to as multiple myeloma, if not a part of the same process, and that frequently the full blown

picture of myeloma develops even following successful excision of the local lesion without local recurrence. Also solitary myeloma is an inexact designation, as there may be other lesions that don't show up on X-ray examination.

Lane has reported a case of solitary myeloma of the mandible, which, after removal, showed a reversion of the electrophoretic pattern back to normal; and the electrophoretic pattern made from the tumor itself was exactly the same as the serum pattern. This is presumptive evidence that Bence Jones protein and other abnormal proteins are made from the myeloma.

In the X-ray diagnosis of solitary myeloma two types of lesions may be noted:

1) Osteolytic, multicystic area of rarefaction simulating a giant cell tumor. The lesion may be sharpley demarcated and centrally located in the medullary area with or without expanding the cortex. There is no periosteal reaction and often there is a pathological fracture through the tumor. At times thick trabeculae can be noted.

2) A purely destructive lesion located in the shaft of long bones and extending up and down the shaft of the bone. Expansion of the cortex is often present. This lesion does not appear to be cystic and trabeculation is not a prominent feature. This type of lesion is more often seen in the vertebral bodies and often limited to one vertebral body, though, direct extension to another has been noted.

Extramedullary plasmocytomas have a predilection for the upper air passages and are occasionally seen in the stomach, intestines, pancreas, pleura, thyroid, genitourinary tract and in the skin. Plasmacell tumors of the conjunctiva are perhaps more properly called plasma cell granulomas, as most authors are of the opinion that these tumors are inflammatory in nature and that their neoplastic characteristics are indestinct since they are neither destructive nor invasive. In extra-medullary plasmocytomas the metastesis to bone and lymphoid tissue is not uncommon. Bence Jones proteinuria is not noted in these patients unless skeletal involvement can be demonstrated.

Hellwig believes that ultimately the full blown picture of multiple myeloma emerges in most cases.

The differential diagnosis of solitary mueloma is similar to that of multiple myeloma with the exception of the systemic diseases and the errors in metabolism. Giant cell tumor of bone particularly may simulate solitary myeloma, but the giant cell tumor is usually seen at the epiphysis of long bones and is rarely seen in flat bones or elsewhere. Fibrocystic disease of bone is seen in a much younger age group usually before the twentyth year and is associated with asymptomatic fracture of the diaphsis of long bones such as the humerus and femur while multiple myeloma is associated with considerable pain on fracturing. Ewing's sarcoma causes considerable periosteal reaction, cortical expansion, trabeculation, and is not a purely

osteolytic lesion; while multiple myeloma is almost the opposite. In tuberculosis of bone the changes are notably inflammatory rather than neoplastic.

Both multiple myeloma and metastatic carcinoma show bone destructive qualities, appear in the same age range and have similar sites of involvement. Carcinoma will be irregular, infiltrative and show a sclerosing tendency, while multiple myeloma will show a soft tissue mass along the spinal areas. Pathological fractures are common to both. Multiple myeloma will go around joint spaces by direct extension through contiguous structures, while this is rare in carcinoma. Expansion of the cortex is common with multiple myeloma and rather unusual in metastatic carcinoma. Other rare problems are cylindroma of ilium and hemangiomas with multicystic structures. In any event, to make the diagnosis a biopsy should be taken. An excisional biopsy is preferred and this should be followed by 1000-1200r to the area.

PATHOLOGY

The plasmocytomas in multiple myeloma have a predilection for those bones with abundant cancellous spongiosa and red bone marrow, such as the pelvis, spine, sternum, skull and long bones. Examination of these bones shows that the cortex is thinned and frequently eroded, allowing the myelomatous tumor tissues to actually infiltrate the surrounding musculature. Destruction and disorganization of the bone trabeculae may

cause the bone to be brittle or to be easily bent without breaking. The medullary cavity is, in many cases, completely replaced by gelatinous tumor masses. Large, rapidly growing tumor masses are very vascular and may often cause venous bruit, or may appear pulsatile when palpated. The largest of these are found on the wings of the iliac bone, but they may also be seen on the ribs. Plasmocytomas of the spine have a tendency to compress the spinal cord, while the expanding tumors of the calvarium, though rare, may erupt either under the scalp or subdurally, giving rise to local symptoms.

Microscopically, the plasmocytomas present a picture of closely packed young plasma cells with scanty stroma and eccentric nuclei. Mitotic figures may occur but are relatively rare.

Extraskeletal myelomatous involvement is not as uncommon as originally thought. Nodular infiltrates occur in virtually every organ save the heart. The liver, spleen and lymph nodes are the most common sites of extraskeletal involvement. Infiltrations may appear in one of two forms: they may be diffuse, or they may form discrete nodules. Cutaneous infiltrations may simulate multiple neurofibromatosis covering the scalp, fore-head, temples and neck.

Kidney involvement results in a pale, smooth, contracted kidney at necropsy. The kidneys are not consistently contracted. They may be normal in size or even enlarged in some cases.

Microscopically, the outstanding feature is the presence of dense, acidophilic casts plugging the tubules. The tubules are surrounded by foreign body giant cells. Frequently lamellated and calcified areas are seen. The glomureli are normal and show no changes unless amyloid deposits are present. There is usually a pronounced interstitial edema and infiltration of mononuclear cells.

Amyloidosis is associated with multiple myeloma in about 10% (12) of cases. Paramyloidosis is also seen where there are diffuse amyloid deposits in mesenchymal tissues, rather than massive infiltration of the liver, spleen, kidneys, adrenals and blood vessel walls. The gastrointestinal system may be involved from the oropharynx to the rectum, either diffusely involved, or the involvement may be localized to the blood vessels. Nodular amyloidosis of the larynx and joint capsules may also occur. Skeletal muscle and striated muscle of the myocardium are frequently involved, as is the auricular endocardium. Involvement of the myocardium may lead to congestive failure and death.

In Snapper's series the most common causes of death were anemia, cachexia and bronchopneumonia, which was seen in 40% of the cases. Uremia was also a common finding.

DIFFERENTIAL DIAGNOSIS

Multiple myeloma may present as one of several different symptoms complexes. The classical case of multiple myeloma is easily recognized, but the typical case may be easily mis-

diagnosed, as the clinical symptoms fit into no stereotyped classification. The patient presenting with the textbook picture of multiple myeloma is usually anemic and cachectic. He suffers from severe bone pain due to multiple destructive lesions in the bones, and on laboratory examination he has hyperproteinemia, Bence Jones proteinuria, a very rapid sed rate and profound anemia. X-ray presents clear cut "punched-out" oval or round osteolytic areas of complete translucency without new bone formation. Fracture of long bones or ribs, and collapse of vertebrae are common. A generalized demineralization of bone may be noted. Bone marrow examination is accurate in 90% (12) of cases, but may be negative in those cases where bone marrow involvement is patchy.

In the diagnosis of multiple myeloma the following conditions must be ruled out:

1. Skeletal metastasis of carcinoma.

   On x-ray examination the two lesions may appear in the same geographical areas. Multiple myeloma characteristically is sharper edged than the infiltrative carcinoma; and there is no osteoblastic component to the multiple myeloma lesion, while carcinoma may show proliferation or osteitis tendencies. The serum acid phosphatase is elevated in metastatic carcinoma and at normal levels with multiple myeloma. Bence Jones proteinuria may be present in both conditions, and an identical blood

picture can be seen in both. Electrophoretic patterns are helpful; and if the primary site of the carcinoma can be found, the correct diagnosis can be made.

2. Post menopausal osteoporosis
   On x-ray examination the changes may be exactly the same. Age distribution is similar. Compression frac-tures are of course, more common in multiple myeloma.
   On x-ray, the demineralization in post menopausal osteoporosis is usually limited to the spine and the pelvis, while in multiple myeloma, the whole skeleton shows the change. Often there is no hyperglobulinemia, no Bence Jones proteinuria; and myeloma cell proliferation won't be found on bone marrow examination.
3. Hyperparathyroidism
   In this condition there is a generalized demineralization of bone structures resulting in a typical "ground glass" appearance of the skeleton on x-rays. Hypercalcemia and hypercalcinuria are characteristic of both multiple myeloma and hyperparathyroidism, but in the latter a decrease in serum inorganic phosphorus and an increase in the alkaline phosphatase are noted, both of which are not seen in multiple myeloma. Bence Jones proteinuria is not seen in hyperparathyroidism.
4. Giant cell tumor
   The x-rays of this condition and of multiple myeloma may appear to be the same; however, giant cell tumors

never occur in the pelvis, and this is where the two diseases are commonly confused. The only fool proof method for the differentiation is biopsy, as the multiple septum formation seen in the giant cell tumors is also similar to lipoid granuloma, sarcoma, and Pott's disease. Bone marrow examination is also helpful.

5. Lymphotic Leukemia

Plasma cells in the peripheral blood may often simulate lymphocytes, which may confuse the peripheral blood picture. Lymphadenopathy and hepatosplenomegaly associated with lymphatic leukemia are uncommon findings in multiple myeloma, unless amyloidosis is present. A bone marrow examination will usually make the differentiation between these two conditions.

6. Osteomolacia

This condition is rare in the United States. It is characterized by a low serum calcium, low serum phosphorus and elevation in the serum alkaline phosphatase. Also a hypocalcinuria is noted. Thus, the only similarity between this disease and multiple myeloma is the x-ray picture of generalized osteoporosis.

7. Anemia

The anemia of multiple myeloma is usually normochromic and normocytic in character. It must be differentiated, therefore, from hemalytic anemias and toxic states which

depress the bone marrow. In rare cases the anemia may be macrocytic in type, making the differentiation from pernicious anemia necessary. The anemia of multiple myeloma, being due to marrow replacement, is notably refractory to all the usual forms of treatment of other anemias.

8. Albuminuria

Albuminuria is a common finding in nephritis, which in turn is a common finding in multiple myeloma; thus it requires careful screening with the HCl ring test to find Bence Jones proteinuria. In patients with renal insufficiency and uremia, due to multiple myeloma, a normal blood pressure is usually found, though other changes such as hyperglobulinemia and x-ray findings may not be present.

9. Back pain

This common complaint cannot always be diagnosed by x-ray alone, because of dense soft tissue overlay. If the pain is associated with deformity and x-ray findings of vertebral collapse, this is presumptive evidence pointing to multiple myeloma. Often the pain will become generalized and intractable, associated only with demineralization of the axial skeleton. A bone marrow examination is then helpful.

10. Fever of unknown origin

A fever of unknown origin was seen in 50% of Snappers patients, and many times it was present before overt signs of the disease could be found. In many of these patients anemia was present, so a bone marrow examina-tion was done, establishing the true

11. Hepatosplenomeglay

Marked visceral involvement by myelomatous tissue may cause hepatosplenomegaly and lymphadenopathy producing a picture easily confused with reticulum cell sarcoma and other lymphomata. Bone marrow or node biopsy is indicated.

12. Paramyloidosis

The patients may present with congestive failure, massive intestinal bleeding, intestinal obstruction or macroglossia due to amyloid deposits. Gingival biopsy is the only way to disclose the diagnosis.

TREATMENT

Despite 100 years of study, we are little closer to a cure for multiple myeloma than Dr. Watson, who administered steel and quinine". In Bayrd & Hect's series of 83 cases the average span of life was 18 months following diagnosis, despite all forms of treatment. None of the symptoms of the disease seems to have any prognostic value. A high serum calcium may be a poor prognostic sign, but this is not well substantiated.

In most cases surgery is contraindicated due to the multiplicity of sites of involvement and the location of involved areas. Amputation of extremities is done only in cases of extreme pain. Several physical and chemical agents seem to produce a remission of pain and effect improvement in other signs, showing that the disease course has been altered at least temporally.

X-ray is used to relieve pain and to reduce tumor size, thereby decreasing pressure on other organs. The use of external radiation may cause rarefaction of bone, but there are no proven cases of cure. In dealing with compression fractures, laminectomy and x-ray may effect good relief of pain, but there is doubt as to how long life is extended. Radioactive phosphorus has been used, which may be followed by spray radiation of the entire skeleton. This may result in a leukopenia and a thrombocytopenia.

Stilbomidine and other diamidines were used in multiple myeloma because they have proven effective in treating kala-azar, which also has hyperglobulinemia; and it was thought that these drugs might precipitate the ribonucleic acid formed in the cytoplasm of multiple myeloma cells.

Stilbamidine and 2-hydroxystilbamidine have proven effective only in relieving the pain of multiple myeloma (12). These drugs have no apparent influence upon the hyperglobulinemia or upon the Bence Jones proteinuria, to say nothing of altering

appreciably the course of the disease. The patients show a great deal of clinical improvement; however, this is due largely to the effective relief of pain. Many patients became ambulatory, and some find part time employment.

The clinical use of stilbamidine is difficult, as it has many side effects. Stilbamidine must be given by the intravenous route, which is usually followed by a transient hypotension. Though this drug has no effect on the normal kidney, it may precipitate uremia in patients with previously damaged kidneys. This fact alone, in view of the large number of myeloid kidneys and nephritis in multiple nyeloma, limits the usefulness of stilbamidine. Paresthesias are common following administration of stilbamidine. Patients complain of "wooden face", due to the loss of the feeling of touch over the face. There is no loss of pain and temperature in the same area. This pheromenon seems to be caused by the deposition of stilbamidine in cutaneous tissues; and when these areas are exposed to the sunlight, a toxic product is released, causing a toxic peripheral neuro-pathy. 2-hydroxystilbamidine has none of the above side effects nor does it alter the course of the disease.

The oral preparation, Urethane, is a protoplasmic and mitotic poison, and it is thought to work directly on the plasma cell. In multiple myeloma, Urethane reduces bone pain remarkably. It reduces the severity of the anemia, decreases the sed rate and reduces the hyperglobulinemia. Also, the number of plasma cells in the peripheral blood is reduced. Often the patient

shows remarkable clinical improvement. Some become ambultatory again. X-rays show recalcification of bone and reappearance of bone trabecular patterns. The progression of the lesion seems to be checked. With the return of the plasma proteins toward normal, there is a reduction of the abnormal protein content of the serum as measured by electrophoresis. Often the electrophoretic pattern will return to normal, as does the bone marrow.

Randles postutales that with continued therapy, the myeloma cell may become dependent upon Urethane, and when no further clinical or laboratory improvement is found, discontinuence of Urethane therapy may result in further clinical response.

Before the use of enteric coated tablets, nausea and vomiting were the most prominent side effects. Leukopenia and thrombocytopenia are not uncommon, while lives damage is rare.

Thorn has reported several cases of marked clinical and laboratory improvement with cortizone. This entails a decrease in hyperglobulinemia, decrease in serum calcium, an increase in alkaline phosphatase and a disappearance of plasma cells from the bone marrow. Others have reported similar findings, in addition to a decrease in anorexia and pain. In Snapper's series of 23 patients only 3 showed any clinical improvement on cortizone, which was only temporary at best. Subjective improvement can sometimes be obtained, hyperglobulinemia and

Bence Jones proteinuria may be reduced, but the favorable influence of cortizone and ACTH on the course of the disease is discouragingly small. The main value in the drug seems to be in its ability to produce euphoria and to decrease the appreciation of pain.

Neostibosan has been used by Rubinstein. He found that it reduced hemorrhagic tendencies, reduced tumor masses, and improved the plasma protein picture. His report lacks confirmation by other investigators.

Nitrogen mustard has been reported to be of very little benefit. Jacobsen noted that only one patient had any temporary relief of symptoms from the disease.

Large doses of Testosterone propionate, calcium and phosphorus have no effect upon the course of the disease.

SUMMARY

Multiple myeloma is a uniformly fatal disease consisting of proliferation of immature plasma cells, which are derived from the reticulum cells in the bone marrow. The proliferation is diffuse throughout the bone marrow, though in isolated cases marrow involvement may be patchy.

Multiple myeloma is twice as frequently seen in men as in women and is more common in the Caucasian race. There is an increased frequency of the disease in age groups over forty years of age, with the bulk of cases between fifty and seventy years of age. The average survival is twenty months, but most patients expire in less than one year.

Multiple myeloma has no definite characteristic symptoms at the onset, and there is no early definite clinical picture. Severe bone pain is the most common presenting complaint. Pain in the rib cage, low back, hip and shoulders that is aggravated by exercise and reduced by bed rest is typical of multiple myeloma. Pathological fractures are commonly associated with extreme
pain and minor trauma.

A normocythic normochronic anemia is characteristic of multiple myeloma. The anemia results from replacement of the red bone marrow. Thrombocythopenia seen with the anemia may result in hemorrhagic tendencies. Plasma cells are usually increased in the peripheral blood; thus, the disease may appear to be a plasma cell leukemia. The sedimentation rate of the blood is often increased, due to hyperglobulinemia which is seen in 60% of patients (12). Also abnormal proteins such as cryoglobulins contribute to the hemorrhagic tendencies.

Commonly the patient will present with complaints of anorexia, fatigue and weight loss. These symptoms are difficult to explain, except on the grounds of anemia and bone pain. These patients are often cachetic and appear to be suffering from a chronic disease, rather than one which is so rapidly fatal.

Twenty per cent (12) of these patients develop palpable tumors - plasmocytomas which are usually associated with perforation of the boney cortex. These tumors are usually of a rubbery consistency and are commonly found on the ribs and the skull.

Frequent and recurrent attacks of pneumonia are seen in 50% (12) of multiple myeloma patients, due to thoracic defor-mitity, increased viscosity of blood and depression of serum antibodies. Patchy lung involvement causes low grade fever whose origin is usually difficult to demonstrate.

In patients with neurologic symptoms, these are largely due to direct cord compression, due to collapse of a vertebral body. Compression of a spinal nerve may be seen also. In some patients a peripheral neuritis has been noted that is not explained on the basis of direct involvement of the nerve by the myeloma, by compression, or therapy.

Impairment of renal function is a not infrequent finding in those patients who excrete Bence-Jones protein in their urine. Bence Jones protein is thought to be manufactured by the proliferating plasma cells; and since it is of low molecular

weight, it passes the glomerular filter easily and is precipitated in the kidney tubule as a giant cast. Intratubular blockade may cause ensuing renal insufficiency and reabsorption of the protein may cause necrosis of tubular epithelium. In the multiple myeloma patient uremia is never accompanied by hypertension.

It is to be emphasized then that there is a very close relationship between renal failure and Bence Jones protimuria.

Extraskeletal myelomatous involvement is infrequent. In Snapper's series, hepatomegally was noted in 38% of the cases, splenomegaly in 25% of the cases. Infiltration of lymph nodes is even more infrequent than splenomegaly.

The diagnosis of multiple myeloma is principally a hematologic one; therefore, the findings in the bone marrow and the peripheral smear are extremely significant. Bone marrow examination is 90% accurate in the diagnosis and is the most reliable laboratory aid. Peripheral smears usually show an increase in plasmocytes; or they may show leukopenia, thrombocytopenia or anemia, all of which aid the diagnosis. Excessive rouleaux formation on the slide would indicate hyperglobulinemia.

Bence Jones proteinuria is found in 50% (12) of cases of multiple myeloma. This protein is a low molecular weight 30,000-40,000 and may be demonstrated by the nitric acid ring test method. Hyperglobulinemia is seen in 60% (12) of cases and is usually associated with a reversal of the albumin-globulin ratio. The increase in the globulin is usually due to an

increase in the gamma globulin, while increases in the beta and alpha fractions are rarely seen. Sharp discrete peaks occur in the electrophoretic pattern of patients with multiple myeloma as opposed to diffuse broad peaks of globulin patterns seen with kala-azar, cirrhosis, and the collagen diseases.

Paramyloidosis, a deposition of amyloid in mesenchymal tissues such as heart, gastrointestinal tract, blood vessel walls, tongue and joint capsules; and amylaidosis with deposition of amyloid in the liver, spleen, kidneys, adrenals and blood vessel walls are rarely seen in multiple myeloma. These deposits may explain macroglossia, heart failure, and intestinal bleeding in myeloma patients. Gingival biopsy will be positive for deposition of amyloid in blood vessal walls if either of these two conditions is present.

Calcium content of the serum is often elevated due to the rapid demineralization of bones. Elevated calcium levels are often looked upon as bearing a poorer prognosis. Except in cases of uremia the serum of inorganic phosphorus is usually normal. Alkaline phosphates is also unaffected in most cases. Uric acid levels may be elevated due to the increased destruction of plasma cell nuclei.

The presence of a punched out lesion in otherwise normal bone is the classical x-ray finding in multiple myeloma. The lesion is purely osteolytic and is most commonly seen in the skull, ribs, pelvis and long bones. Changes in the spinal column are usually limited to osteoporosis and perivertebral

swelling, though more than one-half of patients will show a compression fracture of a vertebral body some time in the course of the disease. Pathological fractures of the ribs are common. These heal readily with abundant callus formation, due to the elevated calcium levels.

Solitary myelomas or plasmacytomas may remain localized for several years, but most of them eventually become generalized in time. Bone marrow examination should be frequent in order to treat the generalized form of the disease. Extramedullary plasmocytomas also occur with accompanying involvement of bones. These are seen especially in mucous membranes, paranasal sinuses, pharynx and larynx. Some may remain localized, but usually a generalized tumor develops.

In the differential diagnosis post-menopausal osteoporosis, osteomalacia, hyperparathyroidism, skeletal metastasis of carcinoma and giant cell tumor must be considered. Causes of anemia, chronic nephritis, pneumonia, and fever must be investigated. In the absence of bone pain, the clinical diagnosis of multiple myeloma becomes difficult.

At the present state of medical knowledge, no life saving treatment can be offered. X-ray offers palliation only. It will often reduce bone pain and decrease the tumor size, relieving pressure on surrounding structures. Stilbamidine, 2-hydroxy-stilbamidine, urethane, cortizone and ACTH may be followed by short periods of remission. Urethane in particular may reduce the

hyperglobulinemia and Bence Jones proteinuria; therefore apparently having some direct effect upon the basic disease although no permanent cure has been reported.

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