REVIEWS

Myeloma: A malignant disorder of bone and soft tissue

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Abstract

The purpose of this brief report is to review a large series of cases of myeloma, a highly malignant tumor. The disease was first described over 150 years ago, but not named myeloma until 1873. The lesion appears to be caused by the production of plasma cells in the bone marrow occasionally associated with amyloid.

Patients present with pain in bones, principally spine, pelvis, ribs, calvarium and long bones. The sedimentation rate is elevated and marrow shows 10% plasma cells and the sedimentation rate is always elevated. There is no identified genetic cause and the disease is not familial.

The disease has a highly malignant potential. We treated 181 mature adult patients with tumor in multiple sites. 63% were dead of disease at an average of 4.5 years after diagnosis. The use of some new drugs have been helpful, chiefly lalanlidomide or bortezomib. Radiation appears to be useful for some lesions and bisphosphonates sometimes help support the bone structure.

Despite many efforts over the years and the large number of treatment agents introduced, it is apparent that we do not have sufficient ability or knowledge to control this very troublesome disorder.

Key Words

Bone or soft tissue myeloma, Poor outcome despite treatment

1 Introduction and history

Myeloma is a common malignant affliction principally occurring in the bones of mature adults. It was first described by MacIntyre in 1850 [1] who reported on a patient with episodes of fatigue and bone pain. MacIntyre called the disorder "mollities and fragilitas ossium" [1]. Later that year, Henry Bence-Jones tested urine specimens provided by MacIntyre's patients and described the abnormal light chains which later became known as Bence-Jones protein [2]. In 1846, Dalrymple described the microscopic features of the disorder [3]. Ruzitsky in 1873 introduced the term multiple myeloma [4] and Otto Kahler [5] published an extensive review and at one point, the disorder became known as Kahler's disease. At the turn of the century, the increased serum proteins and rapid sedimentation rate were identified as characteristic and the origin of the tumor was defined as arising from plasma cells [6-10] (Figure 1). In 1929, the diagnosis was established by bone marrow aspiration and in 1937, the value of immunoelectrophoresis as a diagnostic instrument was introduced [8-10].

When the disease appears in a single site with few biochemical findings it is known as "solitary plasmacytoma", but many of these became multiple over time [6, 8, 9, 11, 12, 19]. In addition, there are some entities known as monoclonal gammopathies of unknown significance (MGUS) which may or may not be directly related to myeloma [8-10]. Another entity that is often included in descriptions of myeloma is Waldenstrom's macroglobulinemia which is a form of myeloid disease associated with plasma cell abnormalities but principally presenting as a bleeding and visceral disorder [8-10, 14].

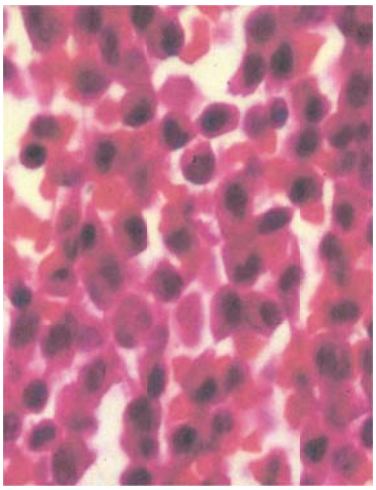

Figure 1. Plasma cells occurring in the lesional tissue (200X)

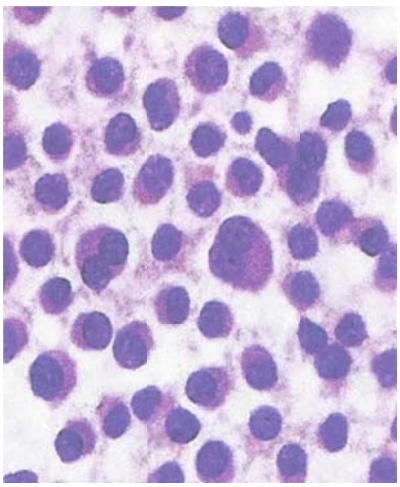

Figure 2. Another characteristic appearance of the plasma cells in the marrow showing some enlarged cells(200X)

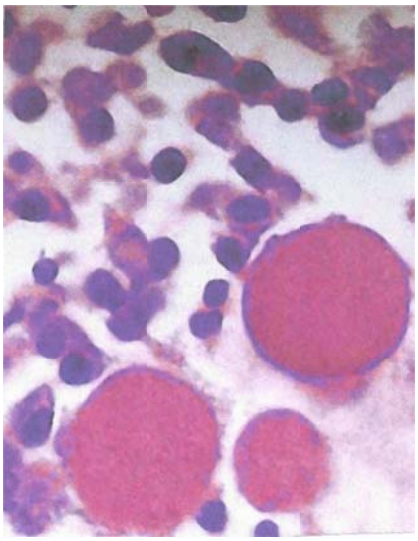

Figure 3. Some of the cells may contain some amyloid which enlarges them and is shown as red in color(200X)

Myeloma occurs principally in older individuals with a mean age of 68 for men and 70 for women [6, 9, 12, 13, 15, 16]. Fewer than 2% of the patients are under 40 years of age whereas over 50% are over 70 [6- 9, 16]. The disease can occur in some animals, principally mice and dogs [9].

2 Causation and pathogenesis

The pathogenesis of myeloma is obscure. Increased familial incidence is uncommon, although it is occasionally seen particularly in African-America patients [6-10, 15, 16, 17]. Endogenous retrovirus infection has been suggested and initial unsubstantiated report suggested human herpes virus 8 as the cause [6-9, 12]. Exposure to chemical and physical agents including benzene, petroleum products, pesticides and radiation have all been implicated but none have been clearly established as causative [6, 9]. Cytogenetic abnormalities are present in at least 60% of the case and these are often complex with translocations mostly involving chromosome 14q, although 11q, 4p and 8q have all been identified and implicated [6-8, 12, 17-19, 20-23]. Interleukin 6 has been described as being essential to both the growth and maintenance of myelomatous plasma cells and may lead to the production of RANK-L which is known to increase the number of osteoclasts [8, 10, 24, 25]. The vascular abnormalities may be related to the production of vascular endothelial growth factor (VEGF) by myeloma plasma cells [8, 9, 24, 26]. Despite these findings there is no evidence for a genetic causation and there does not seem to be a familial pattern of transmission.

3 Clinical presentation of multiple myeloma

Myeloma can be limited, asymptomatic and insidious [11, 27, 28], or can be a very severe, disabling and life-threatening disorder [29]. In the latter disorder, known as multiple myeloma, production of plasma cells in the bone marrow not only causes weakness of bone structure, pathologic fractures and spinal cord compression, but in addition may result in leucopenia, anemia and thrombocytopenia [6, 8, 9, 10, 15, 16, 28, 29] (Figure 1, 2). The cells may contain islands of amyloid (Figure 3). Bence-Jones protein is often present in the urine [6, 8, 9, 12] with corresponding kappa or lambda light chains in the serum. The majority of these patients require extensive treatment but have a relatively poor survival rate. A system for staging was introduced by Durie and Salmon in 1975 [30] which establishes the various patterns related to the extent of the disease.

Durie-Salmon staging system for multiple myeloma

Stage I

Low cell mass: $<0.6 \times 10^{12}$ cells/m^2 plus all of the following: Hgb >10 g/dL, Serum IgG <5 g/dL, Serum IgA <3 g/dL, normal serum calcium; urine monoclonal protein excretion <4 g/day. No generalized lytic bone lesions.

Stage II

Intermediate cell mass: neither Stage I or Stage III.

Stage III

High cell mass: 1.2×10^{12} cells/m^2 plus one or more of the following: Hgb <8.5 g/dL; Serum IgG >7 g/dL; Serum IgA >5g/dL. Serum calcium >12 mg/dL (3 μmol/L). Urine monclonal protein excretion >12g/day. Advanced lytic bone lesions. Stage III is subclassified as IIIA or IIIB based on serum creatinine: IIIA: Serum creatinine<2mg/dl (177 μmol/L). IIIB: Serum creatinine> 2mg/dl.

Another system has been introduced as the International Staging System (ISS) [31].

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- Stage I B2M < 3.5 mg/L and serum albumin = or > 3.5 g/dL.
- Stage II Neither Stage I or Stage III.
- Stage III B2M= or >5.5 mg/L.

Median overall survival for patients with ISS stages I, II and III was 62, 44 and 29 months respectively.

In sharp contrast with the above patterns is the picture of solitary plasmacytoma of bone, which occurs principally in the femoral or axial skeleton [8, 9, 11, 12, 15, 27, 28, 33-35] (Figure 4). The bone marrow studies, bone scans and PET-scanning fail to reveal other lesions and immunoelectrophoretic studies and search for Bence-Jones protein fail to support the presence of extensive disease [34]. These patients often respond well to radiation alone or excision of the local lesion with surgery [6, 8, 9, 12, 15, 27-29, 35-38].

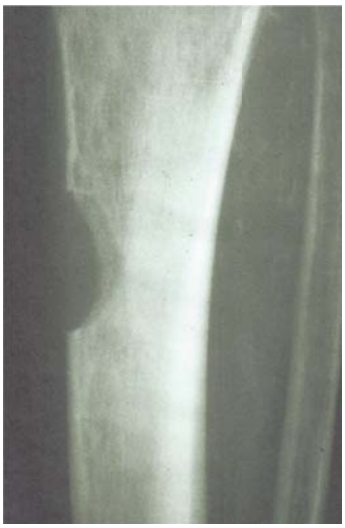

Figure 4. The myeloid tumor cells may cause destruction of the bone, seen here in the tibia

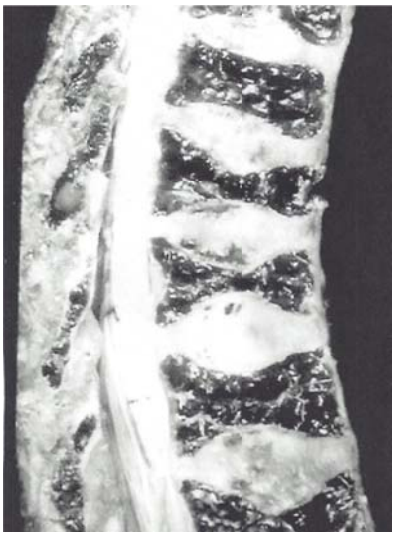

Figure 5. The spine may be involved and show bone destruction and multiple fractures of the vertebrae

Still another form of the disease which remains a puzzle is monoclonal gammopathy of undetermined significance (MGUS) [6-9, 12, 32, 37, 38, 40]. These patients are found by chance to have an IgG or IgA paraprotein in the serum but no other features to suggest myeloma. These affected patients may have Gaucher disease or Hashimoto's syndrome as well as others [39, 40]. The bone marrow is normal with fewer than 10% plasma cells and the patients are asymptomatic. They still

must be watched and have serial immuno-electrophoretic studies to be certain that the values for the paraproteins do not rise.

Another very rare and puzzling entity associated with myeloma is POEMS syndrome which includes polyneuropathy (P), organomegaly (O), endocrinopathy (E), myeloma (M) and skin changes (S) [9, 10]. These patients have a very complex presentation but fortunately they seem to respond well to high dose chemotherapy and stem cell transplant [8, 9, 10].

4 Clinical studies in patients with multiple myeloma

Patients with multiple myeloma often present with bone pain associated with a fracture, most often of one or several vertebrae [6, 9, 10, 15, 16, 29, 41] (Figure 5). They may appear chronically ill and many have weight loss, fevers, abdominal distress and neurologic disturbances. Physical examination show bone tenderness in multiple sites including the spine, pelvis, ribs, calvarium and long bones (Figure 6). Laboratory studies show increased amounts of serum IgG or IgA paraproteins on immunoelectrophoresis, Bence-Jones protein in the urine, beta 2 microglobulin (B2M) and kappa or lambda light chains in the serum and a series of abnormalities in blood studies including anemia, leucopenia and thrombocytopenia [6, 9, 12, 15, 16, 29, 41]. The sedimentation rate is almost always elevated and the alkaline phosphatase is usually normal or low. Calcium may be greatly elevated and bone marrow studies are likely to show greater than 10% plasma cells [6, 9, 12, 15, 16, 41].

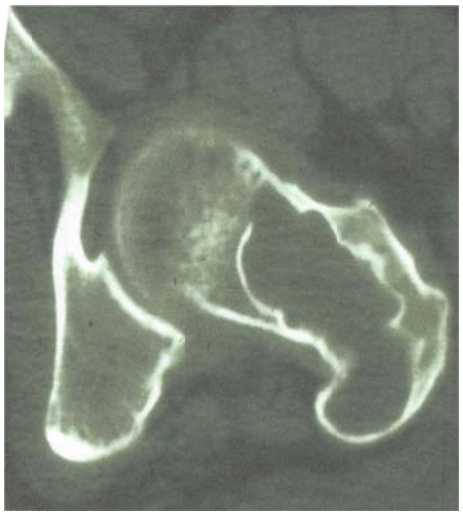

Figure 6. A very destructive lesion of the proximal femur which is likely to result in a fracture which is difficult to treat

5 Treatment of multiple myeloma

There are many forms of treatment for patients with multiple myeloma. Chemotherapy with agents such as vincristine, dexamethasone, bischolorethylnitrosurea, melphalan, cyclophosphamide, prednisone, thalidomide and doxorubicin have all been introduced and are often helpful in reducing the patient's symptomatology and decreasing the extent of the marrow disease [6, 9, 19, 21, 37, 42-46, 48]. A recent addition which seems to be quite effective is bortezomib (Velcade) [50]. It is frequently used in combination with cyclophosphamide and dexamethasone, or with lenalidomide (Revlimid and dexamethasone). Other combinations include melphalan plus prednisone and thalidomide or lenalidomide plus dexamethasone [46-48].

Radiation for local lesion is often successful in reducing pain and preventing further fractures [17, 21, 37, 53]. Allogeneic marrow transplantation is utilized for severe cases [18, 51-53] but in the elderly patients has a high risk of complications. Autologous stem cell transfer is safer particularly for older individuals but includes the risk of re-infusing malignant cells [9, 21, 33, 55, 61, 62]. Orthopaedic management for diffuse disease is principally applied to treatment of fractures, spinal collapses with damage to the cord and destroyed and painful joints [8, 9, 15, 16]. Often bisphosphonates in the form of

pamidronate or zoledronate seem to be helpful in strengthening the bones [57-59] but a recent concern regarding osteonecrosis of the mandible has limited our enthusiasm for the treatment [56]. For patients with solitary plasmacytomas, resection or radiation or both have made good success and many patients have become asymptomatic.

6 Comments, local results and conclusions

Myeloma is a fairly common neoplasm that can severely affect the patients and in many cause their death.

We have data on 181 patients (Table 1) who presented to our MGH Tumor Service with multiple myeloma treated from 1972 to 2010. The average age was 58 and 63% of the patients were males. The most prevalent presenting sites were proximal femur, pelvis, lumbosacral spine, proximal arm, shoulder and scapula. 113 patients (63%) are dead of disease with an average duration of 4.5 years after diagnosis.

Patients treated more recently have a slightly improved median survival. Of 71 patients treated prior to 1995, 48 patients (68%) died of disease at less than 3 years. Of 36 patients treated from 1995 to 2000, 20 (56%) died of disease at approximately 4 years. Of the 74 patients treated from 2001 to 2010, 38 (51%) died of disease with an average survival time of 6 years.

The remarkable feature for multiple myeloma is that despite the fact that the disease was discovered over 100 years ago, we still have no real understanding of the origin of the process, nor of the best possible treatment protocol for these distressed patients. We continue to study the genetics, the clinical nature of the disease and a large number of treatment protocols and let us hope for some improvement in outlook for these patients.

Table 1. Statistics for the series of 181 cases

			Number deceased	*p*-value
Total cases seen	181		117 (65%)	
Gender	Males	116(64%)	74 (64%)	N.S.
	Females	65 (56%)	43 (66%)	
Age :	Average age 58 (27-85)			
	Ages 27-40	18 (10%)	10 (55%)	
	Ages 41-60	67 (37%)	41 (61%)	
	Ages 61-85	96 (53%)	66 (69%)	$p<.0001$
Anatomic Site				
	Proximal femur	37	19 (63%)	N.S.
	Pelvis	29	20 (68%)	$p<0.001$
	Spine	14	10 (71%)	$p<0.0001$
	Humerus	30	20 (60%)	N.S
	Shoulder	5	2 (40%)	$p<0.0001$
	Scapula	16	10 (62%)	N.S
Date of Treatment				
	Patients treated prior to 1995	71	48 (68%)	
	Patients treated from 1995-2000	36	20 (56%)	
	Patients treated from 2000-2010	74	38 (51%)	$p<0.0001$

Note. N.S means not significant

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