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OSTEOLYTIC LESIONS IN PLASMA CELL MYELOMA

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ABSTRACT

The purpose of this study was to evaluate the frequency of osteolytic lesions and their pathogenesis in plasma cell myeloma (PCN). The study was conducted in Ghurki Trust Teaching Hospital (GTTH), Combined Military Hospital, Jinnah Hospital and a Private Clinic at Lahore from January 2002 to November 2007. A total of 26 indoor male and female patients from Orthopaedic, ICU and Medical wards were included in the study. Among these patients, 18 cases reported to GTTH, 2 each from CMH Lahore and JHL respectively and 4 cases reported to a Private Clinic. Clinical parameters were further differentiated into Male n = 15; 57.6%, Female; n = 11; 42.3% and mean age was 63 year. Lymphadenopathy was seen in 5 patients (n=5, 19.2%), hepatomegaly in 8 patients (n = 8, 30.7%), splenomegaly in 7 (n=7, 26.9%) and bone pain in 20 patients (n = 20; 76.9%). Osteolytic bone lesions as revealed by conventional X-ray skeleton was seen in majority of patients (n=17; 65.3%). After fulfilling the criteria for the diagnosis of Plasma cell myeloma, frequency/ prevalence of osteolytic lesions were assessed and compared with clinical and laboratory parameters. Multiple osteolytic lesions revealed, by conventional radiography, were most commonly seen in the skull, verterbrae, ribs, pelvis and proximal long bones. However, use of MRI indicates that skeletal abnormalities exist in nearly all patients with myeloma. These osteolytic lesions evolve from imbalance between osteoblasts and asteoclasts interplay with primary derangement originating in bone marrow microenvironment. The basic stimulus is interaction of malignant plasma cells with bone marrow stromal cells and the production of different cytokines and growth factors. These inflammatory factors produce proliferation and differentiation of osteoclasts, inhibition of osteoblasts and formation of osteolytic lesions. The resultant demineralisation is manifested as raised serum calcium level.

INTRODUCTION

Plasma cell myeloma (PCM) is one of the lymphoproliferative disorder characterised by proliferation of a clone of immunoglobulin secreting- B lymphocytes. The homogeneity of immunoglobulin or paraprotein produced by these cells indicate their descent from a single precursor[1] .

The incidence is 3 per 100000 population. About 60% of patients are men. More than 90% are older than 40 year of age. No specific agent for PCM has been found. Predisposing factors are radiation exposure, chromic antigenic stimulation, environmental exposure, particularly benzene and the use of hair dye. In addition human herpes virus 8 (HHV-8) has been found in the non-malignant bone marrow dendritic cells of patients with myeloma[2].

Multiple complex karyotypical changes are observed in the malignant plasma cells of most patients. Common translocation involve chromosome 14 at the site of heavy-chain gene locus, chromosome 11 at the site of cyclin-d, and chromosome 16 at the site of FGF receptor 3. In 20% of patients there is deletion of long arm of chromosome 13 and mutation of ras gene. In 15-20% of cases there is mutation of p52 and abnormalities in C-MUC protooncogene which is associated with more advanced and clinically more aggressivedisease[3].

Plasma cells usually constitute 20% to 80% of the marrow cells in PCM. They have abundant basophilic cytoplasm, eccentric nuclei with paranuclear clear zones and usually show prominent nucleoli. In addition, binucleate and trinucleate forms are also present. These features are suggestive of malignant plasma cells[4].

The disease may be localized in 7% of cases, indolent or silent in 3% disseminated and progressive in 90% of cases. Manifestations of disease progression arise from skeletal involvement, plasma protein abnormalities and the development of renal disease. Haematopoiesis is often impaired at the time of diagnosis. About 60% of patients have anaemia, 15% leucopaenia and 15% thrombocytopaenia. About 10% of patients present with leucoerythroblastic blood picture.

Multiple osteolytic lesions are present in about 70% of patients, single osteolytic lesions or diffuse osteoporosis in 15% and normal skeletal radiograph in 15%[5].

PATIENTS AND METHODS

This study was performed in admitted as well as outdoor patients from GTTHM, CMH, JHL and a

Fig. 1: *Bone marrow smear shows plasma cells with binucleated forms and a mitotic figure.*

Fig. 2: *X-ray of skull showing punched out osteolytic lesions.*

Private Clinic at Lahore from Jan 2002 to Nov 2007. A total of 26 patients were included in this study. Inclusion criteria were age, gender, presenting clinical features and signs at diagnosis including the standard Durie-Salmon (DS) clinical staging system. Diagnosis was established according to standard definitions with presence of at least two out of three of the following criteria: a) paraproten detectable in serum or urine together with a subnormal concentration of at least one monoclonal immunoglobulin class, b) 30% or > 30% malignant plasma cells in the bone marrow, c) osteolytic and or osteoporotic bone lesions compatible with PCM. The conventional radiologically defined osteolytic bone lesions were compared with the sympromatic presentation with bone pain, extent of marrow involvement by plasma cells, serum monoclonal paraprotein concentration, B_2 microglobulin level and hepatic / splenic enlargement.

Table 1: *Osteolytic lesion in 17 patients with L.Ns / liver / spleen involvement.*

Sr. No.	Age/ Sex	Bone pain	L.Ns	Liver	Spleen	osteolytic lesion
1.	79/M	+	Nil	+	+	+
2.	75/F	+	Nil	+	+	+
3.	50/M	+	Nil	Nil	Nil	+
4.	65/M	-	Nil	Nil	+	+
5.	55/F	+	Nil	+	+	+
6.	50/M	Nil	Nil	+	+	+
7.	90/F	+	Nil	Nil	Nil	+
8.	60/F	+	+	+	Nil	+
9.	53/M	+	Nil	Nil	+	+
10.	60/F	+	Nil	+	Nil	+
11.	53/F	+	Nil	Nil	Nil	+
12.	70/M	Nil	+	Nil	Nil	+
13.	50/F	+	+	Nil	Nil	+
14.	60/M	+	Nil	Nil	+	+
15.	76/M	+	Nil	Nil	Nil	+
16.	64/F	+	Nil	+	Nil	+
17.	70/M	-	Nil	+	Nil	+

RESULTS

A total of 26 patients aged between 50-90 years with a diagnosis of PCM according to standard clinical and laboratory criteria over a period of 05 year and 10 months were reviewed. These consisted of 15 males (57.6%) and 11 females (42.3%) with a male to female ratio of 1.36:1. The overall median age at presentation was 65 years with 11.3% of PCM patients less than 60 years. The main presenting symptoms in 20 patients (76.9%) were bone pain with weakness and fatigue. Among them 17 (65.3%) patients were classified as having diffuse punched out osteilytic lesions involving the skull, lumbosacral vertebrae, pelvis, ribs and femur on conventional radiography. These skeletal distribution pattern were found to be parallel with other international[6] and regional studies conducted in Pakistan[7]. In addition to the skeletal involvement, 16 (61.5%) patients presented with enlargement of liver and spleen while lymphadenopathy was seen n only 07 (26.9%) patients.

DISCUSSION

The progession of PCM is intimately linked to the marrow microenvitonment that include extracellular matrix and stromal cells (fibroblasts, osteoblasts, osteoclasts, vasculat endothelial cells and lymphocytes). Characteristic feature in PCM is increased osteoclast activity which is no accompanied by osteoblast formation[8]. The eytokines have potent role, promoting differentiation, proliferation and survival of osteoclasts, mediating their action principally through nuclear ligand called receptor activator of nuclear factor kappa B ligand (RANKL), cell receptor for nuclear factor (RANK) and intracytoplasmic nuclear factor (NF.KB).[9] Clonotpic B-cells destined to become malignant plasma cells migrate through the endothelial cells and come in contact with bone marrow stromal cells (BMSC). This interaction is facilitated by stromal derived factor (SDF-1) and insulin like growth factor (IGF-1) which have chemoattractive effect on other plasma cells.[10] Important protein molecules expressed after interaction of plasma cells with BMSC are dickkop-1 (DKK-1) which mediate its action through inhibition of Wnt-mediated osteoblast differentiation and proliferation [11-12-13], Fas ligand (Fas L) and ligand which induces tumour necrosis factor related to apoptosis (TRAIL). These produce upregulation of osteoblast apoptosis or cytotoxicity and are found to be significantly increased in the bone marrow of PCM patients with extensive osteolytic lesions.[14-15] Other cytokines which are produced after adhesion of plasma cells with BMSC are interleukin-6 (IL-6), interleukin – 1B (IL-1), interleukin-II (IL-11), tumour necrosis factor (TNF), transforming growth factor-beta (TGF-B), receptor activator of nuclear factor-kappa ligand (RANKL),macrophage inflammatory protein (MIP-1), hepatocyre growth factor (VEGF) and basc fibroblast growth factor (bFGF)[16]. Increased angiogenesis in osteolytic bone lesions is mediated through binding of VEGF and bFGF with their receptor on endothelial cells.

Besides interleukin 6 (IL-6), which is being established as a potent proliferative stimulus for plasma cells, binding of Ligand (RANKL) with its receptor (RANK) on the activation of intracytoplasmic nuclear factor (NF-KB) and its integration within the DNA leads to enhanced production of vascular cell adhesion molecules (VCAM-1),E-selectin and other above mentioned cytokines which have growth promoting and adhesive properties on osteoclasts and related cells of bone marrow microenvironment[17].

In addition to the interactive role of plasma cells –BMSC with upregulation of osteoclast activity, a cloe correlation also exist, between osteonlsts and plasma cells in the form of osteoblast induced expression of matrix metallo-proteinasis 1 (MMP-1), urokinase plasminogen activator (UPA) and hepatocyte growth factor (HGF). These cytokines induce degradation of type 1 collagen and transmigration of plasma cells out of bone marrow micro environment. At molecular level, expression of MMP is mediated through P38 mitogen activated protein kinase pathway (P38 MAPK).[18-19] Bone metabolism in PCM can be assessed using specific markers such as tararateresistant acid phosphatase type -5b (TRAP-5b), C or N (NTS, CTX and ICTP), bone specific alkaline phosphatase (BAP) and psteocalcin[20-21]. NTX, CTX and ICTP are elevated in PCM patients, reflecting the extent of bone disease and survival. In addition novel markers such as bone sialoproteins, RANKL (receptor activator of nuclear factor Kappa B ligand), osteoprotogerin, osteopontin and dickkop have also been found of value in assessing lytic bone disease in PCM. Patients combination of markers have at times helped in assessing disease stage, lytic bone lesions and in monitoring treatment modalities[22]

In **conclusion**, the severity and extent of osteolytic skeletal lesions in Plasma cell myeloma (PCM) evolve from imbalance between osteoblast and osteoclast interplay, with primary derangement originating in bone marrow microenvironment. The basic stimulus evolve from interaction of malignant plasma cells/myeloma cells with bone marrow stromal cells leading ultimately to the production of different cytokines and growth factors. Biochemically, excessive bone resorption is manifested as hypercalcaemia which is seen in 10% of patients at the time of presentation.

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