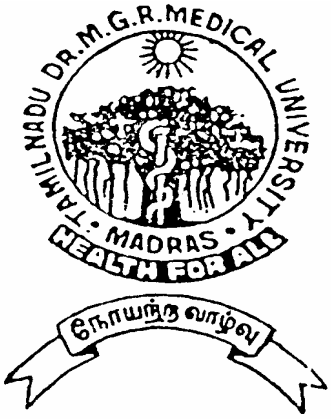
CLINICAL PROFILE OF MULTIPLE MYELOMA AT GRH – MADURAI 2005 - 2007

DISSERTATION SUBMITTED FOR

M.D DEGREE (Branch I) GENERAL MEDICINE



MADURAI MEDICAL COLLEGE

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMIL NADU.

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CERTIFICATE

This is to certify that the dissertation titled "**CLINICAL PROFILE OF MULTIPLE MYELOMA AT GRH – MADURAI 2005 – 2007 "** submitted by **Dr. ATHIRA.U** to the Faculty of General Medicine, The Tamilnadu Dr. M.G.R. Medical university, Chennai in partial fulfillment of the requirement for the award of M.D. Degree (General Medicine) is a bonafide research work carried out by her under our direct supervision and guidance.

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I, Dr. ATHIRA.U solemnly declare that the dissertation titled CLINICAL PROFILE OF MULTIPLE MYELOMA AT GRH – MADURAI 2005 - 2007**”** has been prepared by me.

This is submitted to the **Tamilnadu Dr. M.G.R. Medical University**, Chennai in partial fulfillment of the rules and regulations for the M.D. Degree Branch I (General Medicine).

Place : Madurai

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CONTENTS

INTRODUCTION

Multiple myeloma is a monoclonal plasma cell neoplasm resulting in lytic lesions of the bones and paraproteinemia leading to renal failure, pathological fractures , infections, hyper viscosity syndromes etc. Its the commonest primary bone malignancy in the western world. Every year, almost 15,000 new cases of myeloma are reported in united States(1) compared to the less than 1000 cases reported in India.(2). According to the western data Myeloma is primarily a disease of the elderly with only 18% of the cases reported below 60 years. The median survival is 3 years. Therapy and prognostic factors have been constant source of inspiration for research , as a result we have paradigm of therapeutic modalities. Most of the data regarding myeloma is from the foreign literature, this study is an attempt to analyse the pattern of presentation of Myeloma at Madurai Govt Rajaji Hospital which primarily caters to the rural population in and around Madurai.

REVIEW OF LITERATURE

DEFINITION :

Multiple myeloma / kahler's disease is a malignant monoclonal proliferation of the plasma cells. Its also known as plasma cell myeloma, Myelomatosis.

HISTORY :

November 1st 1845 Saturday .: Dr.William McIntyre, a leading consultant physician at London sends a urine sample to Dr.Henry bence Jones , with the following Quote

Dear Dr.Jones,

"The tube contains urine of very high specific gravity when boiled it becomes slightly opaque. On the addition of nitric acid it effervesces it assumes a reddish hue and becomes quite clear but as it cools assumes the consistency and appearence which you see. Heat liquefies it . what is it?(4)"

The urine belonged to Mr.Thomas Alexander McBean who complained of progressive pain in the chest, back and loin since one year.Dr.Jones, demonstrated the heat coagulation properties of the urine proteins, now is well know as the bence jones proteins of multiple myeloma. The autopsy of Mr.Mc Bean, revealed soft and

brittle ribs, sternum and vertebrae, filled with gelatinous material, which on microscopic examination revealed large round uni or bi nucleated cells which resembled the myeloma cells.The name “mollitis ossium” was given to this queer disease.

The term multiple myeloma was introduced in 1873 by J.Von Rustizky, but the classic illustration of Multiple Myeloma, was given by Dr.otto Kahler in 1889, who described the disease in a fellow Physcian. Dr.Otto Kahler was the first one togive a detailed description of multiple myeloma, hence the disease is also known as “ Kahler’s Disease” in his honour. Wright was the first one to point out that myeloma cells are nothing but plasma cells, by 1917 it was demonstrated that bence jones protein were elevated both in urine and serum, In 1939, myeloma serum globulins were separated by electrophoresis and M component was described. Dr.Mcintyre question was finally answered when korngold and Lipari showed similarities between the urine bencejones proteins and the light chains prepared from both myeloma and normal patients. In their honour the light chains are named as kappa and lambda.

EPIDEMIOLOGY:

The incidence of multiple myeloma is lowest in the south asian and middle east countries. Every year 15000 new cases of multiple myeloma are reported , 11000 deaths are due to myeloma in the united States, incidence being 3/100000, while in India 2003 -2004, the cumulative risk was caluculated to be 0.18/100000, can be blamed partially on faulty reporting. However the incidence of multiple myeloma is highest among the blacks followed by Maoris, Hawaiian , Israeli jews, north Europeans, US and Canadian whites.The incidence of myeloma is much lower even in our other south Asian countries like China and Japan. Its noted that the incidence of Multiple Myeloma is increasing among American Indians in past decade but is definetly nowhere near their native American counter parts.

AGE - Multiple myeloma is predominatly a disease of the elderly, the mean age of incidence being 68yrs.

SEX PREDILECTION – Males are slightly more affected than males.

AETIOLOGY

The cause of multiple myeloma is not clear.

Environmental exposure :

The strongest environmental link to the cause of multiple myeloma is ionizing radiation, 29 people among the Nagasaki bomb survivors died out of multiple myeloma. However some recent studies donot confirm the increased risk of multiple myeloma among these people. However the role of pesticides, chemicals, benzene, smoking

is supported by only epidemiological studies and there is no strong scientific evidence till date.

Genetic predisposition :

The direct genetic link for multiple myeloma is not established, however the racial and gender predilection proposes an genetic component to the etiology. In the large scale multicentric study done by the Mayoclinic , 8 siblings had the disease , in an Sweden based study of multiple myeloma, the relative risk of inheritance in males was 3.86 if the father had Multiple myeloma. Moreover substantial family clustering was found in many cases. There is significant association of HLACw2 and HLA Cw5 to Multiple myeloma.

Chronic Antigen stimulation :

Many M proteins have been shown to be antibodies against specific antigens, such as microbiological antigens, RBC antigens, neural antigens, lipoproteins, rheumatoid factors and coagulation factors. Chronic antigenic stimulation may predispose to the development of multiple myeloma as in cases of chronic osteomyelitis and cholecystitis.A recent case controlled study suggested that females with silicon transplants have a higher risk for developing multiple myeloma.

Virus :

Human herpes virus 8 has been found in the nonmalignant marrow dendritic bone cells of patients with multiple myeloma. Its still not proven that they play a role in the malignant transformation of multiple myeloma.

CYTOGENETICS

The malignant plasma cells carry complex chromosomal abnormalities that increase with disease progression. Microarray analysis has shed more light on sequential genetic changes from normal cells to myeloma cells and the multi step progression from from MGUS to multiple myeloma. Recent advances in cytogenetics

have showed that IgH translocations and aneuploidy states could be the possible early signatures of multiple myeloma. The common translocations include, t(11;14), t(14;16), t(4;14), t(6;14).these translocations, these IgH translocations are mediated by the VDJ recombination errors. These translocations may increase in frequency as the disease. progresses and result in activation of cyclin D1, D2, D3 or myeloma set domains or fibroblast growth factor 3 genes. These changes would trigger of the initial malignant proliferation and help in survival of the malignant plasma cells. However the disease progression is sustained by further chromosomal abnormalities, like P53 mutation, cmyc and ras gene mutation. Probably these bizarre multiple genetic abnormalities makes multiple myeloma still an incurable disease.Chromosome 13 translocations, P53 deletions, cmyc mutation are associated with poor prognosis.Thus genetic analysis is not needed for diagnosis but definetly plays a role in assessing the prognosis.

PATHOGENESIS:

Initially cell production from the bone marrow stem cell results in two lineages with lymphoid characteristics : pre- T cell and pre-B cell. The first will migrate to the Thymus where they will be

differentiated into T cells. The last cells will reach the peripheral blood as " tracer lymphocytes " . This kind of cell is the result of a process of differentiation not related to antigen that produces a great variety of cells which express small amounts of immunoglobulin on their surface. These cells, at some moment of their lives, will be stimulated by antigens or cytokines from helper T cells and will migrate to lymph nodes where they initiate a clonal proliferation which results in plasmablasts that express on their surface IgM and IgA. Those cells can go in two ways: get back to the blood as helper T cells or migrate to the bone marrow. After the activated B cells enter the bone marrow, they stop proliferating and differentiate into plasma cells, under the influence of adhesion molecules and factors such interleukin-6. They start to produce immunoglobulin and die by apoptosis after several weeks or months. What initiates this process is still unclear. The cells in Multiple Myeloma are often immature, may have the appearance of plasmablasts and produce low amounts of clonal immunoglobulin. The cause of the failure in the process of differentiation is not clear, but chromosomal translocation and increase in the expression of oncogen Cmyc could play an important role.The rate of cell proliferation in the beginning of Multiple Myeloma disease is very low compared to the terminal phase. The myeloma cells are aneuploid and their chromosomes have many numerical and structural

abnormalites that seems to prevent the differentiation and death of these cells, which continue to proliferate and accumulate in the bone marrow. All these alterations are correlated with resistance to treatment and short survival characteristc of aggressive disease.Interleukin 6 plays a very important role in the proliferation of myeloma cells. Its not just Proliferative factor but also an survival factor. Interleukin-6 is essential for the survival and growth of myeloma cells, which express specific receptors for this cytokine, and also prevents spontaneously by bone cells and stromal cells after stimulation by myeloma cells. It exerts its effect by triggering atleast two intercellular cascades, JAKSTAT and RAS/MAPK pathways. Cytokines like Insulin like growth factor 1, vascular endothelial growth factor, tumuor necrosis factor alpha, transforming growth factor beta, IL 10 and stromal cell derived factor 1 alpha also play an important role in the proliferation and survival of myeloma cells dexamethasone induced apoptosis.

PATHOGENESIS OF BONE LESIONS

The development of bone lesions in MM is caused by an imbalance between the activity of osteoclasts and osteoblasts. There is an increase in RANKL (receptor activator of nuclear factor κB ligand) expression by osteoblasts (and possibly plasma cells) accompanied by a reduction in the level

of its decoy receptor, osteoprotegerin (OPG). This leads to an increase in RANKL/OPG ratio, which causes osteoclast activation and bone resorption. In addition, increased levels of macrophage inflammatory protein–1α (MIP-1α), interleukin (IL)-3 and IL-6 produced by marrow stromal cells contribute to the overactivity of osteoclasts. At the same time, increased levels of IL-3, IL-7 and DKK1 produced by marrow stroma inhibit osteoblast Different -iation.. These changes lead to osteoclast activation and bone resorption without any repair activity by osteoblasts.

CLINICAL MANIFESTATIONS OF MULTIPLE MYELOMA

Multiple myeloma is usually asymptomatic in early stages. The symptoms in myeloma could be due to the disease activity or due to the complication. The Presenting symptoms could range from just back ache, to pathologic fractures, paraperesis , dyspnoea severe pallor, infection, seizure, stupor, coma……Increasingly, physicians are identifying asymptomatic patients through routine blood screening.

SKELETAL DISEASE IN MULTIPLE MYELOMA:

1.Back Ache - is the most common presenting symptom. Most series report that 70% of patients have back ache at presentation. Backache is predominantly bone pain due to the lytic lesion of the vertebra. The lumbar vertebrae are one of the most common sites of pain.

2 other bone Pain – depending on the skeletal involvement involved, patients can present With varying aches and pains localized to respective structures. 93% of patients have more than one bony involvement.

3.pathological fracture

DEFECTIVE HEMATOPOIESIS

1.Anemia : can present with easy fatigability, weakness and dyspnoea .60% of the Patients at the time of diagnosis have anemia.

2.bleeding : Occasionally a patient may come to medical attention for bleeding resulting from thrombocytopenia.!5% of patients at the tim of diagnosis have thrombocytopenia. In some patients, monoclonal protein may absorb clotting factors and lead to bleeding, but this development is rare.

3.Infection : Abnormal humoral immunity and leukopenia may lead to infection. Pneumococcal organisms are commonly involved, but shingles (ie, herpes zoster) and Haemophilus infections are also more common among

patients with myeloma. Leukopenia is present in 15% of patients at the time of diagnosis.

RENAL DYSFUNCTION

Acute and chronic renal failure is a part of multiplemyeloma , the incidence being 15 – 20%, presenting with uraemic symptoms like nausea, vomiting , hiccoughs, Decreased urine out put, altered sensorium with flapping tremors, signs of fluid overload.Renal dysfunction in multiple myeloma could be due to Myeloma kidney, as a result of precipitation light chains in the tubules , leading to obstruction, inflammation and scarring,.can thus present as fanconi's syndrome. Even glomerular sclerosis ia part of myeloma kidney. The other causes of renal involvement in myeloma is secondary to hypercalcemia and Amyloidosis.

NEUROLOGICAL DYSFUNCTION :

1.Spinal cord compression : symptoms of spinal cord compression are back pain, root pain, band like sensation, weakness, numbness, or dysesthesias in the extremities. Patients who are ambulatory at the start of therapy have the best likelihood of preserving function and avoiding paralysis. This complication occurs in approximately 10-20% of patients at some time during the course of disease.

2.Space occupying lesion in brain – very raely meningeal plasmacytomas, cerebral plasmacytomas can present with seizures and features of raised intracranial tension.

3. Meningitis – secondary to infections especially streptococcus pneumoniae.

4. Peripheral neuropathy - Carpal tunnel syndrome is a common complication of myeloma.. Some peripheral neuropathies have been attributed to myeloma

Metabolic abnormalities -

1.Hypercalcemia : symptoms include confusion, somnolence, bone pain, constipation, nausea, and thirst. This complication may be present in as many as 30% of patients at presentation. In most solid malignancies, this carries an ominous prognosis, but in myeloma, its occurrence does not adversely affect survival.

2.Hyponatremia, Hypokalemia and Metabolic alkalosis – secondary to fanconi's syndrome.

Hyperviscosity - Due to hyperimmunoglobulinemia. Epistaxis may be a presenting symptom of myeloma with a high tumor volume. Occasionally, patients may have such a high volume of monoclonal protein that their blood viscosity increases, resulting in complications such as stroke, myocardial ischemia, or infarction. Patients may report headaches and somnolence, and

they may bruise easily and have hazy vision. Patients typically experience these symptoms when their serum viscosity is greater than 4 times that of normal serum.

Physical examination

- Patients may have pallor resulting from anemia.
- Patients may have ecchymoses or purpura resulting from thrombocytopenia.
- Bony tenderness is not uncommon, resulting from focal lytic destructive bone lesions or pathologic fracture. Pain without tenderness is typical.
- spinomotor system examination may reveal features of compressive myelopathy with definite sensory and motor level , there could also be multiple levels of compression
- .Extramedullary plasmacytomas, which consist of soft tissue masses of plasma cells, are not uncommon. Plasmacytomas have been described in almost every site in the body. Although the aerodigestive tract is the most common location,reports also describe orbital, ear canal, cutaneous, gastric, rectal, prostatic, and retroperitoneal
- hepatomegaly and splenomegaly

PHYSICAL FINDINGS IN AMYLOIDOSIS

A.The shoulder pad sign is defined by bilateral swelling of the shoulder joints secondary to amyloid deposition. Physicians describe the swelling as hard and rubbery. Amyloidosis may also be associated with carpal tunnel syndrome and subcutaneous nodules.

B Macroglossia is a common finding in patients with amyloidosis.

C. Skin lesions that have been described as wax papules or nodules may occur on the torso, ears, or lips.

D. Postprotoscopic peripalpebral purpura strongly suggests amyloidosis. Patients may develop raccoonlike dark circles around their eyes following

anyprocedure that parallels a prolonged Valsalva maneuver. The capillary fragility associated with amyloidosis may account for this observation. The correlation was observed when patients in the past underwent rectal biopsies to make the diagnosis.

WORK UP

The standard evaluation of a patient with suspected myeloma includes:

1) complete hemogram including erythrocyte sedimentation rate.
2) Blood chemistry profile including calcium, urea, creatinine, LDH, albumin, uric Acid, serum electrolytes, total proteins , serum albumin.
3) Serum beta-2 microglobulin and Lactate dehydrogenase may be a mesure of tumour burden especially the former.
4) Creactive protein - a surrogate marker for IL-6
5) Bone marrow aspirate and biopsy with cytogenetics and plasma cell labeling index
6) Complete skeletal survey – Xray of skull and long bones is required in all cases of multiple myeloma. MRI may be required in the case of paraspinal mass, features of compressive myelopathy, radiculopathy. Bone scans are of limited use, PET scans are rarely used to evaluate the extent of the disease. Bone densitometry is useful in followup of multiple myeloma , as it helps in predicting the risk of fractures and casn also help in assessing the response to bisphosphonates.
7) 7.light chains in urine - A routine urinalysis will not detect Bence Jones proteins. There are several methods used by

laboratories to detect and measure these proteins. The classic Bence Jones reaction involves heating urine to 140°F (60°C). At this temperature, the Bence Jones proteins will clump. The clumping disappears if the urine is further heated to boiling and reappears when the urine is cooled. Other clumping procedures using salts, acids, and other chemicals are also used to detect these proteins. These types of test will reveal whether or not Bence Jones proteins are present, but not how much is present. This test is highly unreliable. The best method would be to do a Urine protein electrophoresis and immunofixation in 24 hour urine sample. Urine electrophoresis shows a globulin spike in 75% of patients.

8) Serum protein electrophoresis and immunofixation : To identify M protein And quantification of it. Serum protein electrophoresis (SPEP) shows a monoclonal spike in 85% of multiple myeloma patients.

Urine electrophoresis shows a globulin spike in 75% of patients. Sixty percent of the patients have a monoclonal protein that is immunoglobulin G (IgG), 20 % IgA, 1% IgD or non-secretory, and 15% are light chain only.

DIAGNOSIS OF MULTIPLE MYELOMA

Major criteria –

1.I = Plasmacytoma on tissue biopsy

2.II = Bone marrow with greater than 30% plasma cells

3.III = Monoclonal globulin spike on serum protein electrophoresis, with an immunoglobulin G (IgG) peak of greater than 3.5 g/dL or an immunoglobulin A (IgA) peak of greater than 2 g/dL, or urine protein electrophoresis (in the presence of amyloidosis) result of greater than 1 g/24 h.

Minor criteria -

a = Bone marrow with 10-30% plasma cells

b = Monoclonal globulin spike present but less than category III

c = Lytic bone lesions

d = Residual normal immunoglobulin M (IgM) level of less than 50 mg/dL, IgA level of less than 100 mg/dL, or IgG level of less than 600 mg/dL

The following combinations of findings are used to make the diagnosis:

I plus b

I plus c

I plus d

II plus b

II plus c

II plus d

III plus a

III plus c

III plus d

a plus b plus c or a plus b plus d

Classification of Myeloma

Patients may be classified into one of three myeloma categories (MGUS,Asymptomatic, and Symptomatic) to help to determine treatment options. Patients in some categories do not have to receive treatment immediately, but may receive bisphosphonates if osteoporosis is present, or other supportive care for symptomsand complications. In these cases, postponing therapy may help avoid unnecessary side effects and the risk of complications associated with chemotherapy and may also delay development of resistance to chemotherapy

Monoclonal Gammopathy of Undetermined Significance (MGUS)

MGUS is a common condition where a monoclonal protein is present. However, there are no symptoms, other criteria for myeloma diagnosis are absent, and no cause for the increased protein can be identified. MGUS occurs in about 1%of the general population and in about 3% of normal individuals over 70 years of age. MGUS itself is harmless but over many years approximately 16% of individuals with MGUS will progress to a malignant plasma cell disorder. Characteristics:

- Serum M protein <3 g/dL
- Bone marrow plasma cells <10%

Absence of anemia, renal failure, hypercalcemia, lytic bone lesions.

Asymptomatic Multiple Myeloma Patients with asymptomatic multiple myeloma have a monoclonal protein and slightly increased numbers of plasma cells in the bone marrow. They may have mild anemia and/or a few bone lesions, but do not exhibit the renal failure and frequent infections that characterize active multiple myeloma. In these patients the myeloma is static and may

not progress for months or years. Asymptomatic multiple myeloma includes both Smoldering Multiple Myeloma (SMM) and Indolent Multiple Myeloma (IMM).

- **Smoldering Multiple Myeloma (SMM)**
  - Characteristics
    - Serum M protein >3 g/dL and/or bone marrow plasma cells ≥10%
    - Absence of anemia, renal failure, hypercalcemia, lytic bone lesions

Indolent Multiple Myeloma (IMM) Characteristics

- Stable serum/urine M protein
- Bone marrow plasmacytosis
- Mild anemia or few small lytic bone lesions
- Absence of symptoms.

Symptomatic Multiple Myeloma (MM)

Characteristics

1. Presence of serum/urine M protein
2. Bone marrow plasmacytosis (>30%)
3. Anemia, renal failure, hypercalcemia, or lytic bone lesions

Staging of Myeloma

The process of staging myeloma is crucial to developing an effective treatment plan. The staging system most widely used since 1975 has been the Durie-Salmon system, in which clinical stage of disease (stage I, II, or III) is based on four measurements: levels of M protein, the number of lytic bone lesions, hemoglobin values (a measure of the number of red blood cells in the blood), and serum calcium levels. Stages are further divided according to renal (kidney) function (classified as A or B; Table 3). There is somewhat of an overlap between the various myeloma categories and stages. For example, both patients with smoldering myeloma and patients with Stage I disease do not require immediate treatment, and patients with Stage II and III disease have active, symptomatic myeloma. Increasingly, physicians are relying less on the Durie-Salmon staging system and more on biologically relevant markers as prognostic indicators when making treatment choices.

A new, simpler, more cost-effective alternative is the International Staging System (ISS). The ISS is based on the assessment of two blood test results, beta 2-microglobulin (β_2-M) and albumin, which together showed the greatest prognostic power

for multiple myeloma. This system has only recently been developed, but has already been proven more sensitive in discriminating between three stages of the disease, which indicate different levels of projected survival and suggest increasingly more aggressive treatment strategies. This system is based on the level of beta 2 microglobulin, which is a very good indicator of tumour burden. Several studies done correlating beta2 microglobulin and plasmacell labelling index, have proved that beta 2 microglobulin directly correlates with the plasma cell labelling index , further studies have shown that beta 2 microglobulin is a very good prognostic marker, beta2 microglobulin level > 3.5g/dl have indicated poor prognosis and high five year mortality. Serum albumin also is a prognostic indicator, studies have shown lower is the serum albumin worser is the survival rate .

The following table summarizes the staging criteria.

	SALMON DURIE STAGING	ISS CRITERIA
I	All of the following: ▪ Hemoglobin value >10 g/dL ▪ Serum calcium value normal or ≤12 mg/dL ▪ Bone x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only ▪ Low M-component production rate — IgG value <5 g/dL; IgA value <3 g/dL Bence Jones protein <4 g/24 h	β_2-M < 3.5 mg/dL and albumin ≥3.5 g/dL
II	Neither stage I nor stage III	Neither stage I nor stage III
III	On or more of the following: ▪ Hemoglobin value <8.5 g/dL ▪ Serum calcium value >12 mg/dL ▪ Advanced lytic bone lesions (scale 3) ▪ High M-component production rate — IgG value >7 g/dL; IgA value >5 g/dL — Bence Jones protein >12 g/24 h	β_2-M ≥ 5.5 mg/Dl

Durie-Salmon sub classifications (either A or B)
A: Relatively normal renal function (serum creatinine value <2.0 mg/dL
B: Abnormal renal function (serum creatinine value ≥2.0 mg/dL

FACTORS FAVOURING GOOD PROGNOSIS

Beta-2 microglobulin ≤2.5 mg/l*

C-reactive protein ≤4.0 mg/dl*

No -13/13q- chromosome abnormalities

Plasma cell labeling index less than 1%

Absence of plasmablastic morphology

≤12 months prior treatment

Chemotherapy sensitive disease

Any complete remission

Non IgA isotype (controversial)

Low Interleukin-6 receptor

TREATMENT FOR STAGE I MULTIPLE MYELOMA

Patients with stage I or smouldering myeloma do not need primary therapy because they can do well with out therapy for months to years, before the disease progresses.These candidates should be observed every 3-6 months for disease progression.

TREATMENT FOR STAGE II AND III MULTIPLE MYELOMA

A.PATIENTS SUITABLE FOR TRANSPLANT

B.PATIENTS NOT SUITABLE FOR TRANSPLANT

A. PATIENT SUITABLE FOR TRANSPLANT -

1. all newly diagnosed patients and priorly treated patients

2 preferably below 65yrs

3 preferably normal renal function

4. good performance status.

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplant.

PRIMARY CONVENTIONAL THERAPY:

1.Melphalan/prednisone (MP)

2.Vincristine/doxorubicin/dexamethasone (VAD)

3.High dose Dexamethasone

4.Thalidomide/dexamethasone

5.Liposomal doxorubicin/vincristine/dexamethasone (DVD)

Stem cell transplant : following the induction therapy , stem cell transplant is performed for the eligible individuals. **Autologous stem cell transplant** is usually done . Tandem stem cell transplant refers to planned second course of high dose therapy and stem cell transplant within six months of the first. Allogenic transplants have been limited due to lack of donors and increasing morbidity.

MAINTAINENECE THERAPY

Steroids (category 1 for 50 mg prednisone every other day)

Interferon (category 2B)

Studies have not clearly proved that maintiance therapy reduces disease recurrences.Hence the role of dexamethasone or interferon as maintainence therapy in general is uncertain.

High-dose cyclophosphamide

SALVAGE THERAPY :

1.Patients with progressive disease following allogeneic or autologous stem cell transplant.

2.patients with primary progressive disease following initial autologous or allogeneic stemcell transplant.

3.non transplant candidates with progressive or relapsing disease after the induction therapy.

Options available are:

Repeat primary conventional therapy (if relapse at > 6 mo)

Cyclophosphamide-VAD

Thalidomide.

Bortezomib (category 1)

Thalidomide/dexamethasone_

Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide (DT-PACE)

Arsenic trioxide in combination with vitamin C (category 2B)

High dose steroids.

ADJUNCTIVE THERAPY:

1.Hypercalcemia - Hydration / furosemide, bisphosphonates, steroids and/or Calcitonin.

2.Hyperviscosity - Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity

3.Anemia - Consider erythropoietin for anemic patients

4.Infection - Intravenous immunoglobulin therapy should be considered in the setting of recurrent lifethreatening infection. Consider pneumovax and influenza vaccine. Consider PCP herpes and antifungal prophylaxis if high dose dexamethasone regimen

5. Renal Dysfunction

A.Maintain hydration to avoid renal failure

B. Avoid use of NSAIDs

C.Avoid IV contrast

6.Plasmapheresis for hyperviscosity.

7.Consider prophylactic anticoagulation with thalidomide-based therapy

8.Bisphosphonates

All patients with documented bone disease including osteopenia (category 1)

Use of bisphosphonates in smoldering or stage I disease preferrably in the context of a clinical trial. These patients should have bone survey yearly

Bone densitometry or metabolic studies should be reserved for clinical trial

Monitor for renal dysfunction with chronic use of bisphosphonates

Monitor for osteonecrosis of the jaw

9. Radiation Therapy

Low-dose radiation therapy (10–30 Gy) can be used as palliative treatment for uncontrolled pain, for impending pathologic fracture or impending cord compression. Radiation doses utilized should not preclude future administration of total-body irradiation . Limited involved fields should be used to limit the impact of irradiation on stem-cell harvest or impact on potential future treatments.

10. Consider vertebroplasty.

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AIMS AND OBJECTIVES

To study the pattern of clinical, pathological ,biochemical and radiological presentation of Multiple Myeloma at Madurai Govt Rajaji Hospital.

MATERIAL AND METHODS

Twenty six patients of multiple myeloma admitted to the Oncology department and department of Medicine at Govt Rajaji Hospital, Madurai from july 2005 to Oct 2007 were studied.

An Observational study with regular follow up to assess the response to study was designed.

All the new cases of multiple myeloma admitted to the department of medicine and Department of Oncology Govt Rajaji Hospital were included in the study. The diagnosis of multiple myeloma was based on the following findings:

(1) increased numbers of abnormal, atypical, or immature plasma cells in the bone marrow or histologic proof of plasmacytoma;

(2) presence of an M-protein in the serum or urine.

(3) bone lesions consistent with those of multiple myeloma .

GRH madurai primarily caters to the rural population of Madurai and the surrounding districts.

EXCLUSION CRITERIA

A. plasma cell reactions to connective tissue disorders, liver disease, metastatic carcinoma, or chronic infections were excluded..

B.Monoclonal gammopathy of undetermined significance (MGUS),

C.smoldering multiple myeloma,

D.solitary plasmacytoma,

E. plasma cell leukemia were also excluded.

F. Patients with primary amyloidosis (AL) were included only if features of multiple myeloma predominated.

History taking and clinical examination – All the 26 patients were subjected to detailed history taking and meticulous clinical examination.

Laboratory work up – Bichemical work up included urine bencejones, done with the heat coagulation method, serum albumin, calcium, uric acid done using standard biochemical kits.Serum immuno electrophoresis was done using the agar gel electrophoretic method.

Haematological work up – complete hemogram and bone marrow aspiration studies were done .They were analysed by the Pathologist at the department of Pathology GRH. Madurai.

Skeletal survey - Xray skull PA and lateral view, Xray pelvis PA and lateral view, Xray cervical, thoracic, lumbar spine PA and lateral view , chest xray PA and lateral view, xray humerus PA and lateral

view, Xray hip and femur PA and lateral view was done in all patients. Computerised tomographic scan and Magnetic resonance imaging was done when xray findings were inconclusive.

TREATMENT AND FOLLOW UP –

All patients were subjected to 12 cycles of cyclophosphamide and dexamethasone therapy, and revevaluted at the end of 6 cycles, 9 cycles and 12 cycles.

All the data was analysed using the epidemiological information package 2003 software.

RESULTS

AGE DISTRIBUTION –

Out of the 26 patients studied **53.8%** of patients belonged to **40-60yr** age group, while 34.6% belonged to 60-80yr age group, only 11.6% belonged to 20 -40 yr. The mean age of presentation was 52.11yr., the median was 55 yrs and the range was 28 – 72.

TABLE 1 DEMOGRAPHIC DATA FOR 26 PTS WITH MULTIPLE MYELOMA

AGE	PATIENT DATA
20-40Yr	11.6%
40 – 60 Yr	53.8%
60 – 80 yrs	34.6%
Mean	52.11yrs

SEX DISTRIBUTION –

Males were slightly more affected than females, of the 26 patients **53.8%** were men and **46.2%** were women. The sex ratio of men to women, was **1.2:1.**

TABLE 2 SEX DISTRIBUTIONS IN 26 PTS OF MYELOMA

SEX	PERCENTAGE OF PATIENTS
MALE	53.8%
FEMALE	46.2%

CLINICAL SYMPTOMATOLOGY

Backache was the presenting symptom in **92.3%** of patients. The mean duration of the symptom was **6.5 months**.

COMPLICATIONS –

1) **Infections,** mainly lower respiratory tract infection and urinary tract infection was present in only **7.6%** of patients.
2) **Compressive myelopathy** was present in **15.4%** of patients.
3) **Renal failure** was present in **11.5%** of patients.

TABLE 3 COMPLICATIONS IN 26 PATIENTS WITH MULTIPLE MYELOMA

1.INFECTIONS	7.6% (2/26)
2.COMPRESSIVE MYELOPATHY	15.4%(4/26)
3.RENAL FAILURE	11.5% (3/26)

LABORATORY TESTS

1.Haemoglobin : Anemia (Hb < 12g/dl) is present in all the patients, 76.9% had a haemoglobin of less than 8.5g/dl.

Table 4 Haemoglobin level in 26 patients with Multiple Myeloma

HEMOGLOBIN g/dl	PERCENTAGE OF PATIENTS
<8.5	76.9%
>8.5	23%

Median – 8.0g/dl , Mean – 7.5g/dl, Range – 5.6 – 11g/dl

2.Serum calcium : We had zero incidence of hypercalcemia. The mean calcium 8.5mg/dl.

3.Erythrocyte Sedimentation rate : ESR was raised above 50 mm /hr in all the patients the mean ESR being 72.7mm/hr.

4.Serum Creatinine : only 11.5% of patients had a creatinine of more than 2mg/dl. 46.2% of patients had creatinine values between 1.3 to 1.9mg/dl.

TABLE 4 SERUM CREATININE LEVELS IN 26 PATIENTS WITH MYELOMA

SERUM CREATININE	PERCENTAGE OF PATIENTS
<1.3mg/dl	42.3%
1.3 – 1.9mg/dl	46.2%
>2.0mg/dl	11.5%

5..serum albumin – 65.4% of patients had an serum albumin of 3.0g/dl and less, only 44.6% of patients had a serum albumin greater than 3.0g/dl

TABLE 5 SERUM ALBUMIN IN 26 PATIENTS WITH MYELOMA

SERUM ALBUMIN	PERCENTAGE OF PATIENTS
<3.1g/dl	65.4%
>3.0g/dl	44.6%

Correlation of serum albumin to degree of plasmacytosis: On comparing the serum albumin with degree of plasmacytosis, it was noted that serum albumin was lower in patients with more than 50%

bone marrow plamacytosis compared with patients with less than 50% plasmacytosis with a significant p value of 0.031.

TABLE 6 CORRELATION OF BONEMARROW PLASMACYTOSIS WITH SERUM ALBUMIN

DEGREE OF PLASMACYTOSIS	MEAN SERUM ALBUMIN
<50%	3.2g/dl
>50%	2.9g/dl

P value – 0.031

BONE MARROW EXAMINATION –

Bonemarrow examination revealed 46.1 % of patients had plasmacytosis more than 50%.

TABLE 7 BONE MARROW PLASMA CELLS IN 26 PATIENTS OF MYELOMA

DEGREE OF PLASMACYTOSIS	PERCENTAGE OF PATIENTS
20 – 50%	53.8%
51 – 70%	26.9%
>70%	19.2%

MULTIPLE MYELOMA STAGE AT PRESENTATION :

84.6% OF patients presented in stage IIIA.

TABLE 8 STAGE OF PRESENTATION OF 26 CASES OF MULTIPLE MYELOMA

STAGE	PERCENTAGE OF PATIENTS
IIA	3.9% (1/26)
IIIA	84.6% (22/26)
IIIB	11.5% (3/26)

RADIOLOGICAL FINDINGS AT PRESENTATION:

All the 26 patients had lytic lesions, predominantly involving skull, vertebrae and pelvis, few patients had involvement of ribs, femur and humerus.15.4% had compreesion fractures, 11.5% of patients had osteoporosis.

TABLE 9 RADIOLOGICAL FINDINGS OF 26 PTS WITH MULTIPLE MYELOMA

RADIOLOGICAL ABNORMALITIES	PERCENTAGE OF PATIENTS
LYTIC LESIONS	100%
PATHOLOGICAL FRACTURES	15.4% (4/26)
COMPRESSION FRACTURES	15.4% (4/26)
OSTEOPENIA	11.5% (4/26)
OSTEOSCLEROSIS	0.0%

RESPONSE TO THERAPY – 18 MONTHS FOLLOW UP

Of the 16 patients who could be followed upto 18 months in the period of 2005 -2007, 75% of patients went in for complete remission , 18.7% had relapses, 6.2% had primary progression of the disease and succumbed to it.

TABLE10 STAGE OF THE DISEASE 18 MONTHS FOLLOW UP

Disease status	Percentage of patients
1. complete remission	75% (12/16)
2.relapses	18.7% (3/16)
3.death	6.2% (1/16)

DISCUSSION AND COMPARATIVE ANALYSIS

1.AGE DISTRIBUTION OF MULTIPLE MYELOMA

On comparitve analysis with the mayoclinic proceedings, a 10 year study of 1027 patients with multiple myeloma, around 70% of patients were above 60 years compared to 34.55 of patients in our study and the mean age of presentation is 66 years compared to 53yrs in our study, which was similar to the twelve year study conducted by All India institute of medical sciences, mean age of incidence there being 52 years.

Observing these results and corroborative findings from the AIIMS study, one can conclude that multiple myeloma has an younger age predominance in Indian population compared to western population.

TABLE11 COMPARISION OF MEAN AGE OF PRESENTATION OF MYELOMA

STUDY	MEAN AGE
Kyle etal(Mayo) – 10 yr study 2003	66yr
Gupta etal (AIIMS) – 12 yr study 1995	52yr
GRH Madurai – 2005-07	53yr

The incidence of multiplemyeloma is very low compared to the western counter parts, probably we are not genetically predisposed to the disease and the environmental factors play a major role, especially pesticides, for instance 95% of patients with myeloma at madurai GRH were farmers. This is just an hypothesis and further molecular and epidemiological studies have to be done to prove or disprove it.

2. SEX DISTRIBUTION OF MULTIPLE MYELOMA

In all the three studies there was increased incidence of myeloma in males compared to females, however the sex ratio was lowest in GRH madurai study followed by the Mayoclinic study and the highest was in the AIIMS study, with no statistically significant difference.

TABLE 12 COMPARISION OF SEX RATIO IN MULTIPLE MYELOMA

Study	Sex ratio M : F
Kyle etal – 10 yr study 2003	1.4 : 1
AIIMS – 12 yr study 1995	1.2 : 1
GRH Madurai – 2005-07	2.2 : 1

P value – 0.0592

SYMPTOMATOLOGY- 95% of our patients presented with backache as the presenting symptom, the average duration of 6.5 months. Backache is the most common presenting symptom of multiple myeloma, is present for atleast 6 months according to the literatures.

SEVERITY OF ANEMIA – on comparing significant anemia < 8g/dl was present in only 7% of patients in mayoclinic study compared to 30% in the AIIMS study and 66.9% in our study. Although anemia is an important factor in the salmon durie staging criteria, attributing it to the severity of the disease one must give due consideration to the higher incidence of iron deficiency anemia and chronic blood loss anemia in our population which could be one of the reasons for such wide discrepancies between the Indian and western population. Comparing to the Atul etal AIIMS study, the incidence of anemia is much higher in our study. All our patients are rural population with high incidence of iron deficiency anemia.

TABLE 13 COMPARISION OF HEMOGLOBIN LEVEL IN MULTIPLE MYELOMA

STUDY	HEMOGLOBIN <8 g/dl
Kyle et al – 2003	7%
Gupta et al – 1995	30%
GRH Madurai – 2005-07	66.9%

P = 0.023

ERYTHROCYTE SEDIMENTATION RATES – Multiple Myeloma is one of the few disease with a ESR of more than 100 mm/hr, the mean ESR in our patients was 72m/hr and 100% of patients had an ESR above 50mm/hr, on comparing with the Mayoclinic proceedings , they had 84.5% of patients with ESR more than 20mm/hr. both the studies substantiates that ESR is elevated in majority of cases of multiple myeloma, thus could be used as a adjuvant screening marker .

4. SERUM CREATININE –

Comparing the incidence of renal failure in patients with multiple myeloma, with creatinine of >2mg/dl, there was no statistically significant difference between our study and the mayoclinic proceedings 2003.

TABLE 14 COMPARISION OF SERUM CREATININE LEVEL IN MYELOMA

STUDY	SERUM CREATININE >2mg/dl
Kyle.etal 2003 (Mayo)	19%
GRH madurai 2005 -07	11.5%

5.SERUM ALBUMIN – The mean serum albumin for our patients was 2.9g/dl, on correlating the serum albumin level to the tumour burden reflected by the degree of plasmacytosis, there was a statistical difference in the serum albumin level between the two groups, (p = 0.03). Several studies have clearly shown low serum albumin level as a poor prognostic indicator and correlates with severity of the disease.This study also showed that it has a direct correlation with the tumour burden. According to ISS staging we take serum albumin of 3.5g/dl as a cut off for stage I multiple myeloma. Majority of our patients were in Stage III according to Salmon Durie criteria, that could probably explain the serum albumin level in patients with plasmacytosis of <50% being 3.2g/dl. Clearly although Serum albumin is influenced by the tumour burden, all the factors determining the severity of the disease tend to influence serum albumin.

TABLE 15 CORRELATION OF BONEMARROW PLASMACYTOSIS WITH SERUM ALBUMIN

DEGREE OF PLASMACYTOSIS	MEAN SERUM ALBUMIN
<50%	3.2g/dl
>50%	2.9g/dl

P – 0.03

6.BONEMARROW PLASMACYTOSIS AT PRESENTATION :

40% of our patients had Bone marrow plasmacytosis of >50% as compared to 45% of patients in the Mayoclinic proceedings 2003. There was no statistical difference between the two studies. From this we can infer that multiple myeloma usually presents at an advanced stage, with more than one third of the patients having an plasmacytosis of more than 40%.

TABLE16 COMPARISION OF BONEMARROW PLASMACYTOSIS IN MYELOMA

STUDY	DEGREE OF PLASMACYTOSIS > 50%
Kyle etal 2003 (Mayo)	45%
GRH MADURAI 2005-07	40%

7.RADIOLOGIC FINDINGS IN MULTIPLE MYELOMA –

All our patients had evidence of lytic lesion in the skeletal survey, it was a part of our inclusion criteria. In the Mayoclinical proceedings only 76% had lytic lesions, this difference could be explained with the inclusion of MGUS, smouldering myeloma, non secretory myelomas in the study as opposed to only active symptomatic myeloma patients in our study. The incidence of pathological fractures and compression fractures were similar.

TABLE 17 COMPARISION OF RADIOLOGICAL FINDINGS IN MYELOMA

FINDINGS	Kyle et al	GRH Madurai study
Lytic lesions	76%	100%
Pathological fractures	26%	15.4%
Compression fractures	22%	15.4%
Osteopenia	23%	11.5%

The difference in the pathological fractures and compression fractures in mayoclinic proceedings and our study at GRH Madurai was not statistically significant, with a p value of 0.079. The incidence of osteosclerosis was very less in both the study, 0.5% in mayoclinic proceedings and 0% in our study.

RESPONSE TO THERAPY:

Only 16 patients could be followed up to 18 months in the period of 2 years. All the patients received 12 cycles of cyclophosphamide and dexamethasone. Of the 16 patients, 75% had complete remission. In Atul et al a study of 44 patients of multiple myeloma with 40 month followup , on melphalan and dexamethasone therapy, the complete remission rate at 40 months was 26.1%. well

since there is a gross difference between the duration of the study and the number of patients studied, there is a higher chance of statistical error. Hence further follow up of these patients would be needed to compare the actual complete remission rate with cyclophosphamide and dexamethasone. In comparision with melphalan and dexamethasone.

LIMITATIONS OF THE STUDY

1) Urine Bence Jones Proteins was analysed with the routine heat coagulation method which is not reliable..
2) Beta2microglobulin , LDH, C reactive protein could not be done for all the patients due to the lack of availability of the facilities at our hospital.
3) Plasma labeling index could not be caluculated for our patients due to lack of facility.
4) Follow up of the patients was only for 18 months.
5) 11% of patients were lost for follow up.
6) Osteoporosis in the 11.5% of patients was picked up by the MRI scan which was not done in all patients, nor the DEXA scan was done in all patients, hence the incidence of osteoporosis might be incorrect.

CONCLUSION

1) Multiple myeloma presents a decade earlier in Indian population compared to the world mean age of presentation.
2) Backache is the most common presenting symptom, was present for minimum of 6.5 months.
3) The incidence of anemia is comparatively higher in our patients.
4) There is a definite correlation with bone marrow plasmacytosis and serum albumin.
5) Most of our Patients are in stage IIIA at time of diagnosis.
6) The incidence of renal failure in our patients is comparable to the world statistics.
7) Our patients ’response to alkylating agents and high dose dexamethasone therapy is on par with the international complete response rate.

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RESPONSE CRITERIA FOR MULTIPLE MYELOMA

International Myeloma Working Group Uniform Response Criteria

Response Category	Response Criteria[1]
sCR, stringent complete response	CR as defined below plus: Normal free light chain (FLC) ratio and absence of clonal cells in bone marrow[2] by immunohistochemistry or immunofluorescence[3]
CR, complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and $\leq$ 5% plasma cells in bone marrow[2]
VGPR, very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h
PR, partial response	$\geq$50% reduction of serum M-protein and reduction in 24 h urinary M-protein by $\geq$90% or to <200 mg per 24 h If the serum and urine M-protein are unmeasurable, a $\geq$ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, $\geq$ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was $\geq$ 30% In addition to the above listed criteria, if present at baseline, a $\geq$ 50% reduction in the size of soft tissue plasmacytomas is also required
SD, stable disease (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

RELAPSE SUBCATEGORY RELAPSE CRITERIA

International Myeloma Working Group Uniform Response Criteria

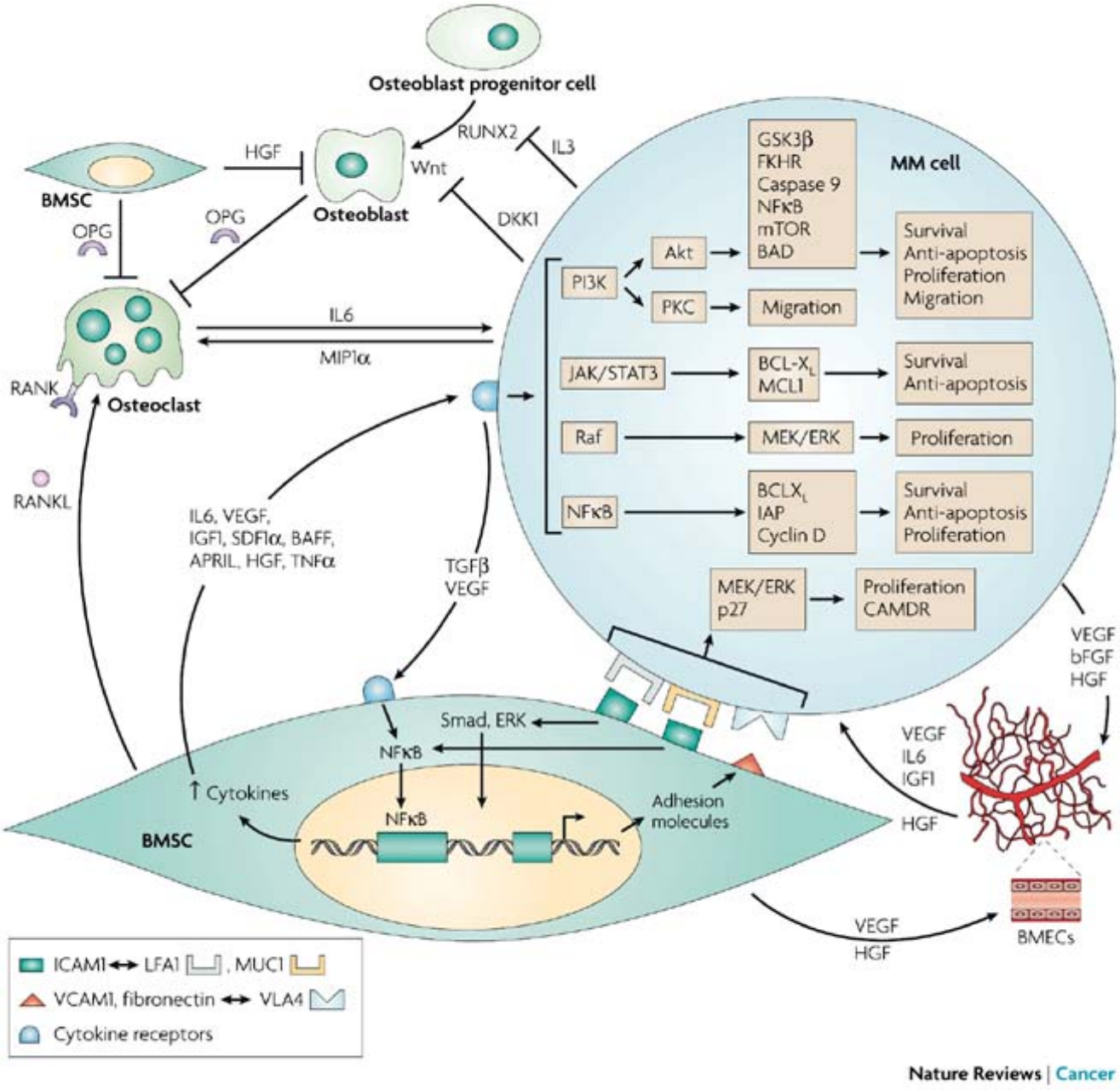
Progressive disease [1] (To be used for calculation of time to progression and progression-free survival and points for all patients Including those in CR) (includes primary progressive disease and disease progression on or off therapy)	Progressh'e Disease: requires any one or more of the following: Increase of ≥25% from baseline in: • Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL) • Urine M-componont and (the absolute increase must be ≤ 200 mg/24 h • Only in patients without measurable serum and urine M-proteln levels: the difference between involved and uninvolved FLC levels. The absolute Increase must be> 10 mg/dL. • Bone marrow plasma cell percentage: the absolute % must be ≥ 1O% • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hyporcalcemia (corrected serum calcium > 11.5 mg that can be aftributed solely to the plasma cell proliferative disorder
Clinical relapse[1]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction ICRAB features). It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice • Development of new soft tissue plasmacytomas or bone lesions • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion • Hypercalcemia (> 11.5 mgldL) • Decrease in hemogloblin of ≥ 2 g!dL • Rise in serum creatinine by 2 mgldL or more
Relapse from CR[1] (To be used only if the end point studied us DFS disease free survival)[4]	Any one or more of the following: (To be used only it the end • Reappearance of serum or urine M-protein by Immunofixation or electrophoresis point studied Is DFS • Development of ≥5% plasma cells in the bone marrow[3] Apperance of any other sign of progression (ie, new plasmacytoma , lytic bone lesion, or , hypercalcemia)

DR.OTTO KAHLER.

“ KAHLER’S DISEASE”

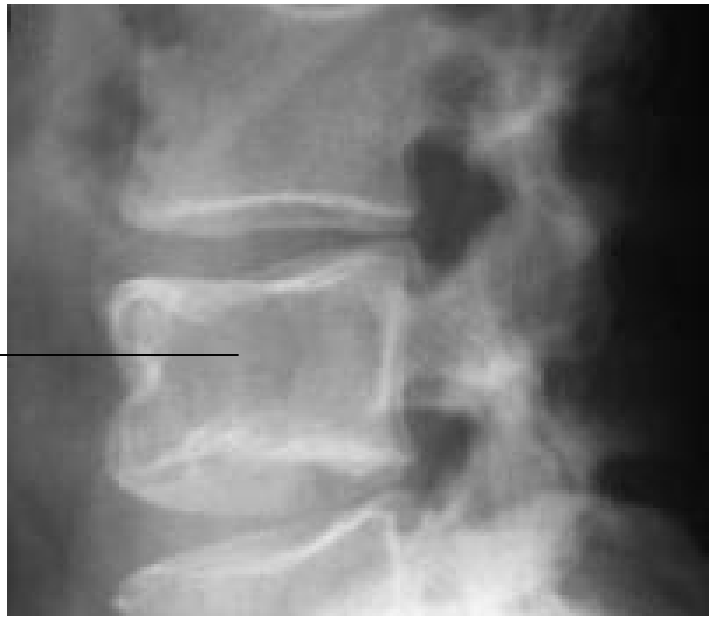
DR.HENRY BENCE JONES.

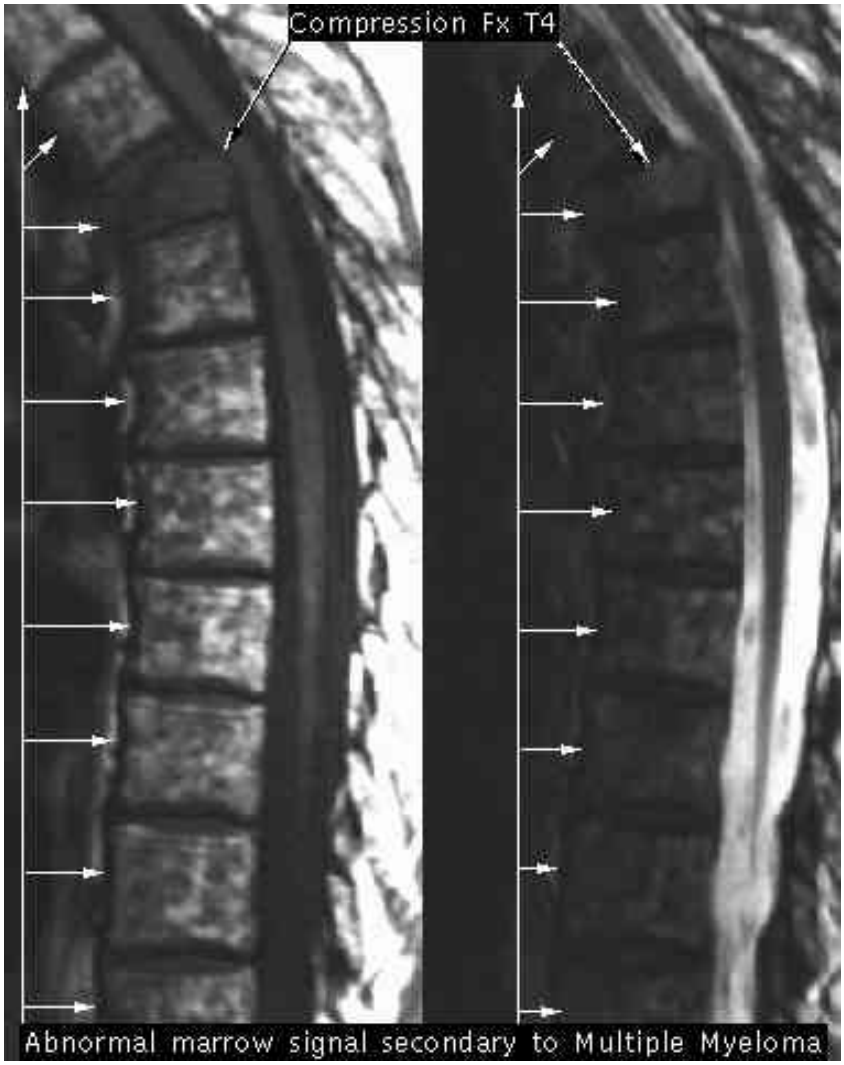
“ BENCE JONES PROTEINS ”



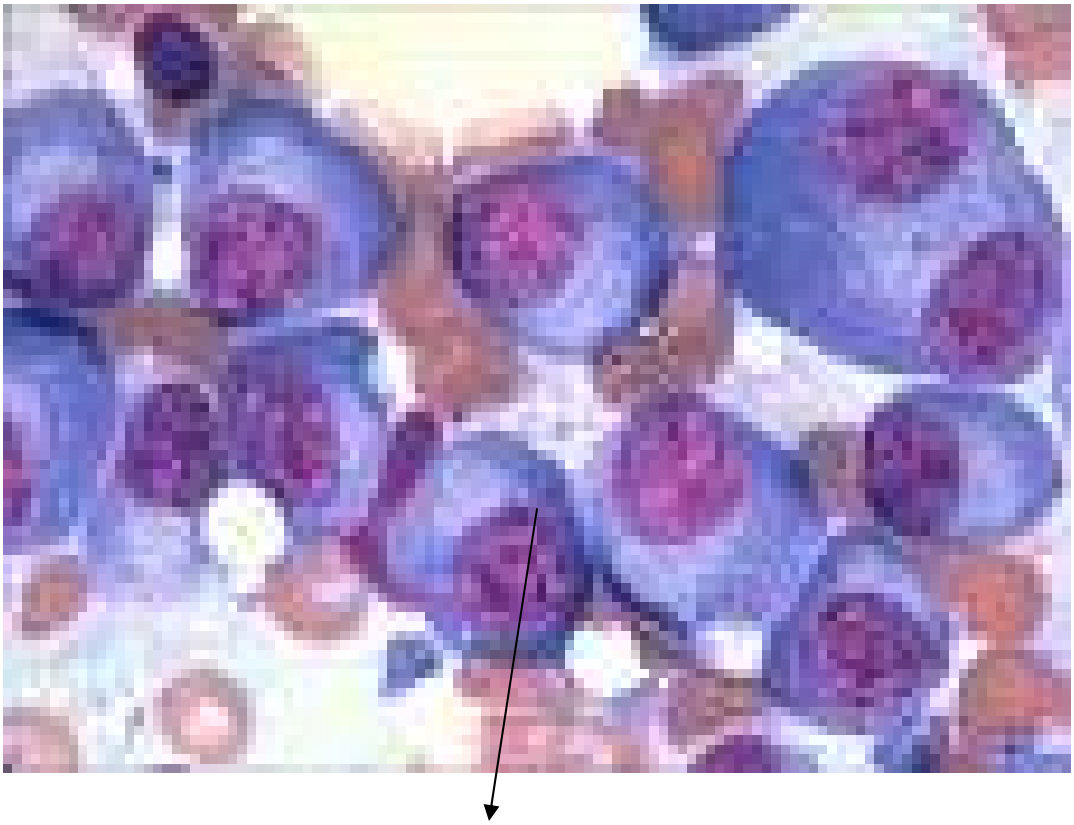
PATHOGENESIS OF MULTIPLE MYELOMA

LYTIC LESIONS IN VERTE BRAE

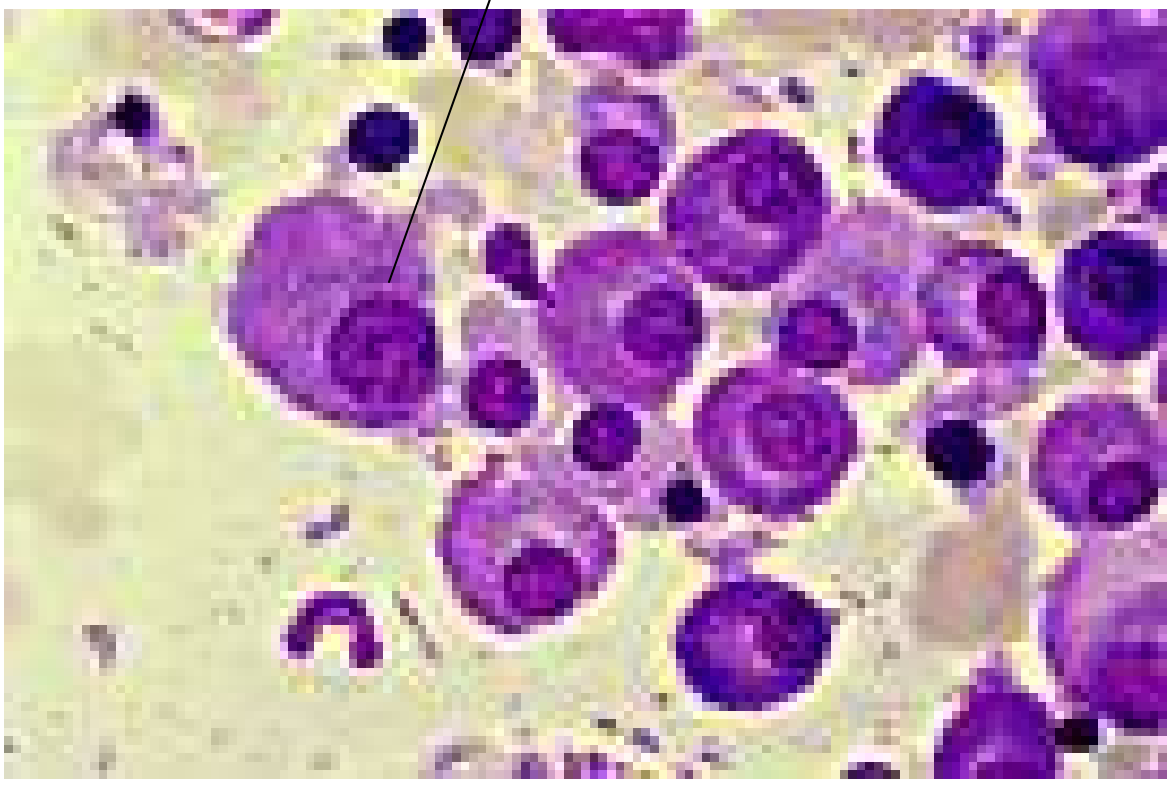



Compression Fx T4
Abnormal marrow signal secondary to Multiple Myeloma

MRI SPINE

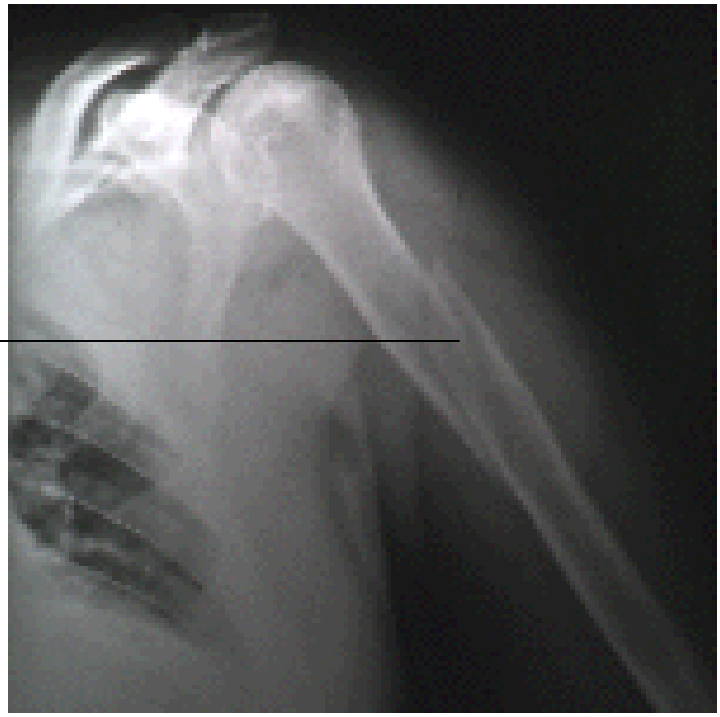


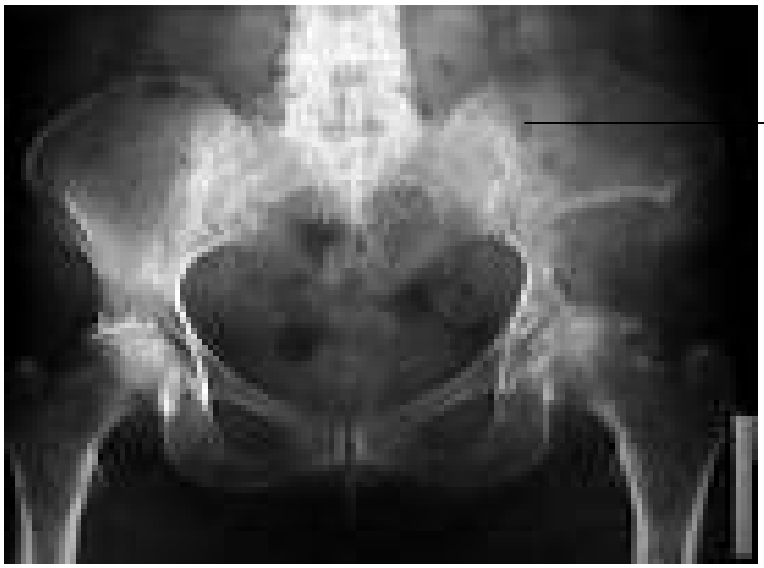
PLASMA CELLS



DR.DURIE.

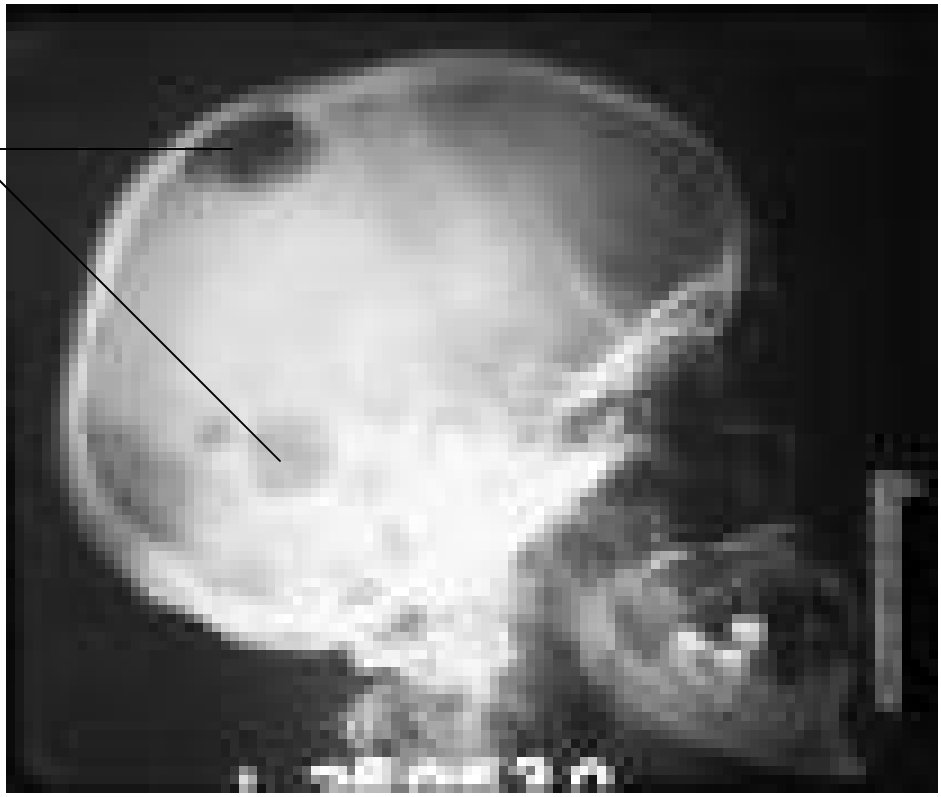
LYTIC LESION WITH PATHO LOGICAL FRACTURE





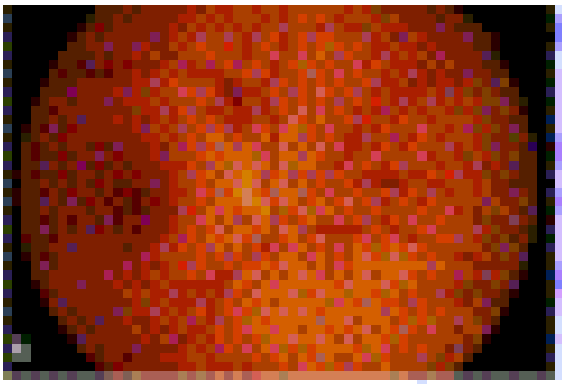
LYTIC LESIONS

LYTIC LESIONS

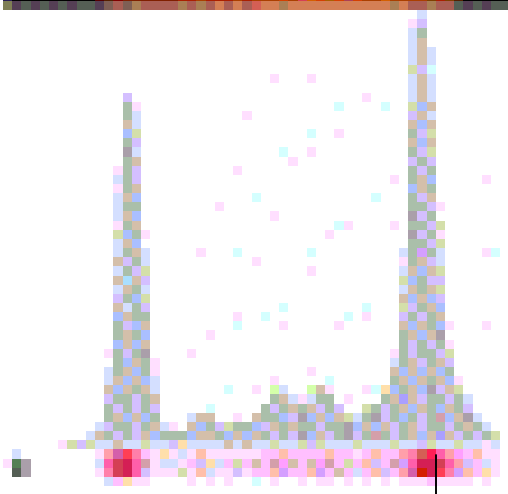


LYTIC LESIONS IN THE SKULL

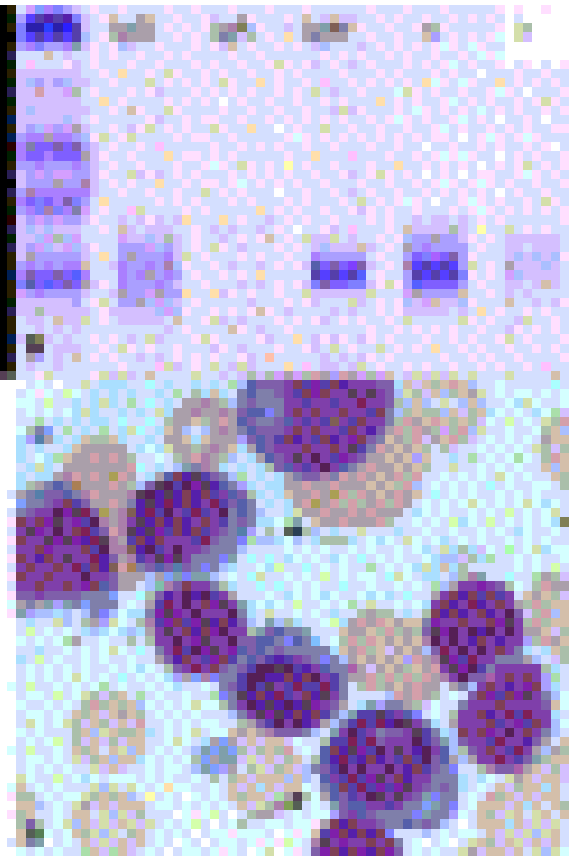
HYPEREMIC FUNDUS WITH PAPILLOEDEMA



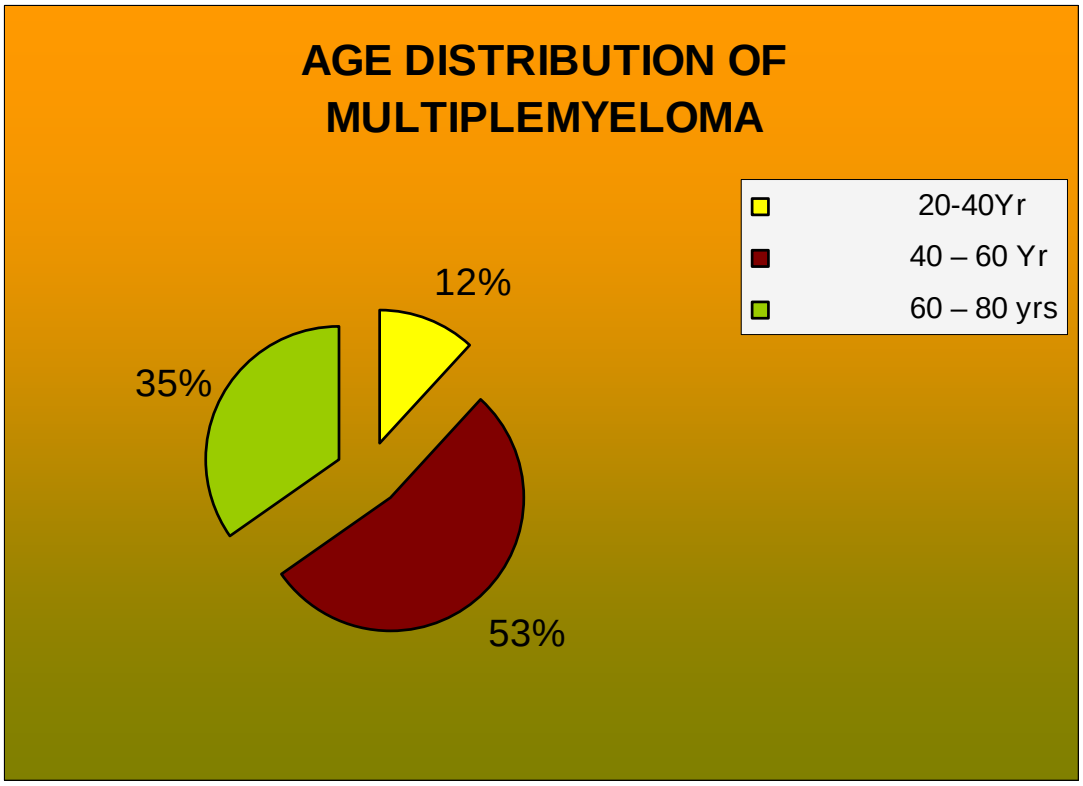
IMMUNOELECTROPHORESIS

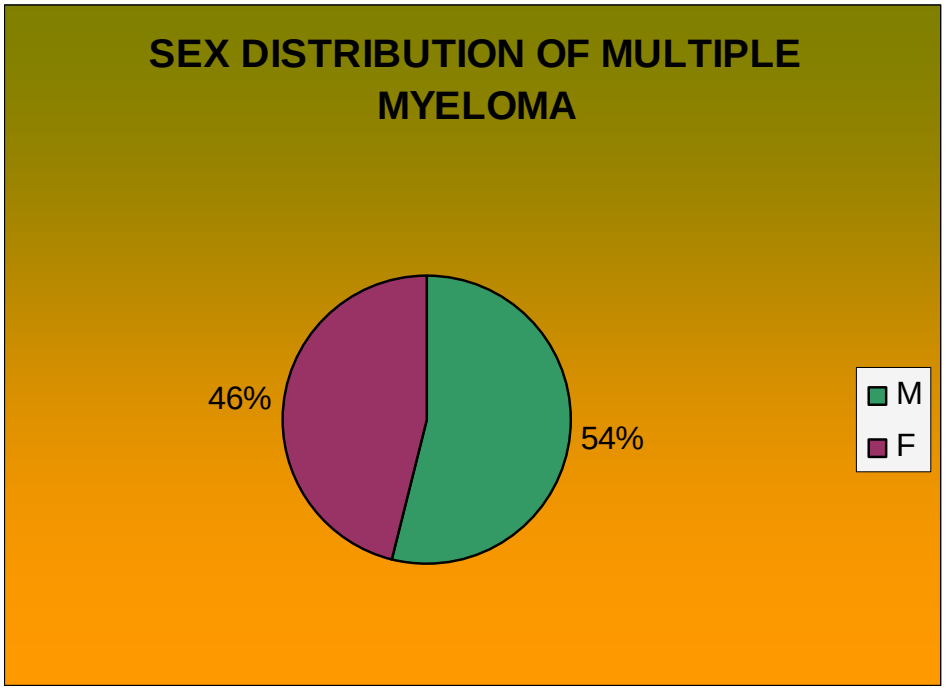


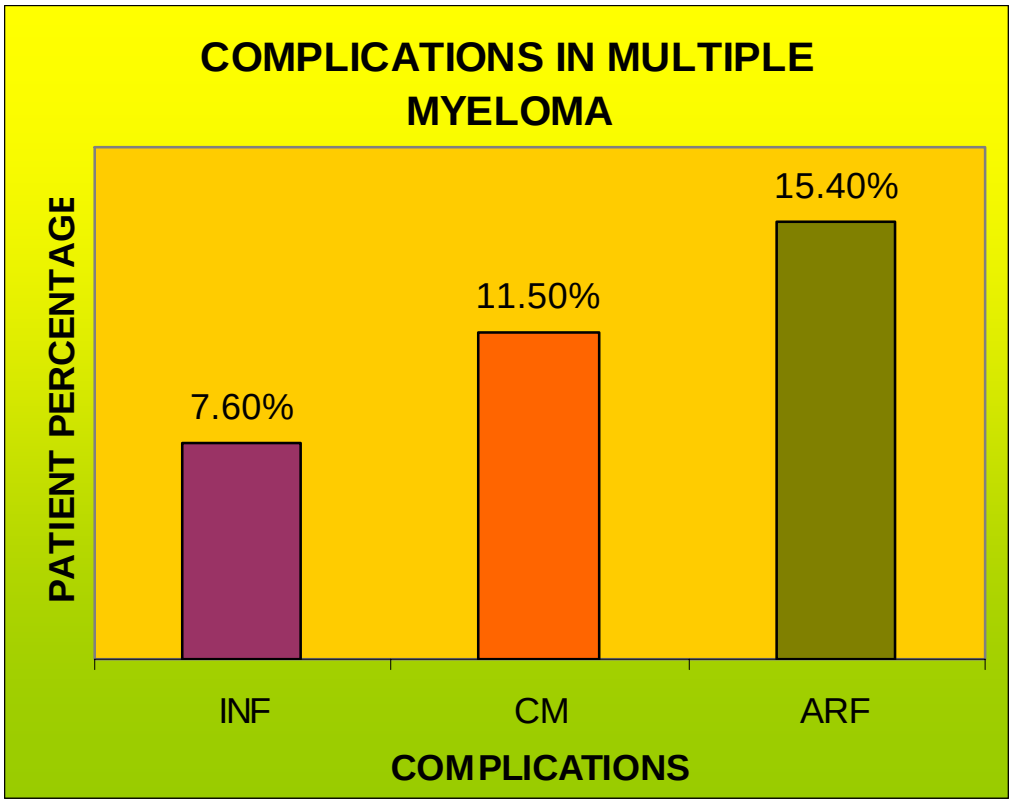
Myeloma band

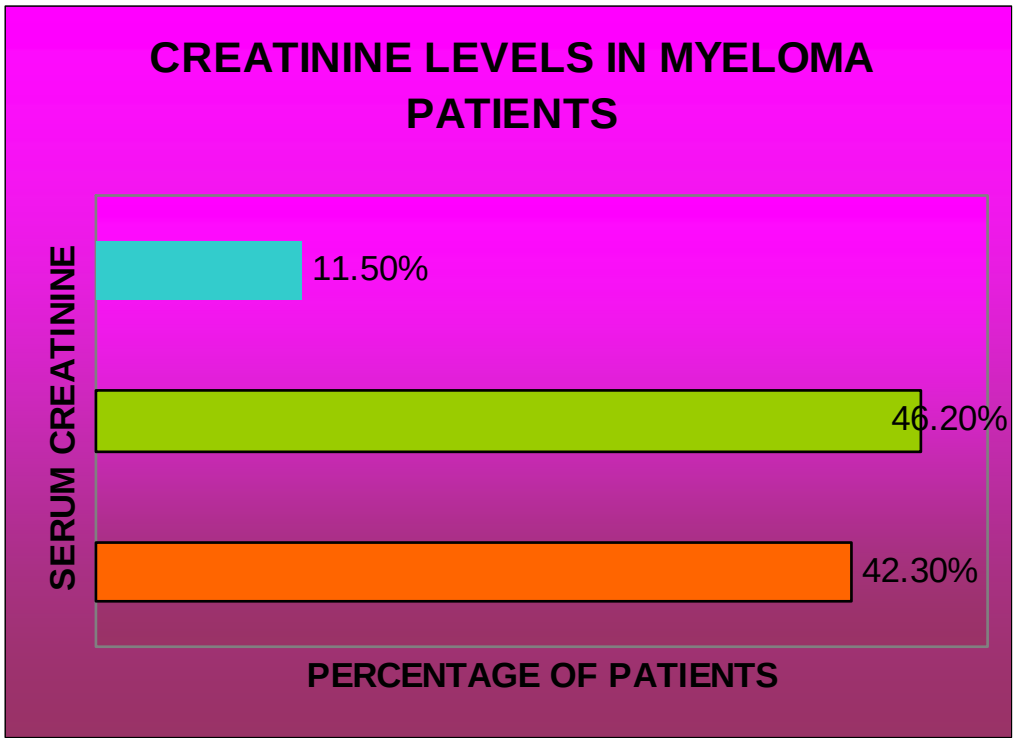


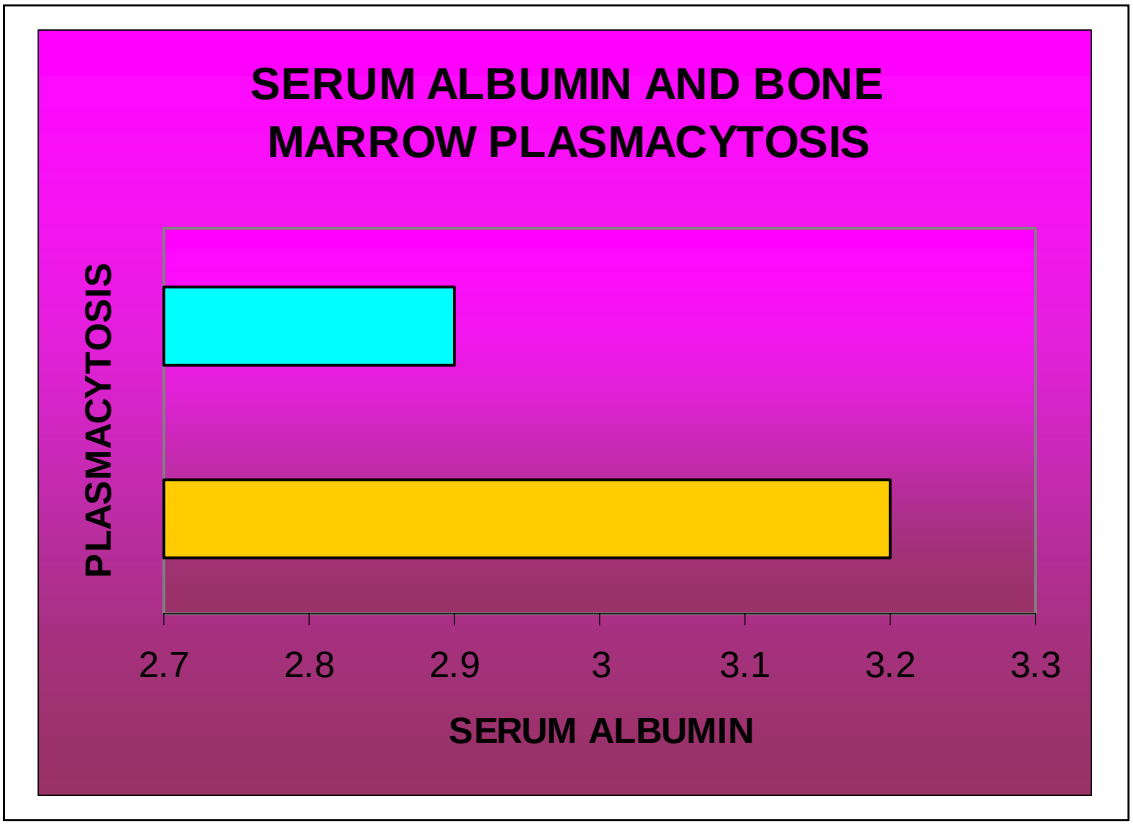
BONE MARROWPLASMACYTOSIS

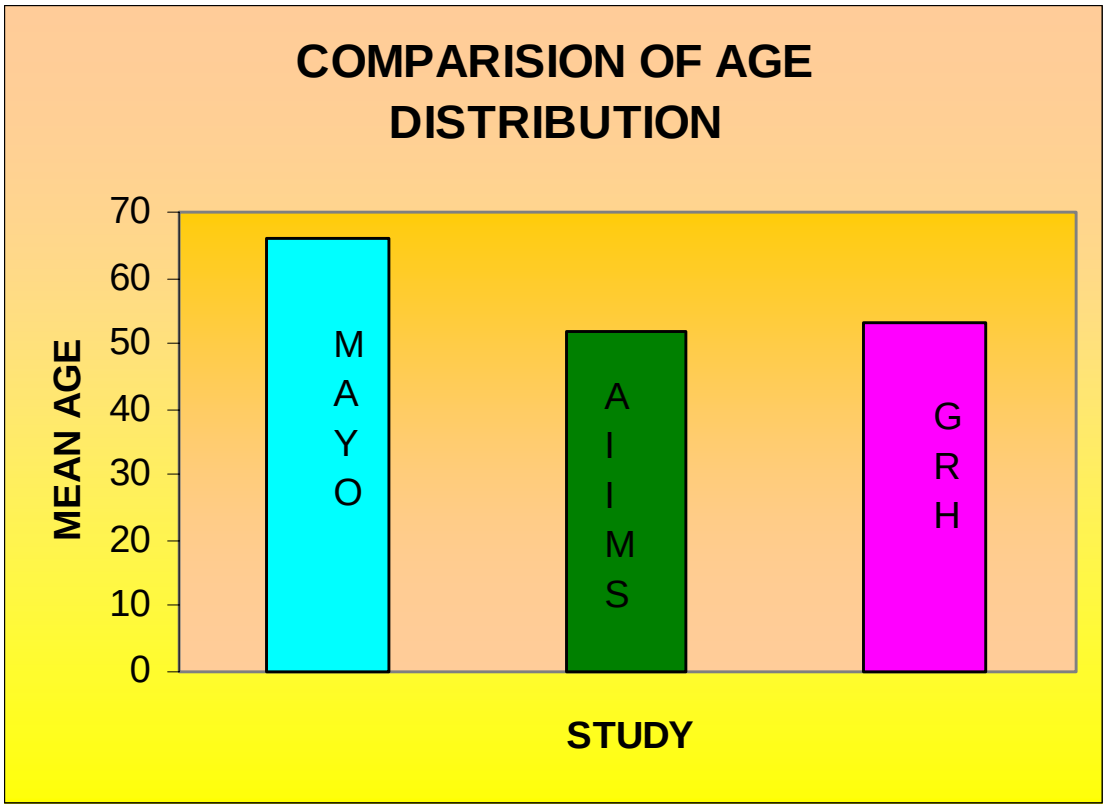

AGE DISTRIBUTION OF MULTIPLEMYELOMA
20-40Yr
40 – 60 Yr
60 – 80 yrs
12%
35%
53%

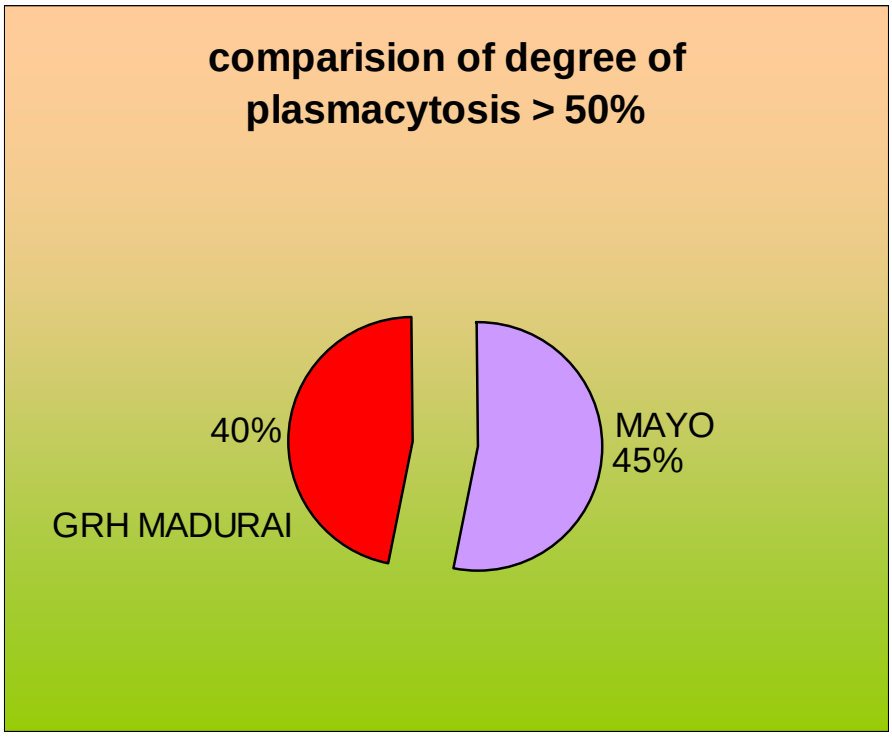

SEX DISTRIBUTION OF MULTIPLE MYELOMA
46%
54%
M
F


COMPLICATIONS IN MULTIPLE MYELOMA
PATIENT PERCENTAGE
7.60%
11.50%
15.40%
INF
CM
ARF
COMPLICATIONS


CREATININE LEVELS IN MYELOMA PATIENTS
SERUM CREATININE
11.50%
46.20%
42.30%
PERCENTAGE OF PATIENTS


SERUM ALBUMIN AND BONE MARROW PLASMACYTOSIS
PLASMACYTOSIS
2.7
2.8
2.9
3
3.1
3.2
3.3
SERUM ALBUMIN


COMPARISION OF AGE DISTRIBUTION
MEAN AGE
70
60
50
40
30
20
10
0
MAYO
AIIMS
GRH
STUDY


comparision of degree of plasmacytosis > 50%
40%
GRH MADURAI
MAYO
45%