INTRODUCTION

Renal failure is a common feature of multiple myeloma provides a clue to the diagnosis of this disease and may pose a major management problem. Depending on the definition of renal failure, this complication occurs in 20-40% of newly diagnosed patients with multiple myeloma. The major causes of renal failure are the precipitation of monoclonal light chains in distal and collecting renal tubules and hypercalcemia. Dehydration, hyperuricemia, and administration of analgesics or antibiotics with nephrotoxic potential also contribute to the development of renal failure ***(San Miguel & Garcia-Sanz, 2005).***

Kidney failure is a known complication of hematologic malignancy. Common causes include direct parenchymal infiltration by leukemic cells, intrarenal leukostasis, tumor lysis syndrome, fanconi syndrome, cryoglobulinemia, paraprotein deposition disease, obstruction, and chemotherapy-induced tubular or vascular toxicity ***(Perazella et al., 1993).***

Leukemia can adversely impact on the kidneys in several ways. In most cases, leukemia-associated decreased kidney function is caused by parenchymal infiltration of leukemia cells, tumor lysis, thrombotic microangiopathy, radiation injury, or toxicity from chemotherapy ***(Humphreys et al., 2004).***

Hematologic neoplasia can affect kidneys in a number of ways. In addition glomerulopathies, tubulointerstitial disease, and fluid and electrolyte abnormalities can occur. These disorders may be related to the disease or be a complication of treatment ***(Maldonodo. et al., 1988).***

Newer drugs, namely the DNA methylation inhibitors azacitidine and decitabine, may have clinical activity in chronic myelomonocytic leukemia (CMML), although the effect on kidney function has not been specifically reported ***(Kantarjian et al., 2007).***

Treatment of the underlying leukemia may improve kidney function ***(Aribi et al., 2007).***

Tumor lysis syndrome (TLS) describes a combination of metabolic abnormalities that occur due to the release of nuclear and cytoplasmic degradation products of malignant cells. TLS is usually seen upon the initial treatment of a newly diagnosed malignancy, but it has been known to occur spontaneously in patients with newly diagnosed cancer, even prior to the start of their treatment ***(Cairo & Bishop, 2004).***

Renal involvement is frequently seen in patients with lymphoma. However, the entity primary renal lymphoma (PRL) is controversial and rare. The term PRL is applied

when the disease is localized to the kidney without any sign of other organ involvement or in whom renal involvement is the presenting manifestation ***(Tefekli et al., 2006).***

Rarely, kidney failure is the presenting sign of lymphoma, and probably kidney failure due to bilateral infiltration of the kidneys is the rarest cause of acute renal failure in lymphoma ***(Chin et al., 1999).***

Aim of the essay

The aim of the essay is to review the renal involvement in different hematologic malignancies as regards the diagnosis and recent investigations in order to assess the impact on therapeutic decisions and prognosis.

CHAPTER (1): MULTIPLE MYELOMA

Multiple myeloma, also known as **plasma cell myeloma**, is a cancer of plasma cells, a type of white blood cells normally responsible for the production of antibodies. Collections of abnormal cells accumulate in bones, where they cause bone lesions, and in the bone marrow, where they interfere with the production of normal blood cells (Fig 1). Most cases of myeloma also feature the production of a paraprotein, an abnormal antibody that can cause kidney problems and interferes with the production of normal antibodies leading to immunodeficiency. Hypercalcemia (high calcium levels) is often encountered ***(Raab et al., 2009).***

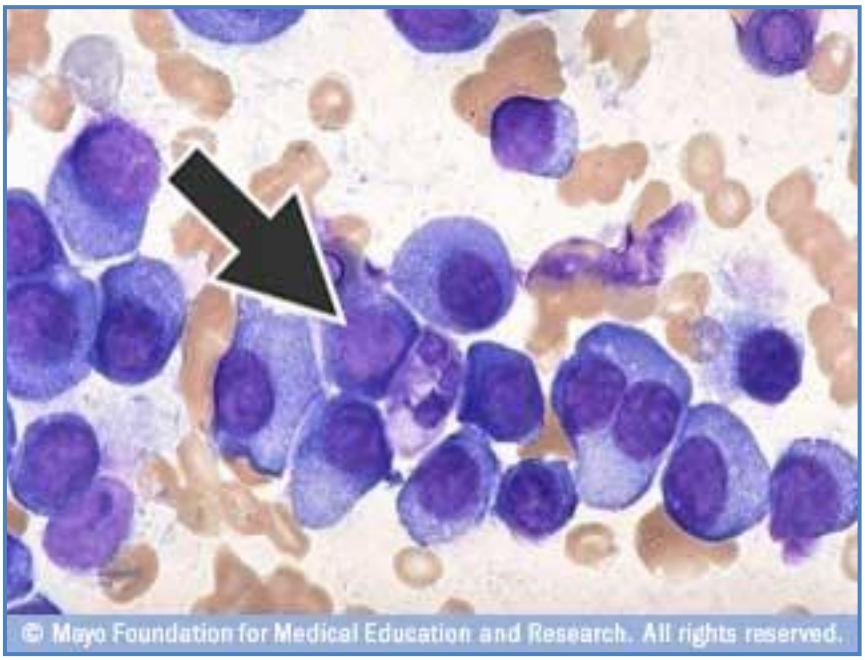


Fig. (1): This bone marrow tissue sample shows myeloma cells (bluish-stained cells). These cells crowd out normal bone marrow cells)

Epidemiology

Multiple myeloma is the second most prevalent blood cancer (10%) after non-Hodgkin's lymphoma. It represents approximately 1% of all cancers and 2% of all cancer deaths. Although the peak age of onset of multiple myeloma is 65 to 70 years of age, recent statistics indicate both increasing incidence and earlier age of onset ***(Collins, 2005).***

The disease develops in 1-4 per 100,000 people per year. It is more common in men, and is twice as common in blacks as it is in whites. With conventional treatment, the prognosis is 3-4 years, which may be extended to 5-7 years or longer with advanced treatments ***(Raab et al., 2009).***

Pathophysiology

A chromosomal translocation between the immunoglobulin heavy chain gene (on the fourteenth chromosome, locus 14q32) and an oncogene (often 11q13, 4p16.3, 6p21, 16q23 and 20q11) is frequently observed in patients with multiple myeloma. This mutation results in dysregulation of the oncogene which is thought to be an important initiating event in the pathogenesis of myeloma. The result is proliferation of a plasma cell clone and genomic instability that leads to further mutations and translocations. The chromosome 14 abnormality is observed in about 50% of all cases of myeloma. Deletion of (parts of) the thirteenth chromosome is also observed in about 50% of cases ***(Kyle et al., 2004).***

Staging

International Staging System (ISS) ***(Greipp et al., 2005).***

- Stage I: β2-microglobulin (β2M) <3.5 mg/L, albumin ≥3.5 g/dL
- Stage II: β2M <3.5 mg/L and albumin <3.5 g/dL; or β2M 3.5 mg/L -5.5 mg/L irrespective of the serum albumin
- Stage III: β2M ≥ 5.5 mg/L

Note that the ISS should be used only in patients who meet diagnostic criteria for myeloma. Patients with monoclonal gammopathy of undetermined significance (MGUS) and asymptomatic myeloma who have renal dysfunction from unrelated causes such as diabetes or hypertension may have elevated β2M levels just from the renal dysfunction and cannot be considered as stage III myeloma. This is one of the main drawbacks of the ISS. It does not really quantify tumor burden or extent unlike staging systems used in other cancers. It is more of a prognostic index rather than a true staging system. For this reason, it is recommended that the ISS be used along with the Durie Salmon Staging System (see below).

Durie-Salmon staging system.

First published in 1975, the Durie-Salmon staging system ***(Durie and Salmon, 1975)*** is still in use:

- Stage I: all of
  - Hb >10g/dL
  - Normal calcium

- Skeletal survey: normal or single plasmacytoma or osteoporosis
- Serum paraprotein level <5 g/dL if IgG, <3 g/dL if IgA
- Urinary light chain excretion <4 g/24h

- Stage II: fulfilling the criteria of neither I nor III
- Stage III: one or more of
  - Hb <8.5g/dL
  - High calcium >12 mg/dL
  - Skeletal survey: Three or more lytic bone lesions
  - Serum paraprotein >7g/dL if IgG, >5 g/dL if IgA
  - Urinary light chain excretion >12g/24h

Stages I, II, and III of the Durie-Salmon staging system can be divided into A or B depending on serum creatinine:

- A: serum creatinine <2 mg/dL (<177 umol/L)
- B: serum creatinine >2 mg/dL (>177 umol/L)

Diagnosis

The diagnosis of myeloma requires (1) 10% or more clonal plasma cells on bone marrow examination or a biopsy proven plasmacytoma and (2) evidence of end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions) that is felt to be related to the underlying plasma cell disorder (table 1) ***(Rajkumar, 2009).***

When multiple myeloma is suspected clinically, patients should be tested for the presence of M proteins

using a combination of tests that should include a serum protein electrophoresis, serum immunofixation, and the serum-free light chain (FLC) assay ***(Katzmann et al., 2006).***

Bone marrow studies at the time of initial diagnosis should include conventional karyotyping to detect hypodiploidy and deletion 13, and fluorescent in situ hybridization designed to detect t(11;14), t(4;14), t(14;16), t(6;14), t(14;20), hyperdiploidy, and deletion 17q ***(Kapoor et al., 2009).***

Gene expression profiling if available can provide additional prognostic value ***(Shaughnessy, 2009).***

Serum cross-laps to measure carboxy-terminal collagen cross links may be useful in assessing bone turnover and to determine adequacy of bisphosphonate therapy, although plain radiographs of the skeleton are typically required to assess the extent of bone disease, PET-CT and MRI scans are more sensitive and are indicated when symptomatic areas show no abnormality on routine radiographs ***(Comenzo et al., 2009).***

The M protein is monitored by serum and urine protein electrophoresis to assess treatment response, the serum FLC assay can be used to monitor patients who lack a measurable M protein ***(Merlini et al., 2009).***

Clinical picture

Because many organs can be affected by myeloma, the symptoms and signs vary greatly. A mnemonic sometimes used to remember the common tetrad of multiple myeloma is CRAB: C = Calcium (elevated), R = Renal failure, A = Anemia, B = Bone lesions. Myeloma has many possible symptoms, and all symptoms may be due to other causes (table 1) (***International Myeloma Working Group, 2003).***

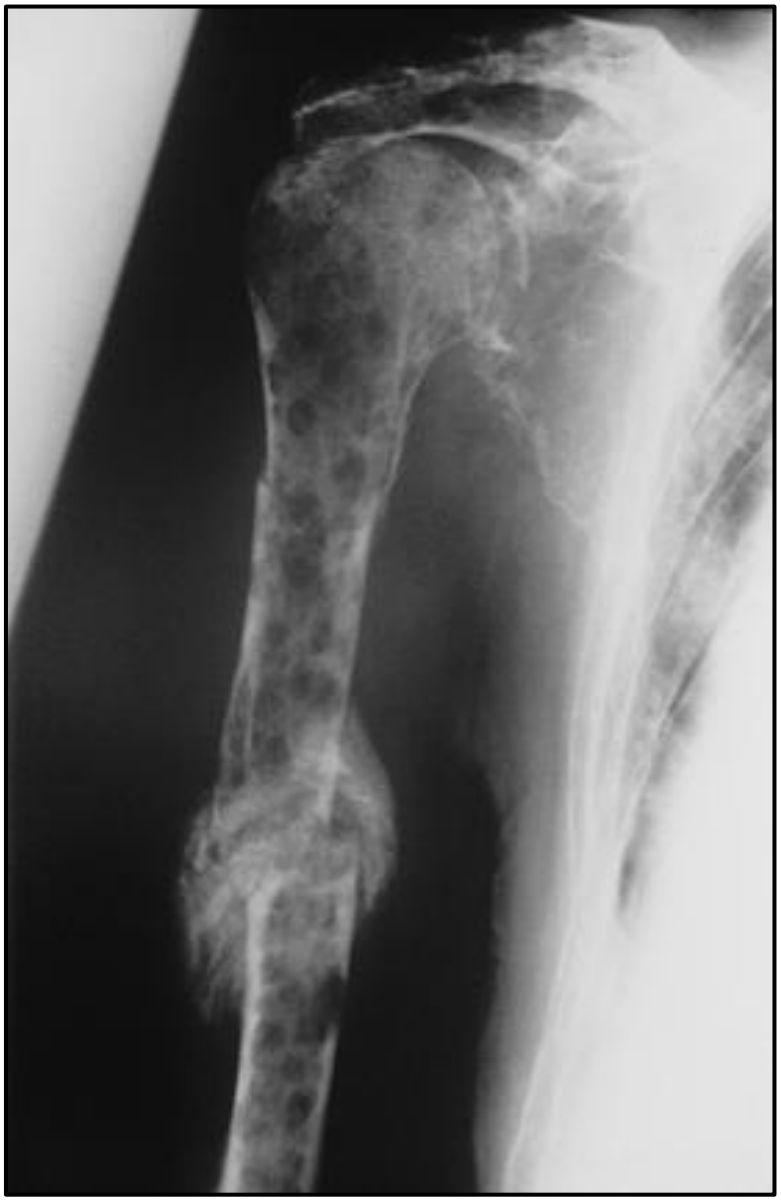
Table (1): Common Clinical Features Associated with Multiple Myeloma.

Clinical Feature	Common Cause(s)
Nausea, confusion, Polyuria	Elevated calcium, renal insufficiency
Fatigue	Anemia, renal insufficiency
Bone pain	Osteolysis, pathologic fractures
Paraplegia	Spinal cord compression
Confusion and blurred vision	Hyperviscosity
Bleeding	Thrombocytopenia
Skin nodules	Plasma cell tumors
Clinical features of amyloidosis	AL amyloid deposits
Bacterial Infections	Immune deficiency

Extra renal features:-

***Bone pain:-** Bone destruction is characteristic, and the associated bone pain a major cause of morbidity in myeloma. Myeloma is associated with abnormal bone remodeling due to increased osteoclastic bone resorption and inhibition of osteoblastic bone formation. This results in pronounced bone loss and the characteristic osteolytic

lesions predisposing to pathological fractures. Widespread bone destruction may lead to hypercalcemia, resulting in a vicious cycle of dehydration, worsening hypercalcemia, and renal failure.



Radiograph showing multiple lytic lesions and pathological fractures of humerus.

The most common presenting complaint is bone pain, commonly affecting the back ***(Singer, 2007).***

Infection:-** The most common infections are pneumonias and pyelonephritis. Common pneumonia pathogens include S. pneumonia, S. aureus, and K. pneumonia, while common pathogens causing pyelonephritis include E. coli and other gram-negative organisms. The greatest risk period for the occurrence of infection is in the initial few months after the start of chemotherapy. The increased risk of infection is due to immune deficiency resulting from diffuse hypogamma-globulinemia, which is due to decreased production and increased destruction of normal antibodies ***(Hargreaves et al., 2005).

Anemia:-** The anemia found in myeloma is usually normocytic and normochromic. It results from the replacement of normal bone marrow by infiltrating tumor cells and inhibition of normal red blood cell production (hematopoiesis) by cytokines ***(Hargreaves et al., 2005).

Neurological symptoms:-** Common problems are weakness, confusion and fatigue due to hypercalcemia. Headache, visual changes and retinopathy may be the result of hyperviscosity of the blood depending on the properties of the paraprotein. Finally, there may be radicular pain, loss of bowel or bladder control (due to involvement of spinal cord leading to cord compression) or carpal tunnel syndrome and other neuropathies (due to infiltration of peripheral nerves by amyloid). It may give rise to paraplegia in late presenting cases ***(Hargreaves et al., 2005).

Renal features:-

Plasma cell myeloma (PCM) is the most common neoplasm causing end-stage renal disease (ESRD) and is the first malignancy that was an indication for dialysis ***(De Meester et al., 2010).***

PCM patients account for 2% of the dialysis population adding 5000 new patients each year worldwide ***(Jagannath et al., 2010).***

Up to 50%of newly diagnosed PCM patient can present with renal insufficiency (serum creatinine >1.3 mg/dl), with 20% with severe renal impairment (serum creatinine >2-2.5 mg/dl) and 10% needing dialysis ***(Knudsen et al., 2000).***

Renal impairment and especially dialysis dependency is an independent poor prognostic factor for survival, with the majority of patients requiring dialysis unable to achieve renal recovery ***(Haynes et al., 2010).***

Pathophysiology of Renal Impairment in Myeloma

Renal dysfunction in multiple myeloma(MM) results primarily from the toxic effects of monoclonal light chain on the kidney, in addition to other contributing factors such as dehydration, hypercalcemia, hyperuricemia, the use of nephrotoxic drugs (nonsteroidal anti-inflammatory drugs, antibiotics, contrast media, etc.), and, rarely, myeloma cell infiltration or hyperviscosity ***(Dimopoulos et al., 2008).***

Light chain deposition disease (LCDD):

Up to 70% of all LCDD cases develop in the course of MM; the remaining 30% may be caused by other diseases. This type of renal manifestation is quite rarely diagnosed on autopsy, whereas it is present in 20% to 25% of the cases of renal biopsies performed in patients with MM (which is obvious given the fact that proteinuria and nephrotic range proteinuria are the best-recognized indications for biopsy). Patients with LCDD are younger than those with other types of renal involvement (median age, 58 years), almost universally manifest with heavy proteinuria, and, in most cases, with elevated serum creatinine. In about 35% of the cases, LC deposits can also be found in other organs, most frequently in the heart and liver ***(Hutchison et al., 2011).***

Myeloma cast nephropathy:

Cast nephropathy is the main cause of renal impairment in MM (~90% of cases) and is characterized by tubular atrophy and tubular-interstitial fibrosis. Normally, light chains are filtered by the glomerulus, reabsorbed, and catabolized by the cells of the proximal tubule. In myeloma, the abundance of light chains overwhelms the capability of the proximal tubular cells, raising the concentration of light chain delivered to the distal tubule. The characteristic finding of "myeloma kidney" is the presence of myeloma casts, composed mainly of light chains and Tamm-Horsfall protein in the distal tubules and collecting ducts ***(Dimopoulos et al., 2008).***

Myeloma cast nephropathy is associated with exceptionally poor prognosis for both renal and overall survival. The disorder is observed in more advanced stages of myeloma and is associated with extremely high plasma Light Chain levels. Myeloma cast nephropathy as an underlying cause of end-stage renal disease (ESRD) is also associated with significantly worsened survival after the start of dialysis compared with ESRD secondary to other forms of renal involvement due to MM ***(Korbet et al., 2006).***

Amyloidosis:

Amyloid (AL type) is found in less than 5% of the patients with MM on autopsy and in 15% to 35% patients with MM and renal symptoms who undergo renal biopsy. Since only from 15% to 35% of the patients with AL amyloidosis suffer from MM, most cases of AL amyloidosis seem to be primary disease. Survival of patients with AL amyloidosis is significantly worse compared with that of patients with LCDD, and the prognosis is worsened mainly by extrarenal deposits ***(Tsakiris et al., 2010).***

In proximal tubule cells, prolonged exposure to myeloma light chains induces apoptosis, DNA degradation, and the production of the inflammatory and proinflammatory cytokines that initiate renal interstitial fibrosis and tubular destruction ***(Herrera et al., 2007).***