Free-light chain multiple myeloma with raised IL-6 in a young Saudi farmer

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ABSTRACT
A case of multiple myeloma in a young Saudi farmer with free kappa chain in the urine is documented. It has revealed other interesting features including short history, multiple osteolytic lesions, high level of blood calcium and increased level of interleukin-6. The latter is a recently recognized indicator of poor prognosis.


Keywords: Multiple myeloma; free light chain; IL-6

Multiple myeloma (MM) is a malignant disease of plasma cells with clinical spectrum ranging from solitary tumors to extensive bone-marrow infiltration. Depending upon the type of immunoglobulin secreted, five main types are recognized: IgG myeloma (52-61%), IgA myeloma (19-22%), IgD myeloma (1-2%) light-chain myeloma (17-25%) and the rare IgE myeloma. It is a disease of the elderly, the mean age at diagnosis is over 60 years and only about 2% of cases occur in persons under 40 years of age. The diagnosis requires bone marrow examination for a documentation of an increase in bone marrow plasma cells, radiological studies for demonstrating the lytic lesions, and/or the evidence of paraprotein in the serum and/or urine. In addition recent studies show increased levels of cytokines such as interleukin-6 (IL-6) and interleukin-10 (IL-10) in such patients. The development of MM is rare occurring before the age of 30 years; this case-report documents such a rare presentation in a Saudi male farmer.

Case Report. A 22 year old Saudi male who works at a farm, and is a non-smoker presented to our hospital on February 11th 1996, with a complaint of inability to walk for three months. This was precipitated by lifting a heavy object when he felt a crack in his back bone followed by progressive weakness in his lower limbs. He sought medical advice in several private health care centers where he was given analgesics and anti-inflammatory agents. There was no history of loss of sensation, loss of sphenetic control, or of impotence. There was no constitutional symptoms. On clinical examination he was alert and oriented, but slightly pale (not jaundice). The cardio-respiratory and central nervous systems were normal, there was no lymph node enlargement or visceromegaly. There was, however tenderness over the dorsal vertebrae and ribs.

Investigations. i. Skeletal Survey: Multiple lytic lesions in 11th dorsal vertebra, parietal bones, both scapulae, and 6th ribs CT-Scan of the mid-dorsal and lower dorsal spine revealed multiple lytic lesions involving a number of mid dorsal vertebrae as well as at D9 and D10. No signs of obvious compression over the thecal sac or the cord at any levels (Figs 1 and 2).

ii. Routine hematological and biochemical investigations at time of admission revealed leucocytosis (WBC 12.4 x 10/L, neutrophil 89%), low hemoglobin (10.6gm/dl), and raised ESR (52mm/1st Hr), BUN (39mg/dl), serum creatinine (3.5mg/dl), and serum calcium (15.7mg/dl).

iii. Bone marrow aspirate and trephine biopsy were consistent with the diagnosis of multiple myeloma. There were clusters of plasma cells of which several were binucleate and showed nuclear and cytoplasmic atypia (Fig. 3).

iv. Immunochemical investigations: Protein electrophoresis on cellulose acetate membrane showed a small monoclonal band in the fast...
gamma(γ) region (Fig. 4). There was no increase in the levels of IgG (979mg/dl), IgA(71mg/dl), IgM(19mg/dl) measured by rate nephelometry, or IgE(120IU/ml) measured by ELLISA. In fact the levels of IgA and IgM were lower than expected (Normal range for Saudis IgA:100-400mg/dl, IgM: 50-200mg/dl) IgD was not measured, but its presence was excluded by the absence of precipitation line in Ouchterlony plate. Urine collected over 24 hrs showed a protein content of 2.4 gm. Cellulose acetate membrane electrophoresis of unconcentrated urine revealed a faint monoclonal band in the gamma region with no albumin band. The monoclonal band was still barely visible suggesting presence of low molecular weight free light chain. This was confirmed by EELISA showing antibodies to heavy chains (i.e. γ, α, μ, δ and ε) and kappa and lambda light chains. Only kappa light chain (without intact immunoglobulin molecule) was detectable in the urine confirming the presence of free kappa-light chain.

v. Immunohistology: Section of bone marrow biopsy were stained by standard alkaline phosphatase-antialkaline phosphatase (APAAP) technique using monoclonal antibodies against human kappa and lambda light chains (DAKO, Denmark). Endogenous alkaline phosphatase was blocked by levamisole: more than 90% of the plasma cells revealed the presence of kappa light chain confirming their monoclonality.

vi. Enzyme immunoassay: Serum collected at the time of presentation was deep-frozen and tested later for interleukin-6 (IL-6) by ELISA using commercial kit (Genzyme, Cambridge, MA). The level of IL-6 in this patient was raised i.e. 32pg/ml (normal range for this lab 1-6pg/ml).

Treatment and follow up. The patient was referred to Oncology unit where he was given 2000c-Gy to his spine and was put on chemotherapy which on day 1 consisted of vincristine 2mg iv, BCNN 34mg iv (20mg/m2), melphalan 40mg po for 4 days, cyclophosphamide 680mg iv (400mg/m2). He received prednisone 70mg a day for 7 days and tapered to 35mg and discontinued. A second course of chemotherapy was given 3 weeks later; it consisted of vincristine 1mg, BCNN 50mg and doxorubicin 50mg on day 1. Prednisone was given 100mg daily for 5 days.

Immunoenzyme profile: serum immunoglobulin and urinary free light chain were retested three months after the course of chemotherapy. There was, however, further reduction in the levels of IgG (651mg/dl) IgA (25mg/dl) and IgM (17mg/dl). Serum protein electrophoresis still showed presence of monoclonal band in the γ-region and concentrated urine revealed presence of monoclonal band consisting of free kappa light chain.
resistance gene i.e. MRD-1, and expression of CD56 on tumor cells. Thus the present case report has several interesting features including short history, young age, multiple osteolytic lesions, free light chain tumor, high level of calcium, and increased production of IL-6. Raised level of IL-6 in contrast to IL-10 is thought to be associated with bad prognosis, a slow response to treatment in this patient supports this viewpoint.

References


Discussion

MM is a neoplastic disease with an incidence of 1-2 per 100,000 population in whites and 2-3 per 100,000 population in blacks per year in the USA. It is not uncommon in Saudi Arabia, and its incidence although not well studied appears similar to that generally reported in the literature. MM is a disease of the elderly, the median age of onset being 68 yrs and 70 yrs for men and women respectively. It is extremely rare before 30 yr of age. Badwey et al., Lazarus and associates, and Ishida and coworkers have comprehensively reviewed the issue of MM in young people. They could document only 32 possible cases occurring before the age of 30 years. Only half of them were found to satisfy the diagnostic criteria of MM. This report presents an additional case to well documented cases of patients with MM with onset before the age of 30 years, and to the best of our knowledge this may be the first in Saudi Arabia and the Middle East. In addition to the early age of onset, this case has other interesting features such as being free light chain (kappa) myeloma and its development in a farmer. Previous epidemiological studies have documented that workers in the agricultural sector are prone to several occupational health hazards, including development of MM. Furthermore light chain myeloma represents only a fifth of all cases of myeloma and as documented in this case report it shows a rapid growth and is often associated with extensive osteolytic lesions with raised serum calcium. A variety of regimen has been developed for the treatment of multiple myeloma, but the response is variable partly due to the biological behavior of the tumor including aneuploidy, activation of multidrugs.