EXTRAMEDULLARY RELAPSE OF MULTIPLE MYELOMA

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Abstract:
Multiple myeloma (MM) is characterized by malignant proliferation of clonal plasma cells that usually produce a unique immunoglobulin molecule (1). Extramedullary myeloma (EM) is a type of MM defined by the presence of extraskeletal (ie. Soft tissue or visceral) plasma cell infiltrates. EM can be present either initially at the time of diagnosis (ie. Primary) or at the time of relapse (ie. Secondary) (2). However both are associated with extremely poor prognosis (3). Here we describe a 56 year old gentleman who underwent an autologous transplant for light chain myeloma (Lambda light chain) in VGPR and who presented six months later with abdominal pain, anorexia and weight loss and was found to have extramedullary relapse of myeloma involving liver, spleen and lungs.

Case Report:
A 56 year old gentleman with no past medical or surgical comorbidities presented with a 3 month history of left sided chest pain in Oct 2011. During evaluation, he was found to have expansile lytic lesion involving the ribs on the left side with an associated soft tissue component. Further investigations revealed anemia (Hb of 8.6g%), deranged creatinine (1.4 g%) with urine Bence Jones proteinuria and a very low Kappa lambda light chain ratio (0.02) and immunofixation electrophoresis is a type of MM defined by the presence of extraskeletal (ie. Soft tissue or visceral) plasma cell infiltrates. EM can be present either initially at the time of diagnosis (ie. Primary) or at the time of relapse (ie. Secondary) (2). However both are associated with extremely poor prognosis (3). Here we describe a 56 year old gentleman who underwent an autologous transplant for light chain myeloma (Lambda light chain) in VGPR and who presented six months later with abdominal pain, anorexia and weight loss and was found to have extramedullary relapse of myeloma involving liver, spleen and lungs.

Keyword: Multiple myeloma, extramedullary myeloma

Introduction
Multiple myeloma (MM) is characterized by malignant proliferation of clonal plasma cells that usually produce a unique immunoglobulin molecule (1). Extramedullary myeloma (EM)
showed Lambda light chain. Bone marrow examination showed 58% plasma cells some with plasmablastic features (IHC showed CD138 positivity and D56 negativity). An extensive skeletal survey was done which did not show any other lytic lesions except for the lesion on the ribs on the left side. A diagnosis of lambda light chain multiple myeloma was made. He received five cycles of chemotherapy with Bortezomib, Dexamethasone and Doxorubicin (PAD). Due to poor initial response, this was followed by 5 cycles of Cyclophosphamide, Thalidomide and Dexamethasone (CTD). He achieved a very good partial response (VGPR) with this combination and hence an autologous transplant was planned. Stem cells were collected with Cyclophosphamide chemomobilization and a CD34 cell dose of 2.68 x 10^6 CD34/Kg was obtained. Autologous autologous stem cell transplant was performed on 17.11.2012 using High dose Melphalan (200 mg/m^2).

Lenalidomide maintenance was started in February 2013. He presented in May 2013 with two weeks history of anorexia, diffuse upper abdominal pain and weight loss. On clinical examination he looked emaciated, and pale. Examination of the abdomen revealed tender firm hepatomegaly of 6 cm below the right costal margin and spleen was also palpable 6 cm below left costal margin. The rest of the system examination was normal. Blood investigations revealed Hemoglobin of 9 gm%, WBC count of 4100/cumm with a differential count of 36% neutrophils, 49% lymphocytes and 15% monocytes; and platelet count of 25000/cumm. Serum creatinine was 1.26mg% and serum LDH was 1499 U/L. His liver function showed conjugated hyperbilirubinemia with transaminitis and elevated alkaline phosphatase (428 U/L). There was hyperuricemia (uric acid of 8 mg %). Ultrasonography of abdomen showed hepatosplenomegaly (Liver-19cm and spleen-16cm) with multiple illdefined hypoechoic and target lesions suggestive of metastasis. CT abdomen and Thorax showed multiple scattered pulmonary nodules and mild left pleural effusion. There was also moderate hepatomegaly with multiple arterially enhancing focal lesions noted involving the entire liver parenchyma measuring 11-18mm, some of them being confluent lesions and mild splenomegaly(fig.1). There were multiple expansile lytic lesions noted involving the ribs and vertebrae, both iliac bones, right femoral head. In view of bicytopenia and previous diagnosis of multiple myeloma, a repeat bone marrow was done which showed 11% abnormal plasma cells. So a differential diagnosis of relapsed extramedullary myeloma vs secondary malignancies was considered. A diagnostic ultrasound guided biopsy of the liver lesions were planned. However patient became febrile and tachypneic with an arterial blood gas analysis showing metabolic acidosis with elevated lactate levels. A clinical diagnosis of sepsis was made and he was empirically started on antibiotics and other supportive measures. His clinical condition progressively worsened and he was shifted to the intensive care unit where he subsequently got intubated and finally succumbed to the sepsis following a cardiac arrest. Due to the uncertainty in diagnosis, consent was obtained from the relatives for a post mortem liver biopsy. Liver biopsy revealed infiltrates of plasma cells and plasmablasts suggestive of relapsed multiple myeloma in the liver.

Discussion:

Multiple myeloma accounts for 80% of plasma cell malignancies(4). It is characterized by the deposit of neoplastic plasma cells in the bone marrow
as well as extramedullary sites (plasmacytoma).
However, the latter is uncommon and present in only 4.6% of patients with multiple myeloma with the commonest extramedullary sites being the lungs, liver and upper respiratory tract (5). Extramedullary myeloma (EM) can be present either initially at the time of diagnosis (ie. Primary) or at the time of relapse (ie. Secondary). Clinically three types of extramedullary lesions can be described: a) a tumour mass adjacent to the bone and extending to the soft tissues (EM-B), b) soft tissue or visceral tumour not connected to the bones (EM-S), c) diffuse infiltration of organs by plasma cells without any focal lesion(1). EM as been mostly studied in patients treated with high dose chemotherapy and especially in cases of relapsed disease. The current notion that EM involvement are more frequent after treatment with novel agents remains to be proven. Bone marrow genetic abnormalities are not associated with extramedullary spread per se(6). This suggests that microenvironmental interactions are key to EM. Possible mechanisms of extramedullary spread include decreased adhesion molecule expression and down regulation of chemokine receptors(6). EM plasmacytomas usually show plasmablastic morphology with negative CD56 expression (6). This is true in our case where patient showed features of plasmablastic myeloma with CD56 negativity at diagnosis. Local growth is the most common mechanism in the development of EM and consists of soft-tissue masses arising from focal bone involvement, particularly vertebrae, ribs, sternum, skull, or pelvis. The hematogenous spread can consist of single or multiple large highly vascularized subcutaneous nodules with a red-purple appearance; multiple nodules, usually small, in the skin, liver, breast, or kidney, although any organ can be involved; lymph nodes; and CNS involvement. In this case the extramedullary involvement seems to secondary to haematogenous spread(6).

The incidence of EM has been estimated to be 10-15% of all MM relapses(7). Usmani et al in 1964 studied the incidence of EM at the time of diagnosis and at the time of relapse. The presence of EM at the time of diagnosis of MM was found to be between 2.4% - 4.5% while at relapse, it was 3.4% -7.2%. In another study by L. Pour et al, who studied 226 relapsed MM patients, excluding patients who had EM at diagnosis, the incidence of EM was 24%, 14% with EM-S and 10% with EM-B respectively (1). Even in the era of new drugs extramedullary myeloma is an incurable disease. In the study by L.Pour et al there was significant difference in survival between the patients in the EM-B Vs EM-S groups (12 months Vs 4 months)(1). Our patient presented with an aggressive relapse within 3 months after an autologous transplant and had a rapid progressive course. Outcomes of treatment at the time of relapse are associated with very poor outcomes and hence more aggressive strategies need to be considered early in their treatment plan.

References:


