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A NEWLY DIAGNOSED MULTIPLE MYELOMA WITH EXTRAMEDULLARY INVOLVEMENT OF THE LIVER: A RARE CASE REPORT FROM SYRIA

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ABSTRACT

Multiple myeloma is a malignant clonal proliferation of plasma cells in the bone marrow preceded by monoclonal gammapathy of undetermined significant. Extramedullary myeloma is an uncommon finding refers to the infiltration of neoplastic monoclonal plasma cells in either organs or soft tissues, with a more aggressive clinical course and poorer outcome. We herein describe a case of 65-year-old patient who presented with fatigue and severe low back pain. Ultrasound and CT scan of the abdomen showed multiple liver nodules. Biopsy of the liver nodules showed CD138 and kappa light chain-restricted positive cells consistent with extramedullary spread of multiple myeloma to the live. After 2 cycles of Cyclophosphamide, Revlimid, and Dexamethasone (CRd) the patient showed a partial response. Therefore, we decided to follow-up the same regimen. No controlled prospective studies have defined the standard treatment for multiple myeloma with extramedullary spread particularly to the liver. Treatment of multiple myeloma with extramedullary disease follows guidelines for multiple myeloma.

KEYWORDS: Multiple Myeloma, Extramedullary myeloma, Liver involvement, Nodular lesions.

INTRODUCTION

Multiple myeloma is a malignant clonal proliferation of plasma cells in the bone marrow preceded by monoclonal gammapathy of undetermined significant (MGUS).[1] Soft tissue involvement of Multiple myeloma (MM) is referred to as extramedullary myeloma (EM). EM has been described since the 19th century with a spectrum of presentation depending on the location of the tumor most commonly in organs containing reticuloendothelial cells such as liver, kidney, skin, and lymph nodes.[2] The incidence of EM with newly diagnosed MM is variable, ranging from 7% to 18%.[3,4] Moreover, 6% to 20% of patients develop EM later in the course of the disease.[3,5] In another case series, in 936 patients treated for MM, only 66 presented initially as EM with liver involvement in 21%.[6] Overall, the incidence of EM is higher at relapse than at diagnosis.[4,7] The mechanism of extramedullary involvement by multiple myeloma has been extensively reviewed by Blade et al.[7] We report the case of a patient with skeletal pain and multi nodular hepatic lesions who was ultimately diagnosed with MM with extramedullary spread to the liver.

CASE PRESENTATION

A 65-year-old male who had no significant background family or medical history, was admitted in the department of Hematology in Tishreen University Hospital (TUH)-Lattakia-Syria, for a diagnostic workup for fatigue and worsening low back and ribs pain. At addmition, physical examination showed a pallor, marked hepatosplenomegaly and lumbosacral region tenderness. Admission labs included hemoglobin 6.7 g/dL, creatinine 2,3 mg/dl, AST 24 IU/l, ALT 19 IU/L, and ESR 104 mm/hr. Routine Ultrasound (US) of the abdomen revealed, an enlarged liver with multiple nodular lesions of various size (Figure 1, A+B). The largest one in the right lobe (Figure 1, C), was barely visible on non-contrast enhanced computed tomography (Figure 1, D).

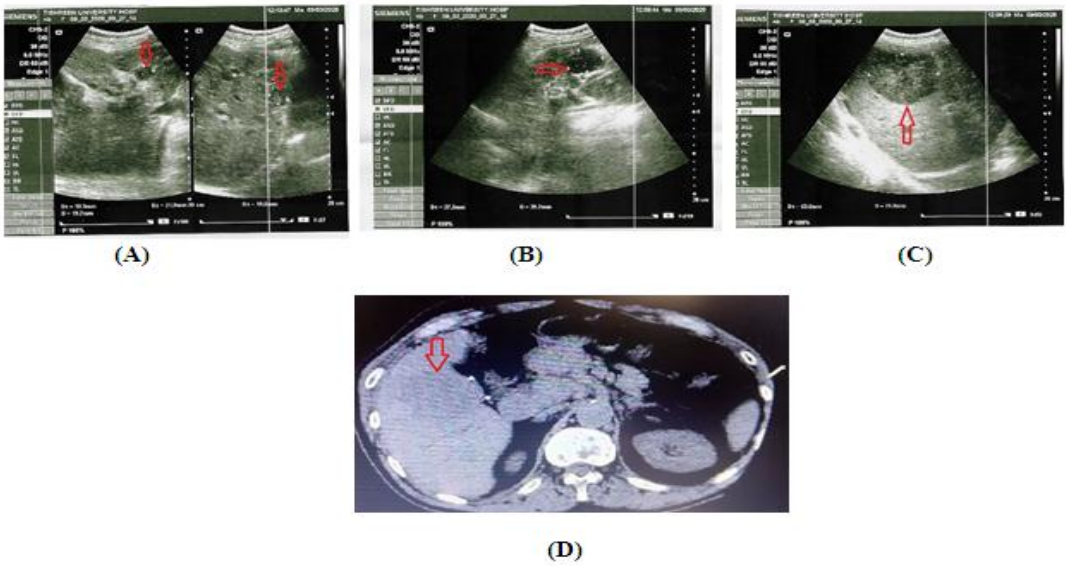

Figure 1: (A+ B) Ultrasound of the liver showing multiple hypoechoic nodules (red arrows); (C) Ultrasound of the liver showing isoechoic mass of (63 * 74) mm (red arrow); (D) CT scan showing a barely visible hypodense mass in the right lobe of the liver (red arrow).

Ultrasound-guided biopsy of the hepatic lesion was performed and 1 week later showed a plasma cell neoplasm. Immunostaining revealed CD138 diffusely positive, kappa/lambda ratio 10/0, which confirms plasma cell origin and shows kappa-restricted plasma cell infiltration (Figure 2, A+ B+ C). During this time bone marrow biopsy was performed and showed a normocellular bone marrow associated with increased number of plasma cells, CD138 was positive for 60% of cells (figure 3, A+ B). Serum protein electrophoresis detected a monoclonal gammapathy. Ig quantification showed IgG 5000 mg/dl (normal 600-1600 mg/dl), IgM 4.6 mg/dl (normal 40-230 mg/dl), and IgA 30 mg/dl (normal 70-400 mg/dl). Serum immunofixation was positive of IgG/kappa monoclonal gammapathy.

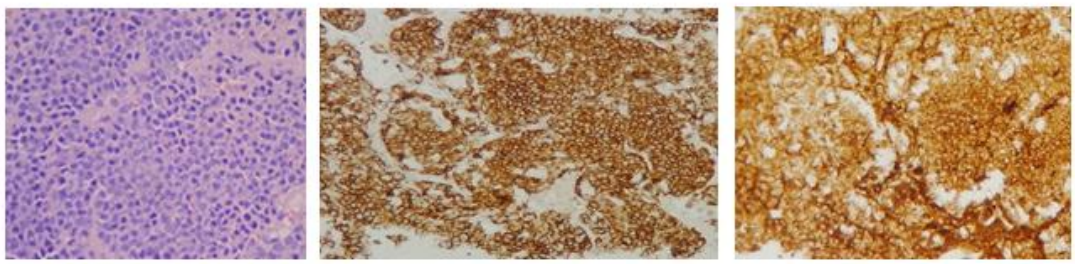

Figure 2: (A) liver fine needle aspirate (FNA) and core biopsy showing a monomorphic population of plasma cells with eccentric nuclei and clock-faced chromatin. (B) Liver FNA immunohistochemical staining revealed CD138, highlighting plasma cells. (C) Kappa light surface antigen showing all plasma cells positive for stain.

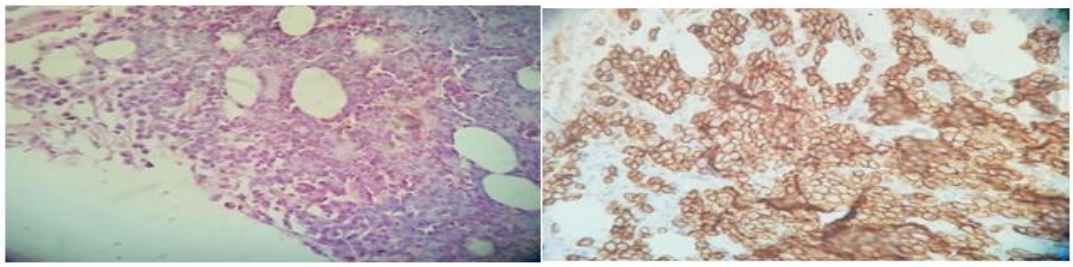

Figure 3: (A) Bone marrow showing normocellularity with increased scattered plasma cells. (B) Bone marrow immunohistochemical staining showing CD138, highlighting plasma cells occupying 60% of total cellularity.

Protein in 24 hrs. Urine was 936 mg, and Bence Jones protein was negative in urine test. Kappa light chain of 620 mg/L (normal 170-370 mg/dl), lambda light chain of 17.8 mg/L (normal 90-210 mg/dl), and kappa/lambda ratio of 34.8. Additional laboratory investigations were an increased beta-2- microglobulin 9.06 mg/dl (normal 0.9-2.7 mg/dl), deceased albumin 2.7 g/dl (normal 3.4-5.4 g/dl), and increased LDH 609 U/L (normal 250-450 U/L). A myeloma fluorescence in situ hybridization panel was negative to 17p13 deletion. The patient was therefore diagnosed with Multiple Myeloma (MM) with extramedullary involvement of the liver. According to the Revised International Staging System (R-ISS), prognostic stage was III, which has median progression-free survival of 29 months. Treatment was initiated with CRd regimen (Cyclophosphamide, Revlimid, and Dexamethasone). After 2 cycles, he showed a partial response, so decided going on the same regimen for another 4 cycles.

DISCUSSION

Multiple myeloma (MM) is characterized by a proliferation of malignant plasma cells with strong dependence on the bone marrow (BM) microenvironment. In fact, MM is considered the prototype of cancer in which the malignant cells interact with the microenvironment.[8,9] It has recently been shown that virtually all cases of MM are preceded by a monoclonal gammapathy of undetermined significance (MGUS), an asymptomatic condition exclusively confined to the bone marrow.[1,10] Clinical manifestations are related to tissue and/or organ impairment, resulting in the so-called CRAB acronym: elevated serum calcium, renal function impairment, anemia and/or bone involvement.[11] Extramedullary myeloma (EM) is defined by the presence of plasma cells (PCs) outside the bone marrow in a patient with multiple myeloma (MM). EM develops because of 'BM escape' of a subclone of plasma cells (PC). This subclone migrates out of the BM infiltrating soft tissues losing dependence on the BM microenvironment.[6] According to Bladé et al, EM may have two different origins: 1) direct mechanical extension from the bone marrow when they disrupt the cortical bone and spread into the adjacent soft tissues or 2) hematogenous metastatic spread when the decrease of selected cell surface adhesion receptors allows for bone marrow release.[9] When MM effects the liver, diffused (sinusoidal, portal, mixed) and nodular patterns of microscopic plasma cell infiltration have been described.[12] Diffused rather than nodular hepatic infiltrations is the predominant pattern of liver involvement. Perez-Soler et al.[2] reported 128 patients with MM. Histologic findings were available in the liver of 21 patients. A diffuse infiltrative pattern of plasma cells was observed in 10 patients, but no case of nodular liver infiltration was seen. Soft tissue involvement of multiple myeloma particularly on the liver is rare as emphasized by the incidence described by Talamo et al.[12] in 2,584 patients, wherein only 11 patients had liver involvement, 9 of them had nodular infiltration (0,35 %), like the case of our patient. Another longitudinal study, Usmani *et al.*[6] report their experience on extramedullary disease involvement in a large series of 1,965 patients with MM treated at the Myeloma Institute for Research and Therapy at the University of Arkansas, USA. These patients had baseline PET scans to document EMD both at diagnosis and at the time of disease progression. The frequency of EMD at diagnosis was 3.4% (66 of 1,965) and around 5% at the time of relapse or progression. The most frequent location at diagnosis was skin while at progression the most striking feature was liver involvement. The presence of EMD was associated with a significantly shorter progression-free survival and overall survival.[13] Treatment of this archaic disease is still a moving target considering newer diagnostic criteria, new staging system and more effective therapeutics.[14] Extramedullary myeloma is one of the special circumstances where treatment is not well defined due to its rarity, molecular, and proliferative heterogeneity. Initial treatment depends on risk stratification and prognostication.[15]

In our case, treatment initiated with CRd regimen: Cyclophosphamide (300 mg/m2 weekly for 3 weeks), lenalidomide (25 mg daily for 3 weeks), and dexamethasone (40 mg weekly), lenalidomide dosage was decreased from 25 mg to 10 mg in our case because of renal insufficiency.[16] The addition of lenalidomide (Revlimid) may have been responsible for the improvement in response as documented by a few case reports. Xie et al. successfully treated secondary multiple myeloma with extramedullary liver Plasmacytoma in a renal transplant patient with CRd regimen.[17] Similarly, Felici et al. utilized the CRd regimen on a patient with bilateral retro-orbital localization.[18]

CONCLUSION

The approach to a patient with multiple liver nodules is a diagnostic challenge. The presence of anemia, kidney dysfunction, skeletal pain and hepatosplenomegaly made the authors suspect Multiple Myeloma. Furthermore, there were no specific imaging features for extramedullary myeloma involvement of the liver. Ultimately, biopsy was done to confirm the diagnosis. However, extramedullary Myeloma is a poor prognostic sign and a harbinger of an aggressive clinical course in the contest of Multiple Myeloma.

Declarations

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication: written consent to publish this information was obtained from study participants.

Availability of data and materials: All data generated or analyzed during this study are included in this

published article [and its supplementary information files].

Competing interests: no conflict of interest.

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Authors' Contributions: Corresponding author analyzed and interpreted the patient data.

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