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Fatal fulminant hepatic failure during treatment of multiple myeloma

Multipl myeloma tedavisi sırasında ölümcül fulminan karaciğer yetmezliği

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Liver is one of the most commonly involved organs in hematological diseases. Multiple myeloma (MM) is a hematological malignancy with rare extraosseous and extramedullary involvement . Although there is a few clinical data about hepatic involvement postmortem evaluations were able to demonstrate plasma cell infiltration in liver. We are reporting a 58-year-old male patient who had the diagnosis of MM since three years and had received five courses of VAD chemotherapy, thalidomide and two courses of radiotherapy to paravertebral involvement sites. The patient progressed and received VAD courses as salvage chemotherapy. He developed hepatic failure and despite consequent therapeutic plasma exchanges and supportive measures the patient status worsened and he died of fulminant hepatic failure. We were not able to demonstrate any sign of myelomatous involvement in post-mortem liver biopsy. We are reporting the fulminant disease course and discussing the possibilities for hepatic failure in a MM patient, whose postmortem liver biopsy revealed only non-specific reactive hepatitis.

Key words: ***multiple myeloma, fulminant hepatic failure, chemotherapy***

Karaciğer, hematolojik hastalıklarda en sık tutulan organlardan birisidir. Multipl myeloma ekstramedüller ve kemik dışı tutulumu nadir görülen bir hematolojik hastalıktır. Karaciğer tutulumu ile ilgili çalışmalar az da olsa, bazı postmortem çalışmalar hepatik plazma hücre infiltrasyonunu gösterebilmiştir.Bu yazıda 58 yaşında, üç yıl önce multipl myelom tanısı alan, 5 kür VAD kemoterapi protokolü, talidomid ve iki kez paravertebral tutulum bölgelerine radyoterapi uygulanmış bir erkek hastayı sunuyoruz. Hastada terapötik plazma değişimlerine ve destek tedaviye rağmen karaciğer yetmezliği ilerlemiş ve hasta fulminan karaciğer yetmezliği nedeniyle kaybedilmiştir. Postmortem karaciğer biyopsisinde myelomatöz tutulumla ilişkili bulgu gösterilememiştir. Bu yazıda hastalığın fulminan seyrini ve post-mortem karaciğer biyopsisinde sadece non-spesifik reaktif hepatit bulunan multipl myelom hastasında karaciğer yetmezliğinin nedenlerini değerlendirdik.

Anahtar kelimeler: ***multipl myeloma, fulminan karaciğer yetmezliği, kemoterapi***

Multiple myeloma (MM), a clonal disease of plasma cells involving mainly the bone marrow may show involvement of extramedullary sites like spleen, liver, lymph nodes, kidneys, thyroid, adrenal glands, testis, pleura, pericardium, skin, and even the intestinal tract (1). Liver is one of the mostly preferred sites for involvement by hematological malignancies, but liver involvement in MM is less common (2). Palpable hepatomegaly is reported in 13-20% of patients with MM, 20% with accompanying splenomegaly and only splenomegaly in 5-13% (2,3). In the study of Mattmüller et al, only 27 % of patients had hepatomegaly due to liver infiltration (2).

Liver dysfunction in MM can be attributed to six main reasons (3): infiltration, amyloidosis, myeloid metaplasia, extra hepatic cholestasis, reactive changes and toxic hepatitis. Infiltration can be diffuse (sinusoidal, portal or mixed) or nodular.

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Although one may predict that the liver infiltration by plasma cells is the terminal event in MM, it may be present at the time of diagnosis, even without the clinical or biological evidence of liver involvement (3). Diffuse hepatomegaly is almost always found in patients with amyloidosis (3).

If we consider the events causing ascites, the MM is one of the most uncommon cause, 'myelomatous ascites' definition is present in the literature, indicating that the liver involvement may be extensive (4). We are reporting the fulminant disease course and discussing the possibilities for hepatic failure in a MM patient, whose postmortem liver biopsy revealed only non-specific reactive hepatitis.

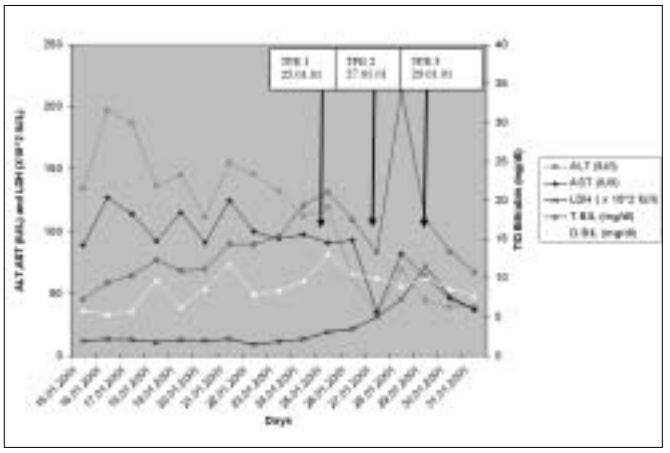

Figure 1. The daily course of liver function tests during hospitalization

Case report

A 58 –year- old male patient was diagnosed as non-secretory MM, stage IIIA, in 1998. After an attack of pulmonary embolism, he was admitted to our hospital, following five courses of VAD protocol (last one on November 1999), he received two courses of radiotherapy to Th3-Th4 and Th10-L5 vertebrae and right humerus, pelvic bone and right femur. He achieved a plateau phase and was followed up by magnetic resonance imaging for bone-lesions during and he received thalidomide during year 2001.

On admission to our hospital (January 2001) his blood count was as follows: WBC: $1.6x10^9$/L, Plt: 16^9x10^9/L, Hb: 8,9 g/L, Hct: 25.7%, MCV: 85.1fL, PMN: $1.1x10^9$/L. On physical examination coarse ralles were heard at posterior lung bases. The liver was palpable 3 cm below the costal margin whereas Traube was dull on percussion and the tip of the spleen was not palpable. The bone marrow aspiration revealed a plasma cell infiltration of 20% and the marrow biopsy specimen was reported as hypercellular bone marrow, with diffuse atypical plasma cell and plasmacytoid cell infiltration. Because he was refractory to VAD thalidomide therapy was started. He was generally subfebrile. The patient was receiving amlodipine for hypertension, proton pump inhibitor for persistent dyspepsia and amoxycillin for dental infection. On the second day of thalidomide therapy the patient developed icterus. Serum biochemistry was as follows; the total bilirubin: 7.24 mg/dl, direct bilirubin: 5.88 mg/dl. The viral profile was reported as EBV IgG (+), HSV Type1 IgG (+), HSV Type2 IgG (+), Anti-HBs Ab (+), CMV IgG(+).

There were no serological sign of viral infection, anti-HCV, HCV-RNA, and HBV-DNA results were also normal. Detailed liver injury tests were shown in Figure 1, which demonstrated a progressive deterioration within days. On abdominal ultrasonography, there was no detectable pathology of intra or extra hepatic bile ducts. The only abnormal finding was hydronephrosis of the right kidney. Consultant hepatologist did not decide to perform a liver biopsy because of a risk of subsequent hemobilia and ursodeoxycholic acid 3x500 mg po was started. Deterioration of liver functions progressed and according to presumptive diagnosis of myelomatous infiltration of the liver thalidomide and dexamethasone were started. As the progressive course continued an additional VAD course was initiated. Therapeutic plasma exchange with fresh frozen plasma was initiated on 10th, 12th and 14th days of hospitalization consequently in the context of progressive liver failure and deterioration of haemostatic parameters.

On the following days his hepatomegaly progressed and the patient lost his consciousness, developed flapping tremor and hepatic coma. Soon after the start of mechanical ventilation support he died of fulminant hepatic failure on the 16th day of his submission. Postmortem percutaneous liver biopsy was taken with written permission of his family. Pathological examination showed unexpectedly 'non-specific reactive hepatitis' and both iron and amyloidal staining were negative. After his death, blood culture reports revealed non-fermentative gram negative bacilli and Acinetobacter baumanii septicemia.

Discussion

Liver involvement in MM, an uncommon finding, may be present even without any evidence in laboratory tests or physical examination at the time of diagnosis. Especially in patients with hepatomegaly and deterioration of liver function, myelomatous infiltration or amyloidosis must be considered in the apsence of secondary causes to explain the condition.

In our case we used some adjunctive medications, including thalidomide, which may explain liver toxicity. However liver dysfunction was present before thalidomide

use and was discontinued due to progressive liver failure. Also, the drugs (amlodipine as antihypertensive, lactulose, proton pump inhibitor and amoxycilline for dental infection) used during the two days period were applied in therapeutic dose range and were stopped to prevent progressive liver deterioration. These medications are not suspected for liver toxicity (5-7)

Another possibility is a late onset autoimmune hepatitis secondary to the previous radiation of pelvis, including the region of liver which was also a rare possibility and was eliminated with the pathological evaluation (8-10).

In conclusion, a clinician should bear in mind that the hepatic involvement is a possibility in any MM patient, even without any underlying condition or sign. Establishing a diagnosis and confirmation by histopathological examination may not always be possible like in our patient. Percutaneous liver biopsy may not always show the area of involvement. In this case we were not able to demonstrate a myelomatous liver infiltration. However, still it has not been ruled out. Another explanation can be the Acinetobacter septicemia to cause these clinical and laboratory findings. Pathological findings of non-specific reactive hepatitis may be one of the known pathological forms of multiple myeloma, although the clinical findings were so severe that one may easily tend to consider toxic hepatitis. Thrombotic thrombocytopenic purpura is another pathological entity, which deserves to be excluded in discussion because of fever, neurological findings, hyperbilirubinemia and thrombocytopenia. But the apsence of hemolysis, thrombosis and renal dysfunction are not consistent with this clinical entity (11).

Fulminant hepatitis may be the terminal clinical situation in any MM patient and clinicians may not be able to find any reason to explain the clinical condition. Pathological specimens and the clinical data may not be sufficient to elucidate the etiology of the hepatic failure. All the other possible causes of fulminant hepatic failure must be excluded and liver biopsy must be performed, if possible.

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