Hepatic and Renal Plasma Cell Lesions in a Patient with Multiple Myeloma in Hematological Remission

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Abstract. Plasma cell myeloma is characterized by plasma cell infiltrations, the presence of paraprotein and mostly skeletal destruction with osteolytic lesions. Liver or kidney infiltration has been described in patients with end stage multiple myeloma (MM), while the features of this malignant dissemination is not clearly understood. An atypical form of MM relapse is presented in a patient being in bone marrow remission, with simultaneous lesions in liver, kidney and suspicion of brain involvement. This case is an interesting model of refractory MM extraosseous involvement, that a clinician should be aware of when carrying out differential diagnosis.

Multiple myeloma (MM) is characterized by plasma cell bone marrow infiltration, the presence of serum and urine monoclonal protein and usually osteolytic lesions (1). The development of plasmacytomas in various organs in the absence of bone marrow disease has been reported (1, 2). Liver (3-7) or kidney infiltration (8) has been described, usually in the setting of overt MM.

We present the case of a 49-year-old male, who was admitted to our department in November 2003, due to fever of unknown etiology lasting for more than 15 days, and who had developed an unusual pattern of MM relapse with the co-existence of hepatic and renal plasma cell infiltration. The diagnosis of MM had according to been made 55 months earlier at the outpatient clinic of our department. He was classified as IgG\(\lambda\) MM stage IIA according to the Durie-Salmon and 3 according to the new ISS staging system after the excision of a plasmacytoma of the left iliac bone. At that time his laboratory profile was as follows: hemoglobin 11.0 g/dl, serum calcium normal, serum IgG 2.30 g/dl, 24-h-urine protein excretion 10.9 g/24 h; the bone marrow infiltration was 80% by plasma cells and plasmablasts. LDH level was 650 U/l (upper normal limit: 475 U/l) and \(\beta_2\)-microglobulin 7.5 mg/l ( upper normal limit: 2.4 mg/L). Skeletal X-ray examination revealed an osteolytic lesion and a left iliac bone mass corresponding to a biopsy proven plasmacytoma; cytogenetic analysis, cardiac ultrasound, as well as routine liver and kidney biochemical tests were normal.

Our patient subsequently received local irradiation to the plasmacytoma followed by chemotherapy with 4 cycles of VAD regimen. The patient entered complete remission with no marrow plasmacytosis, undetectable paraprotein by immunofixation and even undetectable heavy chain recombination (IgH) by PCR. He was offered an autologous bone marrow transplantation, but was afraid and skeptical of the outcome. He relapsed 18 months later and received thalidomide in combination with dexamethasone. Initially he improved, but relapsed again with multiple plasmacytomas of the spine, ribs and pelvis. Melphalan was added to thalidomide-dexamethasone without response.

As mentioned, he was admitted due to a daily fever with chills fluctuating up to 39°C, that was resistant to empirical antibiotic therapy. Routine biochemical tests, including renal function tests, were normal except for an increase in alkaline phosphatase and \(\gamma\)-GT. CRP was elevated to 121.0 mg/l (upper normal limit: 475 U/l) and \(\beta_2\)-microglobulin 7.5 mg/l ( upper normal limit: 2.4 mg/L). Skeletal X-ray examination revealed an osteolytic lesion and a left iliac bone mass corresponding to a biopsy proven plasmacytoma; cytogenetic analysis, cardiac ultrasound, as well as routine liver and kidney biochemical tests were normal.

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which were confirmed by MRI (Figure 1A). A 24-h urine collection revealed deterioration of proteinuria at level of 3.33 g/24 h. Meanwhile the patient was receiving antibacterial and antifungal medication without response. Blind biopsies were obtained from the kidney as well as CT-guided biopsies from the liver masses.

Renal biopsy revealed infiltration of the interstitium by numerous cells morphologically resembling plasmablasts and plasma cells, as well as edema (Figure 1D,E). Liver biopsy revealed plasmablastic infiltration as well (Figure 1B,C). The patient started complaining of temporary visual disturbances consisting of blurred vision and diplopia. Cerebral CT scan showed a small not well defined lesion under the third ventricle, which was not further investigated since 24 h later our patient had a cardiac arrest, was successfully resuscitated and intubated, but unfortunately died a few hours later.

In the course of MM extraosseous involvement with the form of tumor masses is not rare. The present case is reported because of the simultaneous appearance of hepatic and renal neoplastic lesions consisting of plasma cells and plasmablasts. Hepatic lesions resembled to metastatic solid tumor tissue. The fact that the patient was in bone marrow remission raises questions regarding the mechanisms of developing extramedullary disease. A detailed laboratory work-up did not point to amyloidosis, possible autoimmune disease, or a solid tumor.

Direct infiltration of the kidneys with plasmablasts is also a very rare mechanism of proteinuria in MM. Sakhija et al. (8) found over 60% cast nephropathy in a retrospective study of 204 MM patients. In 27 patients renal histology showed a 3.6% frequency of nodular glomerulosclerosis and plasma cell infiltration. Renal insufficiency usually results from interstitial nephritis with light chain casts, hypercalcaemia, amyloidosis, excessive use of non-steroidal anti-inflammatory drugs for pain control or other nephrotoxic agents (9).

Fever was also a puzzling symptom; all the tests for a possible infection were negative in the investigational process. In retrospect we hypothesized that the fever was of central origin due to the brain lesion that was ultimately detected. Although the nature of the lesion remained obscure a possible brain plasmacytoma could not be excluded.

In a retrospective study at a single center (4), 128 patients with MM were reviewed to assess the incidence and manifestations of liver involvement. Screening was by clinical signs of liver disease and abnormal liver function tests, while liver biopsies were available in 21 patients. In ten of the patients, liver histology demonstrated plasma cell infiltration. There was no mention of the macroscopic appearance of the liver, infiltration was sinusoidal, portal or mixed. In the literature there are only 7 cases of previous reports of patients presenting as space-occupying lesions of the liver (5, 6).

The spread of malignant cells and the formation of neoplastic-like lesions indicate that there are mechanisms of migration and extramedullary adhesion of plasma cells. When liver involvement is documented the origin of plasma cells is unclear. This atypical localization of neoplastic plasma cells suggests a role of cytoadhesion molecules, particularly CD56 (NHK-1a epitope of NCAM) and CD11a (the ε-chain of the β-2 integrin LFA-1), which have been implicated in the cellular processes of recirculation and homing (10). Expression of adhesion molecules is found to change over the course of the disease in a manner that corresponds with the migration of MM cells from the bone marrow into peripheral blood (11). Organ involvement (liver, spleen and kidney) is found in plasma cell leukemia but our patient did not present a leukemic picture.

The expression of multiple cell adhesion molecules, such as CD44, CD49d (VLA-4), CD54 (ICAM-1), CD56 and CD138 (syndecan-1) is important for mediating adherent myeloma cells to marrow stroma, triggering the secretion of cytokines in stromal cells (12). Syndecan-1 was measured in our patient’s serum at diagnosis in the context of another study and was very high (3000 ng/ml) which might be an early indicator of unfavorable prognosis (13).

Thalidomide administered as a single agent produces a response rate of about 40% in patients with refractory or relapsed MM (14). However, it is suggested by some authors that thalidomide-based regimens for refractory MM may be followed by discordant responses of the monoclonal protein levels and the bone marrow plasmacytosis (15).

In the present case, the patient had been treated with a relatively low dose of thalidomide plus melphalan-dexamethasone and maintained hematological remission, but it was not possible to control the extramedullary manifestations of his MM. In conclusion, the present report describes an unusual case of aggressive MM with direct renal involvement with a pattern of liver infiltration resembling metastatic disease.

References


Figure 1. Hepatic space occupying lesions in multiple myeloma relapse. A) Liver MRI, B) micrograph of hepatic biopsy, x40; C) hepatic immunohistochemistry; CD138 positive staining, x20; D) microscopic picture of renal biopsy showing plasmablast infiltration, x40; E) renal immunohistochemistry with CD138 positive staining, x20.


