Liver involvement by multiple myeloma presenting as hypervascular focal lesions in a patient with chronic hepatitis B infection

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ABSTRACT

Extramedullary myeloma refers to the infiltration of neoplastic monoclonal plasma cells in either organs or soft tissues. The disease is clinically and radiologically underestimated compared with the autopsy findings and is usually associated with a more aggressive clinical course and poorer outcome. A minority of patients with extramedullary myeloma show hepatic involvement, usually in the form of diffuse parenchymal infiltration. When focal infiltration is present, variable imaging findings have been described both on CT scan and MRI. We report the case of a 63-year-old male with hepatitis B virus-related liver disease and biopsy-proven multiple myeloma involving the liver, manifesting as hypervascular focal liver lesions on MRI. A brief review of the literature is also proposed.

SUMMARY

Extramedullary multiple myeloma (e-MM) is a rare but clinically and radiologically underestimated entity that is associated with poor prognosis.

An increasing incidence of e-MM has been reported in recent decades, both at diagnosis and during follow-up. The latter may be partly explained by the widespread use of novel therapeutic agents that have led to a significant improvement in survival. In addition, the use of more sensitive imaging techniques (i.e. CT scan, MRI and 18-fluorodeoxyglucose-positron emission tomography), recently included into the routine staging systems, such as the Durie–Salmon Plus, may also have contributed to the increasing detection of e-MM lesions. Younger patients or patients relapsing after stem cell transplantation are the ones most commonly affected.

Although hepatic involvement is observed at autopsy in up to 30% of patients, ante-mortem diagnosis is significantly less common. Diffuse and nodular patterns of plasma cell infiltration have been reported, the former being more common. Imaging appearances of hepatic multiple myeloma (MM) manifesting with focal/multifocal pattern are non-specific, and heterogeneous features have been described in few published reports and case series so far. Most often, focal liver lesions have been observed as non- or mildly enhancing on CT scan and as moderate or minimally enhancing on MRI; hepatic involvement has been noted in only one case, described as hypervascular liver lesions on CT scan (Table 1). Nevertheless, a proper comparison among the different patterns is not feasible as most of the studies did not describe the details of the CT scan and MR techniques applied. The differential diagnosis of hypervascular focal liver lesions mainly includes hepatocellular carcinoma and hypervascular metastases, while hepatic involvement by MM is not routinely considered.

We present the ultrasound, CT scan and MRI features, and the corresponding pathological findings of hepatic myelomatous involvement manifesting as hypervascular liver lesions in a patient with MM and hepatitis B virus (HBV)-related liver disease.

CLINICAL PRESENTATION

A 63-year-old male with a diagnosis of HBV infection [hepatitis B surface antigen (HBsAg) positivity, HBV DNA 2578 IU ml⁻¹], on treatment with tenofovir, was admitted to our hospital for routine abdominal ultrasound examination. The patient had immunoglobulin Gκ MM that was diagnosed in

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2001 and staged as III A according to the Durie–Salmon staging system; he had been heavily pretreated and had relapsed multiple times. Previous treatments included four courses of vincristine, adriamycin and dexamethasone; thalidomide; two autologous stem cell transplantation procedures; four cycles of bortezomib and dexamethasone; multiple bisphosphonate infusions; several radiotherapy treatments for bone lesions; and finally allogeneic stem cell transplantation from a matched, unrelated donor performed in December 2011. At the time of the ultrasound examination, the patient was receiving donor lymphocyte infusions owing to further relapse, including vertebral and sacral bone lesions and increased serum monoclonal protein levels; laboratory hepatic damage markers, in particular aspartate aminotransferase and alanine aminotransferase, were only slightly increased, while bilirubin was normal. Alpha fetoprotein level was also measured and was normal (6.3 ng ml\(^{-1}\), normal range < 8 ng ml\(^{-1}\)).

**Table 1. Imaging features of myelomatous nodular involvement of the liver**

| Publication       | Ultrasound         | CT                              | MRI                                |
|-------------------|---------------------|---------------------------------|-----------------------------------|
| Mathieu et al\(^a\) | Hypodense, enhancing from the periphery to the centre | \(T_1\) weighted: hypointense outer layer, hyperintense rim, isointense core \(T_2\) weighted: hyperintense outer layer, hypointense rim, hyperintense core |                    |
| Nguyen et al\(^b\) | “Target” appearance | Hypodense | \(T_1\) and \(T_2\) weighted: hyperintense Moderate enhancement |
| Kelekis et al\(^c\) | “Target” appearance | Enlarged liver without discrete nodules in unenhanced phase | \(T_1\) weighted: slightly hypointense \(T_2\) weighted: hyperintense |
| Ng et al\(^d\)    | “Target” appearance | Slightly hypodense, mild enhancement | \(T_1\) weighted: slightly hypointense \(T_2\) weighted: hyperintense |
| Patlas et al\(^e\) | Hypoechoic/mixed echogenicity | Hypodense on unenhanced and post-contrast phases | Minimal enhancement |
| Monill et al\(^f\) | Non-enhancing nodules |                                               |                                  |
| Tan et al\(^g\)   | Arterial enhancement Isodense/mildly hypodense on delayed phase |                                               |                                  |
| Present case       | Hypoechoic          | Arterial enhancement Isodense on portal venous and delayed phase | \(T_1\) weighted: slightly hypointense \(T_2\) weighted: hyperintense Arterial enhancement with contrast washout and capsule appearance on portal venous phase Diffusion-weighted imaging: restricted diffusion |

“Target” appearance: hypoechoic halo surrounding the echogenic/isoechogenic core.

Figure 1. Ultrasound imaging of the liver showing a hypoechoic, well-delimited lesion in segment 8 (a, black arrowhead) and 6 (b, black arrowhead) measuring 8 and 11 mm in maximum diameter, respectively. Mild diffuse increased echogenicity of the liver parenchyma is also present, consistent with fatty infiltration.

INVESTIGATIONS/IMAGING FINDINGS

Ultrasound imaging showed five well-circumscribed hypoechoic focal lesions measuring 5–12 mm in maximum diameter, distributed throughout the liver (Figure 1). A mild diffuse increased echogenicity of the liver was also present, consistent with fatty infiltration, without clear ultrasound signs of cirrhosis. A multiphasic contrast-enhanced CT scan of the abdomen was performed to better characterize the lesions and revealed the presence of nine focal liver nodules measuring 6–16 mm in maximum diameter. The lesions were isodense on pre-contrast CT scan, showing mild contrast enhancement on hepatic arterial phase images and isoenhancing to the surrounding liver on portal venous and delayed phase images (Figure 2). MRI
examination was subsequently performed (1 month later). In our institution, the MRI protocol (Table 2) for the upper abdomen includes multiple breath-hold gradient echo in-phase and out-of-phase $T_1$ weighted imaging, a respiration-triggered spectral adiabatic inversion recovery turbo spin echo $T_2$ weighted sequence and a dynamic study using volumetric interpolated breath-hold examination $T_1$ weighted sequence with fat saturation before and after i.v. injection of 0.1 ml kg$^{-1}$ of gadobenate dimeglumine (MultiHance, Bracco, Milan, Italy). The latter sequence was repeated on the axial plane 30, 70 and 300 s after contrast administration and in the hepato-specific phase at about 1 h after contrast administration. Diffusion-weighted imaging was performed before the dynamic study with a respiration-triggered single-shot echo-planar sequence acquired on the axial plane with $b$ values of 50, 400 and 800 s mm$^{-2}$. An apparent diffusion coefficient map was obtained. Multiple focal liver lesions measuring 10–25 mm in maximum diameter were depicted, appearing hyperintense on $T_2$ weighted images and hypointense on pre-contrast $T_1$ weighted images. All the lesions showed hyperenhancement on hepatic arterial phase images; the largest ones (three lesions > 20 mm) showed hypoenhancement to the surrounding liver parenchyma (i.e. washout appearance) and capsule appearance on the portal venous and delayed phases (Figure 3), whereas others exhibited isointense signal to the surrounding liver during both the portal venous and delayed phases. Moreover, all the lesions were hypointense on the hepatobiliary phase images. All the lesions were hypointense on diffusion-weighted images ($b = 800$ s mm$^{-2}$) but showed variable restriction on the apparent diffusion coefficient map. No signal dropout was appreciable on the $T_1$ weighted gradient echo out-of-phase images compared with the in-phase images to suggest intralesional fat. No additional pathological findings were detected. Percutaneous ultrasound-guided liver biopsy of the largest subcapsular lesion on the left lobe (Figure 3) was performed using an 18-gauge cutting needle and histopathological and immunohistochemical analysis revealed the presence of plasma cells with anaplastic features, consistent with liver involvement by MM. The presence of

| Sequence parameters | 2D GRE | 2D TSE SPAIR | 3D GRE VIBE with fat-saturation | EPI |
|---------------------|--------|--------------|---------------------------------|-----|
| Weighting           | $T_1$  | $T_2$        | $T_1$                           | Diffusion |
| Orientation         | Transversal | Transversal  | Transversal                     | Transversal |
| Repetition time (ms) | 118    | 1700         | 4.23                           | 1900  |
| Echo time (ms)      | 2.35/5.04 | 65           | 1.48                           | 69    |
| Field of view (mm)  | 337*400 | 285*380      | 275*400                        | 285*380 |
| Matrix size         | 230*256 | 259*320      | 179*256                        | 153*192 |
| Section thickness (mm) | 6      | 6            | 4                              | 6     |
| Intersection gap (%)| 20     | 30           | 20                             | 30    |
| Number of sections  | 27     | 25           | 60                             | 25    |
| Number of signals acquired | 1      | 1            | 1                              | 2     |
| Acquisition time (s) | 24     | 110          | 12                             | 187   |

2D, two-dimensional; 3D, three-dimensional; EPI, echo-planar imaging; GRE, gradient echo; SPAIR, spectral adiabatic inversion recovery; TSE, turbo spin echo; VIBE, volumetric interpolated breath-hold examination.
A neoformed vascular structures was also demonstrated, in line with the hypervascularity observed on CT scan and MRI (Figures 4 and 5).

**DIFFERENTIAL DIAGNOSIS**
Differential diagnoses of the focal liver lesions in our case included the following:

- hepatocellular carcinoma
- hypervascular metastatic disease (*i.e.* melanoma, primary neuroendocrine tumours, renal cell carcinoma, thyroid carcinoma and sarcoma)
- hepatic MM.

**TREATMENT**

The patient was treated with four cycles of vincristine, cyclophosphamide and doxorubicin and underwent close clinical and laboratory monitoring.

3 months after starting this treatment, an abdominal ultrasound examination was performed: the previously described hepatic lesions were not apparent anymore and no new lesions were observed. The overall clinical and laboratory status was slightly improved as well.

**Figure 4.** Photomicrographs of the histopathological specimen showing (a) diffuse infiltration of the liver by monomorphic plasmacytoid cells with hyperchromatic nuclei (empty arrowheads). The adjacent hepatic parenchyma shows macro- and microvesicular steatosis (black arrowheads) (hematoxylin and eosin ×4). (b) The selected area in (a) is shown with greater magnification, better demonstrating atypical plasma cells and mitotic activity (curved arrow), and the presence of neoformed vascular structure (stars) (×10).

**Figure 5.** (a) Immunohistochemical staining shows CD-138 cytoplasmatic and plasma membrane expression in plasmacytoid cells (black arrowhead), whereas hepatocytes (empty arrowhead) and fibroblasts (stars) show only plasma membrane positivity and complete absence of CD-138 expression, respectively. (b) Immunohistochemical analysis of hepatocyte-specific antigen antibody (OCHIES) expression shows cytoplasmatic staining in hepatocytes (empty arrowhead) and lack of significant expression in plasmacytoid cells (black arrowhead) and fibroblasts (stars) (×10).
OUTCOME AND FOLLOW-UP
To the best of our knowledge, data concerning the prognostic impact of hepatic e-MM are not available but, more generally, the presence of e-MM has been associated with an aggressive course. Indeed, the presence of e-MM at any time during the course of the disease is associated with shorter progression-free survival and overall survival.  

Periodic evaluation for progression of MM is recommended, including a complete history and physical examination as well as laboratory tests.

LEARNING POINTS
1. In patients with MM, care should be taken about considering extramedullary myelomatous localization in the differential diagnosis of hypervascular lesions of the liver.
2. Imaging appearances of hepatic MM manifesting with focal/multifocal pattern are heterogeneous.

CONSENT
Informed consent to publish this case, including images and data, was obtained and is held on record.

REFERENCES
1. Varettoni M, Corso A, Pica G, Mangiacavalli S, Pascutto C, Lazzarino M. Incidence, presenting features and outcome of extramedullary disease in multiple myeloma: a longitudinal study on 1003 consecutive patients. *Ann Oncol* 2010; 21: 325–30. doi: http://dx.doi.org/10.1093/annonc/mdp329
2. Durie BGM. The role of anatomic and functional staging in myeloma: description of Durie/Salmon plus staging system. *Eur J Cancer* 2006; 42: 1539–43. doi: http://dx.doi.org/10.1016/j.ejca.2005.11.037
3. Moulopoulos LA, Granfield CA, Dimopoulos MA, Kim EE, Alexanian R, Libshitz HI. Extramedullary multiple myeloma: imaging features. *AJR Am J Roentgenol* 1993; 161: 1083–7. doi: http://dx.doi.org/10.2214/ajr.161.5.8273615
4. Oshima K, Kanda Y, Nannya Y, Kaneko M, Hamaki T, Suguro M, et al. Clinical and pathologic findings in 52 consecutively autopsied cases with multiple myeloma. *Am J Hematol* 2001; 67: 1–5. doi: http://dx.doi.org/10.1002/ajh.1067
5. Mathieu D, Elouaer-Blanc L, Diviné M, René E, Vastile N. Hepatic plasmacytoma. *J Comput Assist Tomogr* 1986; 10: 144–5. doi: http://dx.doi.org/10.1097/00004728-198601000-00033
6. Nguyen BD, Dash N, Lupetin AR. MR imaging of hepatic plasmacytoma: a case report. *Clin Imaging* 1992; 16: 98–101. doi: http://dx.doi.org/10.1016/0899-7071(92)90120-X
7. Kelekis NL, Semelka RC, Warshauer DM, Sallah S. Nodular liver involvement in light chain multiple myeloma: appearance on US and MRI. *Clin Imaging* 1997; 21: 207–9. doi: http://dx.doi.org/10.1016/S0899-7071(96)00022-8
8. Ng P, Slater S, Radvan G, Price A. Hepatic plasmacytomas: case report and review of imaging features. *Australas Radiol* 1999; 43: 98–101. doi: http://dx.doi.org/10.1016/s0446-1673(99).00063.x
9. Patlas M, Khalili K, Dill-Macky MJ, Wilson SR. Spectrum of imaging findings in abdominal extramedullary myeloma. *AJR Am J Roentgenol* 2004; 183: 929–32. doi: http://dx.doi.org/10.2214/ajr.183.4.1830929
10. Monlló I, Pernas J, Montserrat E, Pérez C, Clavero J, Martínez-Noguera A, et al. CT features of abdominal plasma cell neoplasms. *Eur Radiol* 2005; 15: 1705–12. doi: http://dx.doi.org/10.1007/s00330-005-2642-z
11. Tan CH, Wang M, Fu WJ, Vikram R. Nodular extramedullary multiple myeloma: hepatic involvement presenting as hypervascular lesions on CT. *Ann Acad Med Singapore* 2011; 40: 329–31.
12. Roth CG, Mitchell DG. Hepatocellular carcinoma and other hepatic malignancies: MR imaging. *Radiol Clin North Am* 2014; 52: 683–707. doi: http://dx.doi.org/10.1016/j.rcl.2014.02.015
13. Silva AC, Evans JM, McCollough AE, Jatoi MA, Vargas HE, Hara AK. MR imaging of hypervascular liver masses: a review of current techniques. *Radiographics* 2009; 29: 385–402. doi: http://dx.doi.org/10.1148/rg.292085123