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Imaging Features of Extramedullary, Relapsed, and Refractory Multiple Myeloma involving the Liver Across Treatment With Cyclophosphamide, Lenalidomide, Bortezomib, and Dexamethasone

A 55-year-old white woman presented in June 2003 with stage IIIA Durie-Salmon immunoglobulin (Ig) G κ multiple myeloma (MM) and was initially treated with thalidomide and dexamethasone followed by cyclophosphamide, with concurrent bisphosphonate (zoledronic acid), and intensified by autologous stem-cell transplant (ASCT) after high-dose melphalan conditioning. She remained in complete remission until December 2008, when she experienced relapse with occipital plasmacytoma and symptomatic extramedullary disease (EMD) arising from her skeleton. She was treated with an experimental second-generation proteasome inhibitor (NPI-0052, 0.7 mg/m^2 administered intravenously [IV]), combined with low-dose weekly oral dexamethasone. She had evidence of clinical response (disease stabilization and symptomatic improvement). Treatment was completed after 6 months, and she declined maintenance options other than bisphosphonate.

[^{18}F] fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) 18 months later (December 2010) revealed two solid masses in the right hepatic lobe on noncontrast CT scan (Fig 1A), which were intensely FDG-avid on fused axial (Fig 1B) and coronal PET/CT (Fig 1C, bold arrows) with standardized uptake value (SUV_{max} 9.8), raising the suspicion for EMD. FDG-avid osseous lesions (Fig 1C, thin arrows) were also seen. Abdominal magnetic resonance imaging (MRI) in December 2010 revealed a well-defined, vascular, lobulated mass in hepatic segment VII measuring 6.1 × 6.2 cm. The mass appeared mildly hyperintense on T2-weighted image (WI; Fig 2A, long arrow), hypointense on T1WI (Fig 2B, long arrow), with persistent enhancement on arterial (Fig 2C, long arrow), venous (Fig 2D, long arrow), and 5-minute delayed scans (Fig 2E, long arrow). A similar smaller lesion (1.4 × 1.3 cm) was noted in hepatic segment 8 (Figs 2A to 2E, short arrows). A large wedge-shaped area of relative hyper-enhancement in the anterior right hepatic lobe (Fig 2C, thin long arrow) was likely perfusional. Delayed post–contrast coronal MRI revealed multiple lumbar spine and pelvic bones enhancing lesions (Fig 2F, arrowhead). Her liver function remained normal with no hepatomegaly or abdominal pain. Liver biopsy was not performed because of the strong clinicoradiologic suspicion and potential bleeding risks. Laboratory tests revealed normal total protein at 6.3 gm/dL, a serum free κ light chain of 4.6 mg/dL (range, 3.3 to 19.4 mg/dL), low serum free λ light chain at 1.79 mg/dL (range, 5.7 to 26.3 mg/dL), and a κ-to-λ ratio of 2.88 (range, 0.26 to 1.65), serum IgG of 702 mg/dL,

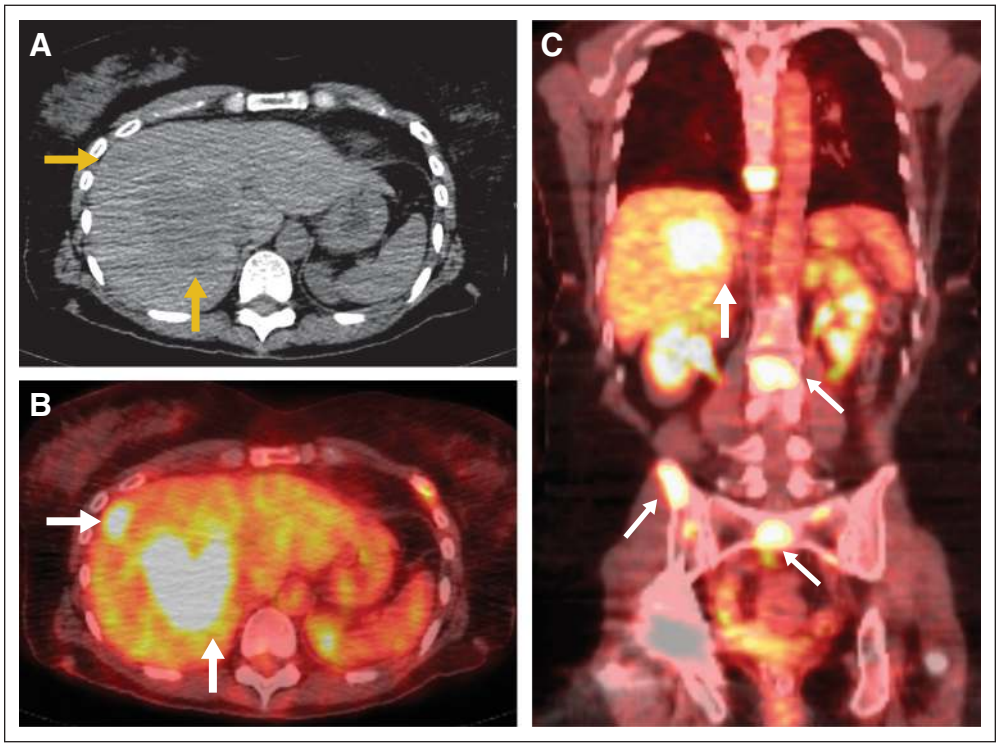

Fig 1.

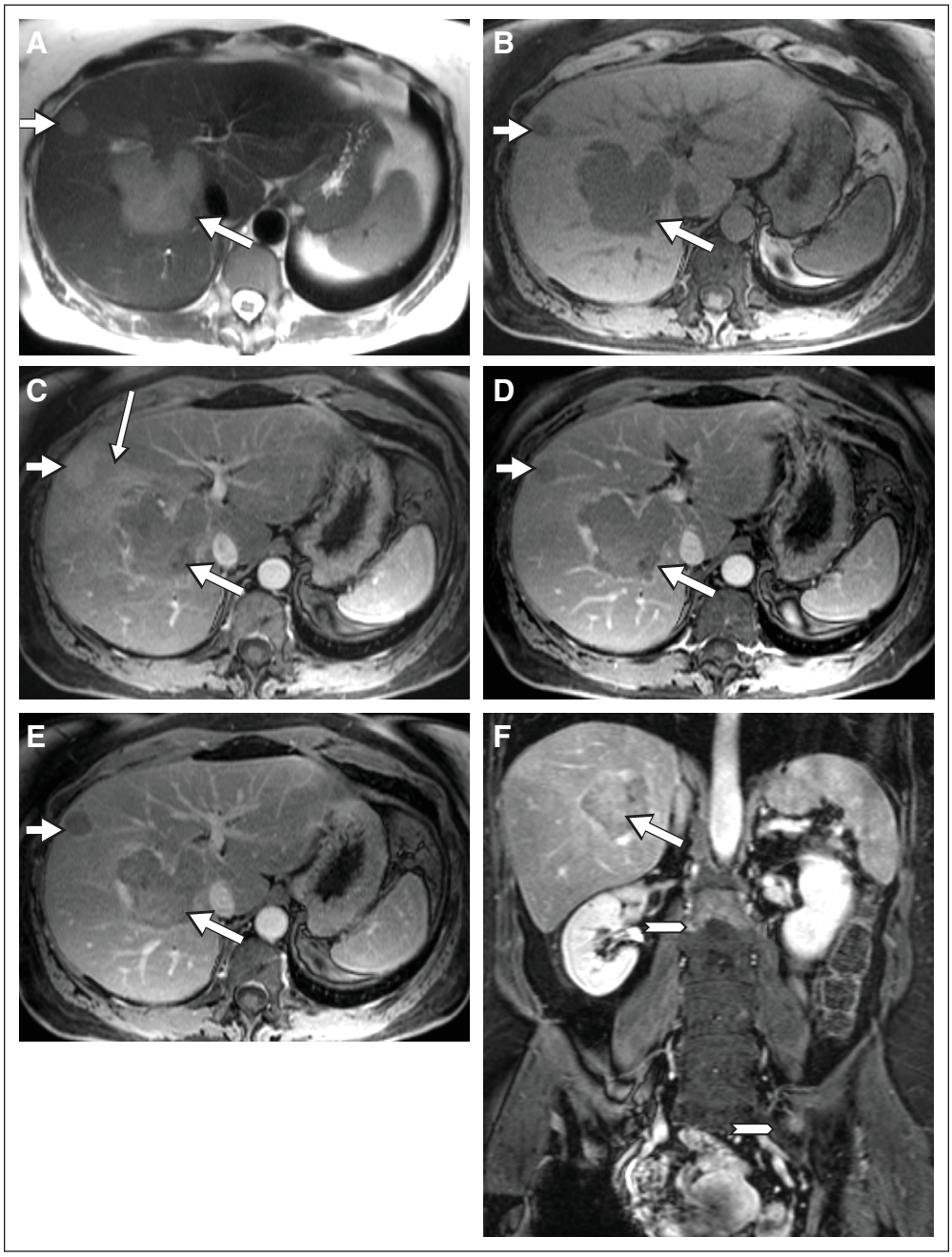

Fig 2.

and IgA of 69 mg/dL (range, 70 to 400 mg/dL), with an IgM of 43 mg/dL, β2 microglobulin of 2.4, and total urine protein of 25 mg/24 hours, with a κ-restricted M protein detected on immunofixation only. Serum protein electrophoresis/immunofixation revealed 0.28 gm/dL of IgG κ. Other blood tests were normal. Bone marrow aspirate and biopsy demonstrated less than 5% plasma cells, with no clonal features and otherwise normal hematopoiesis.

She was enrolled in a prospective phase I/II trial evaluating bortezomib and plerixafor in January 2011. [^{18}F]FDG PET/CT in March 2011 revealed multiple new osseous FDG-avid lesions with increase in size and FDG uptake of liver lesions (SUV_{max} of 12) consistent with rapidly progressive disease. In March 2011, she was started on a salvage regimen containing cyclophosphamide 25 mg/kg IV on day 1; bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, and 11; lenalidomide 10 mg orally days 1 through 14; and dexamethasone 40 mg orally days 1, 2, 4, 5, 8, 9, 11, and 12 given every 3 weeks (CRVD), with monthly bisphosphonate infusions. She tolerated therapy well and also received radiation therapy for a persistently symptomatic bone lesion (affecting the L2 vertebra). After four cycles, abdominal MRI in May 2011 revealed significant hypointense signal on T2 WI (Fig 3A, long arrow), a more than 50% decrease in dominant hepatic mass size on T1 WI (Fig 3B, long arrow), measuring 3.9 $\times$ 2.9 cm, and enhancement decrease on post–contrast arterial (Fig 3C, long arrow) and venous scans (Fig 3D, long arrow), but increased enhancement on the 5-minute delayed

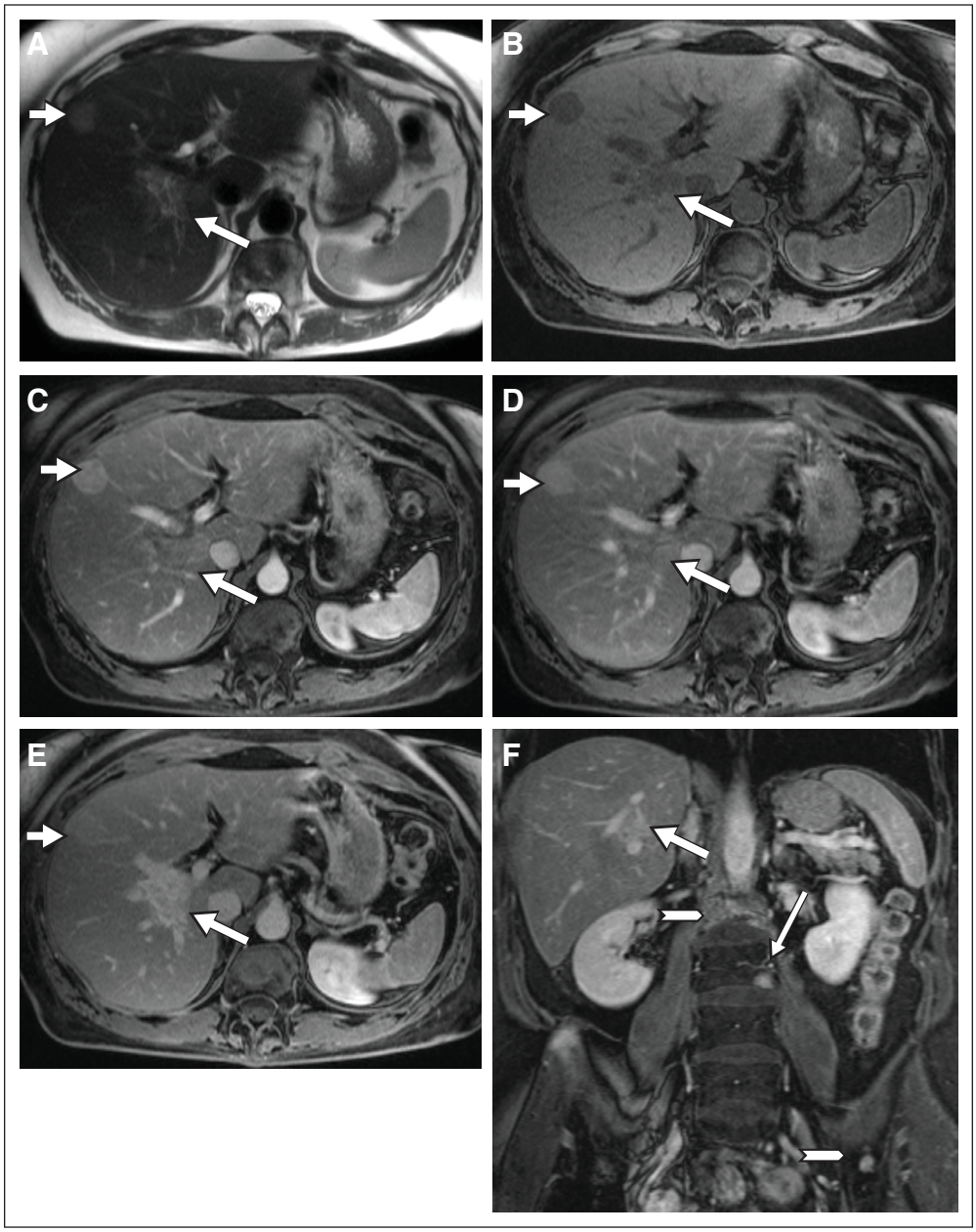

Fig 3.

scans (Fig 3E, long arrow). These findings were suggestive of fibrotic changes within the previously vascular lesion, likely in response to treatment. However, a second smaller right hepatic lobe lesion (Figs 3A to 3E, short arrow) had minimally increased, but no definite new liver lesion was noted. Bone lesions in lumbar spine showed persistent enhancement (Fig 3F, arrowhead and thin arrow).

PET/CT on June 13, 2011, revealed significant decrease in FDG avidity of osseous lesions with decrease in size of segment 8 hepatic lesion (SUV_{max} 5.9, previously 6.5), with the hepatic segment 7 lesion completely resolved in response to previous treatment. She has gone on to receive eight cycles of CRVD and achieved sustained partial response, with disappearance of M protein and continued improvement in her EMD and bony involvement. Maintenance with lenalidomide and bortezomib is planned. Allogeneic transplant is also being considered given her younger age, but in the absence of a sibling match, this treatment modality is being approached with caution.

Discussion

MM is a malignant plasma cell dyscrasia and the second most common hematologic malignancy after non-Hodgkin's lymphoma.[1] Although plasma cell proliferation generally occurs inside the bone marrow, extramedullary involvement (defined as soft tissue tumor arising from bony lesion or distant EMD outside of both marrow and bone) can also be observed. The reported incidence of EMD of 7% is increasing, likely due to more sensitive imaging technology and the prolongation of survival in MM with the use of highly effective novel agents as well as ASCT.[2,3] Importantly, autopsy reports show a higher

than expected incidence, with 63.5% extraosseous involvement described in one series.[4] Extraosseous disease is more common in younger, male patients; nonsecretory/IgD/κ light chain subtypes; advanced stage MM; extensive bone disease; and plasma cell leukemia.[2] Most common involved sites include the aerodigestive tract, soft tissue, liver, spleen, lymph nodes, testis, kidneys, pleura, and peritoneum.[2]

MRI, FDG PET/CT, and CT are increasingly used to evaluate EMD and to monitor therapeutic response. On imaging, hepatic EMD commonly presents as diffuse infiltration with hepatomegaly and rarely as unifocal or multifocal nodules.[5] The frequency of hepatic infiltration in MM autopsied patients is 30%, with discrete liver nodules in 13% of patients.[4] Liver involvement is more common in patients with IgA subtype and high IgG levels.[4] Clinically, this can manifest as extrahepatic biliary obstruction, ascites, nonobstructive jaundice, and hepatomegaly, but is more often asymptomatic.[6-10] On CT, focal hepatic lesions usually appear as a solid, noncalcified mass with less enhancement.[5,11] At MRI, they appear as mildly hyperintense on T2WI and hypointense on TWI, with either uniform moderate[7] to minimal enhancement[11] on postcontrast images. Whole-body [^{18}F]FDG PET/CT helps in easy localization of both osseous and extraosseous EMD, which appear as moderate to intense FDG-avid lesions with SUV_{max} more than 2.5.[5,7,12] The reported ability of combined spine/pelvis MRI and whole-body [^{18}F]FDG PET/CT to detect both osseous and extraosseous active MM sites is high, with a sensitivity in excess of 90%.[12] Because clinical and radiologic manifestations can vary, biopsy is often required.[11] Differential diagnosis of focal FDG-avid liver lesions on PET/CT with less enhancement on MRI include EMD, lymphoma, solid tumor metastasis, and cholangiocarcinoma.[5,11] However, in our clinical scenario, in which advanced MM manifests as multiple lytic, FDG-avid bone lesions, focal mildly T2WI hyperintense liver lesions, and less enhancement on postcontrast images, together with increasing paraprotein, the diagnosis can reasonably be narrowed to EMD.

EMD is usually associated with chemotherapy resistance, poor prognosis, and short median overall survival, with reports of $\leq$ 15 months in some series.[6] Several case reports have described especially poor prognosis with nodular hepatic EMD.[6-10] There are no established guidelines regarding treatment options for EMD in MM. Therapeutic options consist of systemic treatment (eg, chemotherapy combined with novel targeted agents), radiation, surgical resection, or a combination of all three. Several reports describe the lack of sustained efficacy of thalidomide against EMD both at diagnosis and relapse.[13] However, thalidomide-based multiagent regimens have shown efficacy in EMD among patients who have experienced relapse who underwent allogeneic or ASCT.[13]

Interestingly, bortezomib has proven efficacy in EMD in numerous case reports.[13] Ali et al[14] and Moriuchi et al[15] reported four cases in which bortezomib used as a single agent or with dexamethasone failed to achieve meaningful response in EMD, suggesting the importance of combination approaches with multiple agents. For example, multidrug chemotherapy consisting of bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide has proven effective in patients with EMD, but the toxicity profile of this regimen can limit its utility.[1] Second-generation novel drugs such as pomalidomide have shown promising results and may be useful when combined with other active agents, such as bortezomib.[16]

We describe a successful radiologic partial response after four cycles of bortezomib and lenalidomide–based therapy (CRVD). Hepatic EMD showed mixed response on MRI after four cycles, but sustained response on [^{18}F]FDG PET/CT after the fifth cycle of treatment. The dominant liver lesion impact on MRI can potentially be explained by the antiangiogenic and synergistic properties of lenalidomide and bortezomib,[17] exemplifying the role that rational combination therapeutics play in the management of MM.[18]

To the best of our knowledge, this is the first report of hepatic MM response to treatment imaging appearance on multiphasic postcontrast MRI and [^{18}F]-FDG PET/CT, illustrating the utility of this imaging strategy in this setting. Additional studies are warranted to characterize the role of advanced imaging technology in EMD.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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