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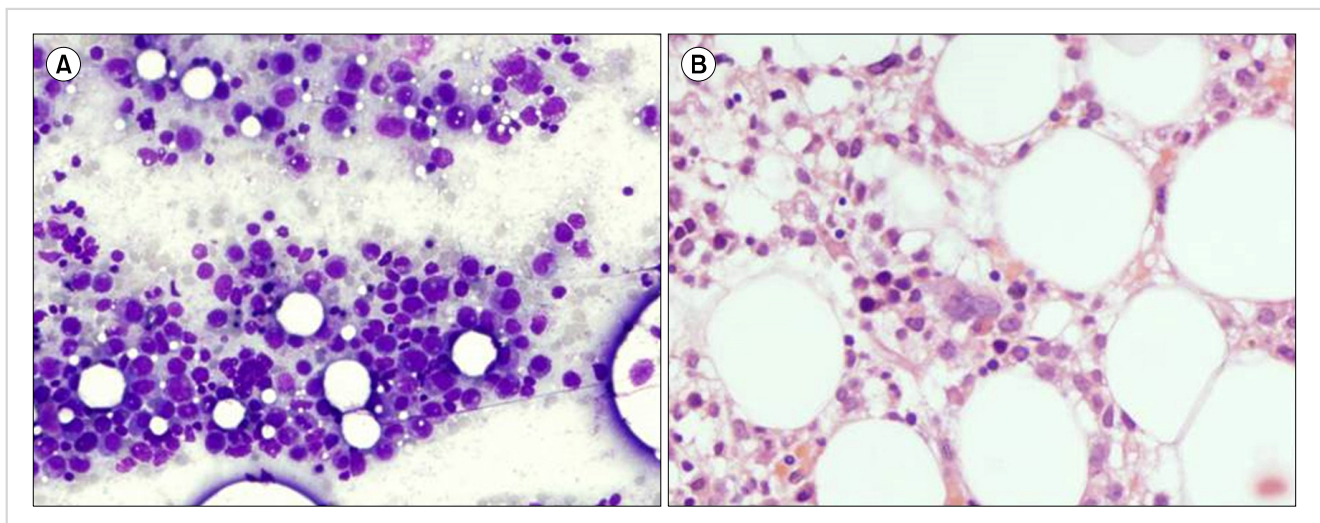
## Post-liver transplant myeloid maturation arrest

**TO THE EDITOR:** Liver transplantation (LT) has become an effective therapeutic modality for a variety of end-stage acute and chronic liver diseases. Over time, the survival rates have been steadily increasing, but complications remain common in the early and late post-transplant period, contributing to significant morbidity and mortality. Marrow suppression resulting in anemia, thrombocytopenia, and leu-

kopenia is often seen in post-LT patients [1]. However, maturational arrest of the marrow elements at a precursor stage occurs infrequently. Here we present two cases of marked myeloid maturation arrest in the post-LT period in the context of a cytomegalovirus (CMV) infection.

### Case 1

A 52-year-old man had chronic liver disease (CLD) and cryptogenic cirrhosis decompensated with ascites, jaundice, acute kidney injury, and hepatic encephalopathy with eccentric portal vein thrombosis. He underwent deceased donor LT in September 2013 and was started on standard triple drug immunosuppression with tacrolimus, mycophenolate mofetil, and prednisolone. The explanted liver showed cirrhosis with an occlusive thrombus of the portal vein. In the early perioperative period, pancytopenia was diagnosed (hemoglobin [Hb], 7.3 g/dL; total leukocyte count,  $0.8 \times 10^9/L$ ; platelet count,  $10 \times 10^9/L$ ). The immunosuppressants and antibiotics were optimized accordingly. He later developed multiple episodes of sepsis during the post-operative period. CMV was detected in a bronchoalveolar lavage and later in plasma samples. A CMV detection assay was performed via real-time quantitative polymerase chain reaction (PCR) for the detection of CMV DNA (COBAS R, Roche Diagnostics, Branchburg, NJ, USA). The cut-off value of the CMV DNA load defining a positive result was 1,000 copies/mL. The bronchoalveolar lavage sample showed  $4.60 \times 10^6$  copies/mL and the plasma sample had  $8 \times 10^3$  copies/mL of CMV DNA. Multiple blood transfusions were given per clinical requirements, as was regenerative therapy in the form of granulocyte-monocyte colony stimulating factor (GM-CSF). Despite these measures, the severe pancytopenia persisted. The patient developed severe sepsis (with a multi-drug resistant organism) that led to multi-organ failure and eventually succumbed to the illness.



**Fig. 1.** Bone marrow aspirate (A, May-Grunwald Giemsa stain,  $\times 400$ ) and biopsy (B, Haematoxylin-eosin stain,  $\times 400$ ) of patient 1 showing myeloid maturation arrest.

A bone marrow (BM) aspiration and biopsy done in the postoperative period revealed features of trilineage maturation arrest. The BM showed predominantly myelocytes and metamyelocytes with a few mature granulocytes (5%). Similarly, the erythroid series showed early and intermediate normoblasts with a reduced number of late normoblast. Megakaryocytes were also reduced in number with immature hypolobated forms (Fig. 1).

### Case 2

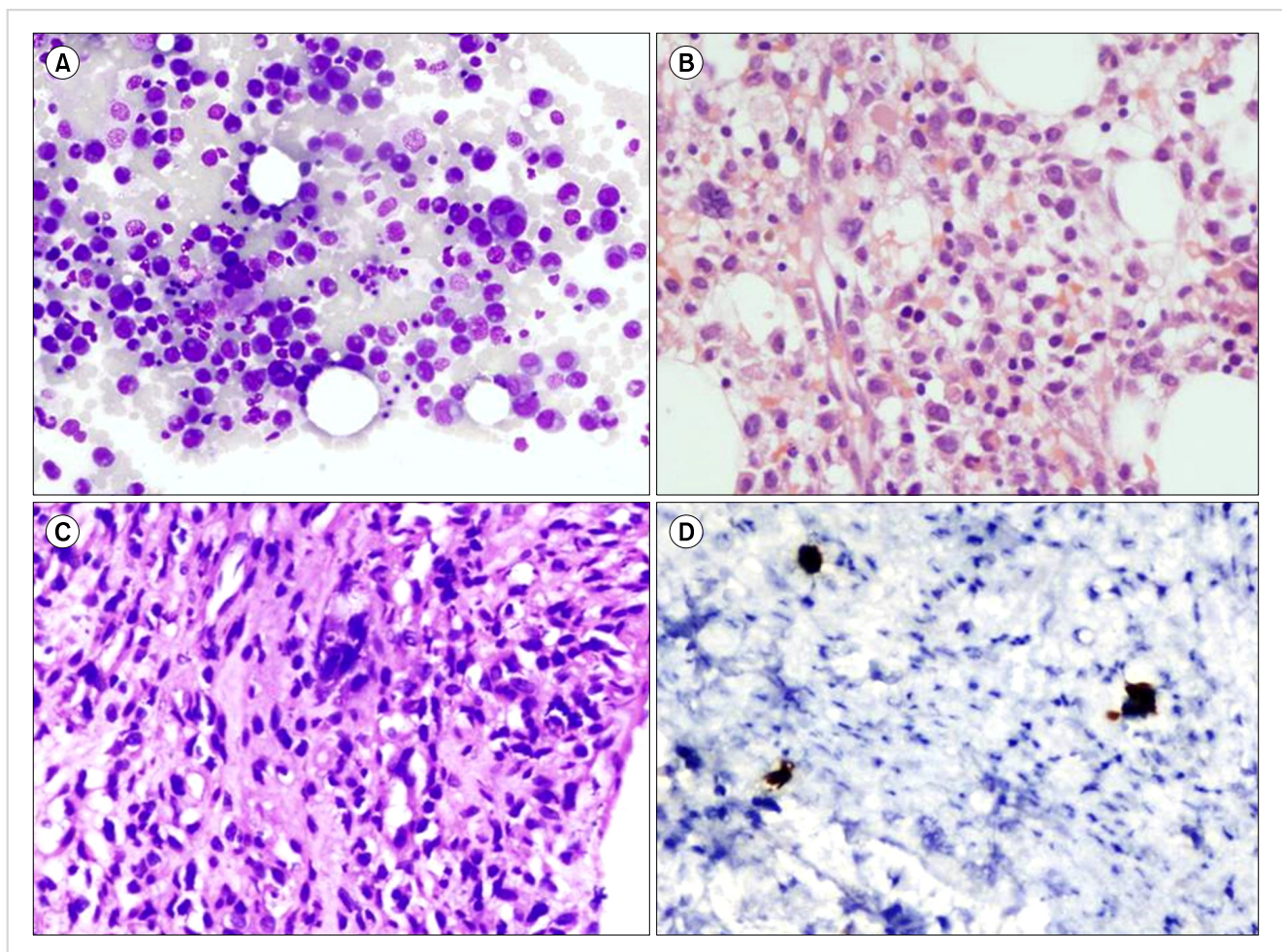
A 53-year-old man with ethanol-related CLD decompensated with ascites and jaundice underwent living donor LT in September 2016 and was started on standard immunosuppression as described above. He then presented to us with complaints of headache and loose watery stools. He was started on antibiotics and other supportive medications. A sigmoidoscopy revealed a diffusely erythematous colonic mucosa with discrete ulcerations and friable mucosa. Biopsies of these areas showed features of CMV colitis, which was confirmed by immunohistochemistry (IHC) staining

performed using anti-CMV monoclonal antibodies 8B1.2, IG5.2, and 2D4.2 (Cell Marque, Hot Springs, AZ, USA). He was started on ganciclovir. A repeat sigmoidoscopy was CMV-negative. However, the patient's symptoms persisted and he developed leukopenia (Hb, 6.4 g/dL; total leucocyte count,  $0.6 \times 10^9/L$ ; platelet counts,  $160 \times 10^9/L$ ). Graft-versus-host disease (GVHD) was suspected and supportive treatment was provided. Regenerative therapy with granulocyte-colony stimulating factor was administered, but the blood counts failed to improve. Patient developed severe neutropenic sepsis and intestinal paralysis and ultimately succumbed to septic encephalopathy and septic shock.

A BM aspiration and biopsy showed hypocellular marrow with myeloid maturation arrest with decreased myeloid precursors and immature forms and evidence of hemophagocytosis (Fig. 2).

### Discussion

LT is fraught with a panoply of hematologic disorders, a common entity being cytopenia. The etiological spectrum



**Fig. 2.** Bone marrow aspirate (A, May-Grunwald Giemsa stain,  $\times 400$ ) and biopsy (B, Haematoxylin-eosin stain,  $\times 400$ ) of patient 2 showing myeloid maturation arrest. A colonic biopsy showed cytomegalovirus (CMV) inclusion bodies (C, Haematoxylin-eosin stain,  $\times 400$ ) and CMV immunohistochemical positivity (D,  $\times 400$ ).

for cytopenia includes infectious, inflammatory, immunological, or chemotherapy-induced causes. Marrow suppression resulting in anemia, thrombocytopenia, and leukopenia is often seen in post-LT patients [1]; however, the maturation arrest of myeloid and other hematopoietic elements occurs comparatively infrequently. Kuan *et al.* [2] reported a case of pancytopenia and myeloid maturation arrest in an autologous stem cell transplant recipient. The underlying pathology in their case was extrapulmonary tuberculosis, whereas the culprit in our cases was CMV infection. Overwhelming infections, especially those resulting in septic shock, may cause extreme neutrophilia on the one hand but neutropenia on the other. The degree and duration of neutropenia have been shown to directly contribute to the risk of post-LT infection [3]. Furthermore, myelo- adverse effects result in reducing or changing the immunosuppressive regimen, which in turn, might affect graft survival [4, 5]. Neutropenia secondary to widespread sepsis results when the rate of mobilization of mature cells from the BM exceeds that of proliferation of newer cells. In these instances, extreme left-shift or maturation arrest occurs, and CMV is commonly seen as a cause of hematopoietic suppression [5]. In addition to the direct effect on the host, the virus also has several indirect effects. A myeloid maturation arrest leading to neutropenia can be seen in CMV infection [6]. CMV has also been associated with the development of hemophagocytic syndrome (HPS) in transplant recipients. HPS is a rare but fatal disorder related to uncontrolled systemic T-cell activation [7]. Although the pathogenesis is not fully understood, viral infections are a factor in the activated T-cell response seen in HPS. An additional contributing factor of neutropenia due to maturational arrest in our cases may be related to iatrogenic impedance of the granulocytic maturation. Immunomodulatory drugs result in dose-dependent down-regulation of the transcription of proteins involved in granulopoiesis regulation [8]. Thus, we must further characterize the effects of various immunomodulator classes on the transcriptional regulation of granulocytic maturation.

GVHD was another rare yet important complication of LT in our patient. The cell-mediated type of GVHD carries a high fatality rate, probably due to delays in diagnosis, as it very often presents with non-specific features mimicking infections and other diseases common in transplant recipients [9].

The management of leukopenia secondary to myelopoietic arrest following LT relies primarily on early recognition through clinical judgement and an in-depth assessment of the patient to rule out an infectious pathology. If the work-up points toward a therapeutic culprit, then an alternative regimen must be attempted. Discontinuation of the likely offending agent does carry significant clinical risk as interruption of the immunosuppressants for even as few as 7 days has resulted in rejection episodes. Drugs used in the treatment of CMV such as ganciclovir and valganciclovir are frequently implicated to cause neutropenia [10].

A pre-emptive CMV strategy consisting of dose interruptions of prophylactic ganciclovir/valganciclovir therapy along with close weekly monitoring of CMV by PCR has been suggested. Leukopenia resulting from anti-CMV therapy may be managed with G-CSF to enable the continuation of full doses of ganciclovir/valganciclovir [11]. Regenerative therapy in the form of G-CSF or GM-CSF may be attempted in cases that are refractive to multiple transfusions. However, this may prove ineffective in cases of severe sepsis since granulocytic cells fail to respond to these growth factors due to downregulation of the G-CSF receptors by the bioactive products released secondary to systemic sepsis (e.g., lipopolysaccharide and tumor necrosis factor) [12].

With respect to HPS, the treatment of triggering factors using antimicrobials and tapering immunosuppressants is of paramount importance in addition to continued supportive treatment in the form of G-CSF and intravenous immunoglobulin or steroids. In refractory cases, treatment with cyclosporine A or anti-thymocyte globulin has been proposed [13].

### Conclusion

In conclusion, myeloid maturation arrest is an uncommon finding in the post-LT setting. Knowledge of the existing risk factors in the recipient combined with an early-stage BM examination plays a critical role in the management of LT recipients since it is associated with a rapid downhill course in our experience. Thus, there is an urgent need to investigate measures to prevent and promptly treat this condition to improve adverse outcomes.

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### Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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## A case of primary plasma cell leukemia exhibiting hemophagocytic plasma cells relapsed with multiple cutaneous plasmacytoma

**TO THE EDITOR:** Cutaneous infiltration in multiple myeloma (MM) is an extremely rare condition with poor prognosis that accounts for only approximately 0.6% of patients with MM according to a recent large-scale study [1]. Primary plasma cell leukemia (PCL) constitutes only 2%–5% of all myeloma cases, with a higher proportion of light-chain-only cases presenting as PCL rather than as MM. Typically, the immunophenotype of PCL differs from that of multiple myeloma (MM) in that it lacks aberrant CD56 expression and more frequently shows an abnormal karyotype [2].

Hemophagocytosis in the bone marrow is a characteristic feature of some aggressive disorders, such as hemophagocytic syndrome by histiocytes, but more rarely by myeloblasts, in acute myeloid leukemia. Furthermore, this characteristic is extremely rare among plasma cells, particularly in PCL, and only a few reports on such cases have been published [3-8]. Herein, we report a rare case of cutaneous infiltration of malignant plasma cells, which initially presented as bicytopenia, combined with primary lambda-type light-chain PCL characterized by marked phagocytosis of erythrocytes and platelets by neoplastic plasma cells.

A 77-year-old woman experienced fatigue for several weeks and presented to our hospital with bicytopenia. A complete blood cell count analysis showed normocytic normochromic anemia with thrombocytopenia and leukocytosis (hemoglobin, 9.6 g/dL; platelets,  $22.0 \times 10^9/L$ ; white blood cell count,  $16.8 \times 10^9/L$ ). Laboratory tests revealed normal levels of calcium, blood urea nitrogen, creatinine, and lactate dehydrogenase. However, magnetic resonance imaging exhibited diffuse bone marrow signal change without definite mass or lytic lesion formation. Serum and urine protein electrophoresis displayed a monoclonal band in the beta region, and immunofixation revealed only lambda light-chain monoclonality with markedly increased serum lambda light-chain level (2,952 mg/L; normal range, 5.71–26.30 mg/L). The  $\beta$ -2 microglobulin level was also increased (12.06 mg/L; normal range, 0.0–2.4 mg/L). A peripheral blood smear demonstrated the presence of atypical plasma cells in various sizes with cytoplasmic vacuolations, which constitute up to 52.0%. Bone marrow aspiration showed hypercellular marrow particles with a myeloid-to-erythroid ratio of 8:1 with decreased megakaryocytes. Neoplastic plasma cells accounted for up to 67.2% of all nucleated cells. Numerous binucleated or multinucleated plasma cells were observed, of which 5.7% displayed prominent phagocytosis, primarily of erythrocytes and platelets (Fig. 1A). Flow cytometric analysis revealed that the plasma cells lacked CD56 expression, which is frequently found in PCL, and no other aberrant expression was observed. In addition, immunohistochemical analysis showed that the plasma cells were positive for CD138 and negative for CD20. Karyotypic analysis revealed an abnormal 45,X,-X,+1,dic(1;8)(p13;p23),del(6)(q22q25),del(8)(p21) karyotype (Fig. 1B). The patient was diagnosed with primary PCL, fulfilling the diagnostic criteria of the International Myeloma Working Group, which suggested more than 20% circulating plasma cells and an absolute plasma cell count of greater than  $2 \times 10^9/L$  [9]. Bortezomib, melphalan, and prednisolone (VMP) therapy was initiated, which reverted her serum lambda light-chain level to normal after one treatment cycle. A second treatment cycle with VMP was planned, but the patient refused further chemotherapy. After 5 months from the termination of the first cycle of VMP therapy, multiple subcutaneous nodules developed on her left upper limb, trunk, back, and lower extremities (Fig. 2A), and her serum lambda light-chain level increased again to 127.65 mg/L.