INTERNAL MEDICINE

□ CASE REPORT □

Myelodysplastic Syndrome Developing Presacral Extramedullary Hematopoiesis with Atypical MRI Findings

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Abstract

A 64-year-old woman was diagnosed to have refractory cytopenia with multilineage dysplasia (RCMD) including an increased number of sideroblasts in the bone marrow (BM). Computed tomography (CT) revealed a presacral mass which showed iso- or high-intensity signals according to T1-weighted and hypo-intensity signals on T2-weighted magnetic resonance imaging (MRI). CT-guided biopsy revealed the presence of hematopoietic tissue with features that correlated with the BM findings. While the formation of extramedullary hematopoiesis in the presacral area is rare, it is important to differentiate it from other parasacral tumors even though such differentiation is often difficult. This patient demonstrated atypical MRI signals possibly due to an increase in the cellular iron content of the erythroid precursors.

Key words: extramedullary hematopoiesis, presacral tumor, myelodysplastic syndrome, sideroblasts

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Introduction

Extramedullary hematopoiesis (EMH) is the proliferation of hematopoietic tissue outside the bone marrow (BM), typically seen in patients with chronic hemolytic anemia, such as thalassemia and sickle cell disease, or myeloproliferative neoplasms, especially primary myelofibrosis, and it is considered to represent the reactive and/or compensatory expansion of hematopoietic tissue outside the BM for anemia or an abnormal BM function (1-3). EMH may also accompany various other hematological and non-hematological disorders, however, EMH associated with myelodysplastic syndrome (MDS) has so far only rarely been reported (4-7). While most cases of EMH are formed in the liver and/or spleen, about 5% of all cases form EMH at other sites of the body (1-3). The formation of EMH in the presacral area is very rare and only thirty such cases have so far been reported in the literature (8-13), and, to our knowledge, no case of presacral EMH associated with MDS has ever been reported. We herein report a case of MDS (refractory cytopenia with multilineage dysplasia; RCMD) with an increased number of sideroblasts in the BM which formed an EMH mass in the presacral region.

Case Report

A 64-year-old woman with MDS was admitted in April 2014 because of general fatigue. In 1997, she was referred to our hospital because of mild macrocytic anemia with a hemoglobin (Hb) level of 9.8 g/dL which had been identified during a regular health check and she was thus diagnosed as having refractory anemia with ringed sideroblasts. However, she declined to receive medical care at that time. In 2005, general fatigue developed and she visited our hospital again. There was a progression of the anemia with an Hb level of around 8 g/dL and the administration of oral corticosteroids was thus started. Ciclosporin was added two years later. However, she stopped receiving these treatments in 2008 before any improvement was seen. In 2011, she visited our hospital once again because of symptoms associated with a worsening of anemia. The Hb level was 6.4 g/dL and the transfusion of red blood cells (RBC) was started. In 2013, she received an erythroid stimulating agent (ESA), epoetin beta pegol, for eight months without any substantial effect. In January 2014, she fell and broke her left femoral bone which needed to be surgically repaired. The frequency of RBC transfusion increased further and she was admitted

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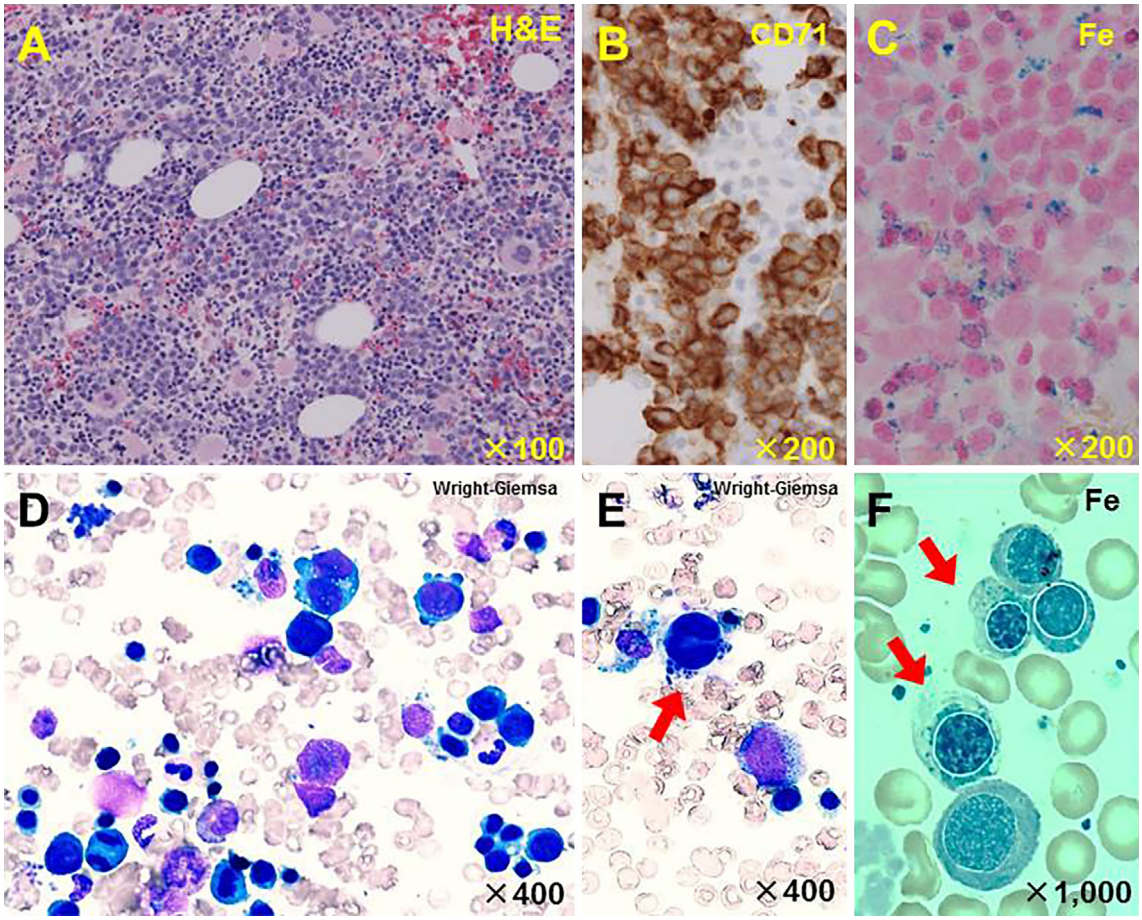

Figure 1. **Bone marrow findings on admission. (A) The clot section of the bone marrow aspirate shows mildly hypercellular bone marrow with an increased number of magakaryocytes and erythroblasts (Hematoxylin and Eosin staining, ×100). (B) Immunostaining with anti-CD71-antibody confirms the increase of erythroid cells (×200). (C) Iron stain demonstrates an increased number of sideroblasts (×200). (D) The bone marrow smear shows increased immature erythroid cells with occasional binucleated erythroblasts (Wright-Giemsa stain ×400). (E) The arrow indicates a micromegakaryocyte (Wright-Giemsa stain ×400). (F) Iron stain shows increased sideroblasts, of which 45% were ring sideroblasts (arrows) (×1,000).**

in April for the evaluation and treatment of the anemia.

On admission, she was anemic and a systolic heart murmur was audible. The liver and spleen were palpable below the lower costal margins. The laboratory data showed the white blood cell count to be 3.7×10^{9}/L with 0.5% myelocytes, 73.5% neutrophils, 4.5% eosinophils, 21.0% lymphocytes, and 0.5% monocytes. The RBC count was 2.39×10^{12}/L with 0.33% reticulocytes, the Hb 7.4 g/dL, the hematocrit 22.1%, and the platelet count 330×10^{9}/L. Coagulation tests were within the reference ranges. Other blood tests did not show any significant abnormalities, except for an elevated serum ferritin level at 1,280 ng/dL. The BM was mildly hypercellular and the magakaryocytes had increased in number and showed a variety of dysplastic features, such as micromegakaryocytes and multiple widely separated nuclei (Fig. 1A and E). The erythroid cells accounted for 60% of the BM nucleated cells and the number of immature cells had increased with occasional binucleated erythroblasts (Fig. 1A, B, and D). Iron staining showed most of the erythroid cells to be sideroblasts, of which 45% were ring sideroblasts (Fig. 1C and F). The myeloid cells accounted for 23% and myeloblasts 1.2% of the BM nucleated cells. Morphological dysgranulopoiesis was not apparent. The karyotype of the bone marrow cells was 47,XX,+8 [20]. The patient was therefore diagnosed with RCMD.

Computed tomography (CT) was performed to evaluate the hepatosplenomegaly detected on a physical examination and revealed a lobulated and well-margined mass measuring 3×5 cm in size in the presacral region which was diffusely contrast-enhanced (Fig. 2A). Magnetic resonance imaging (MRI) showed the presacral mass to have iso- or high-intensity on T1-weighted and hypo-intensity on T2-weighted images and it was diffusely enhanced after the intravenous injection of gadolinium (Fig. 2B-D).

As the differential diagnosis of the presacral mass included mesenchymal or hematological tumors, CT-guided biopsy of the mass was performed. The biopsy revealed the presence of hematopoietic tissue with a fat:cell ratio of 1:1-2

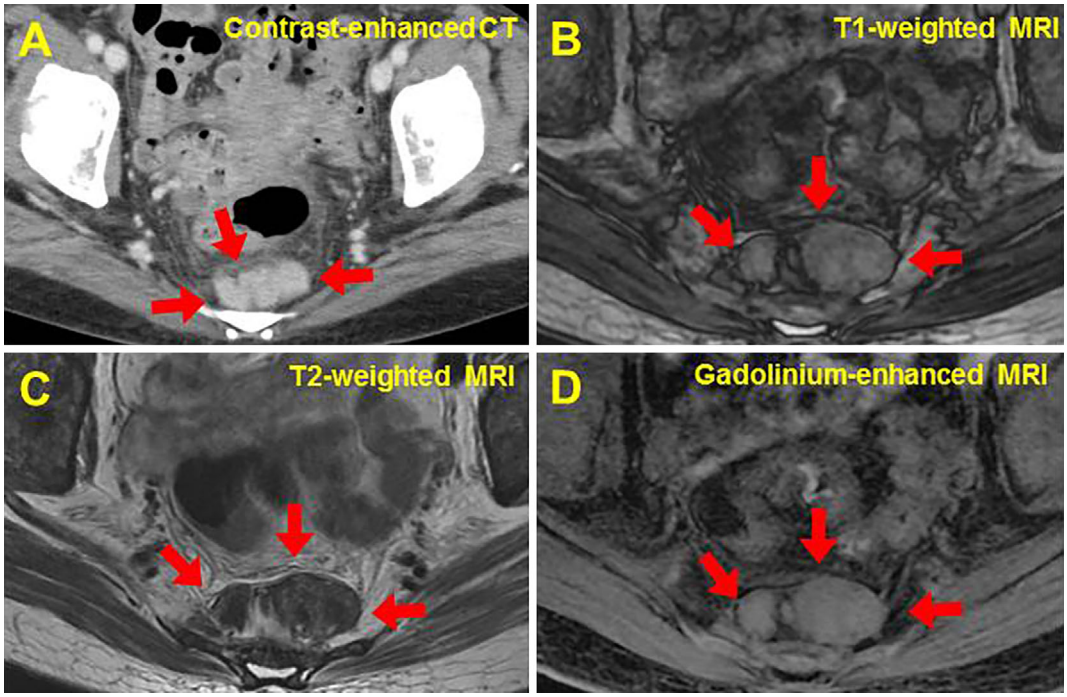

Figure 2. **Computed tomography (CT) and magnetic resonance imaging (MRI) of the presacral extramedullary hematopoiesis. (A) Contrast-enhanced CT reveals a lobulated and well-margined mass (arrows) in the presacral region. (B-D) MRI shows that the mass (arrows) is iso- or high-intensity on T1-weighted (B) and hypo-intensity on T2-weighted (C) images and that it is diffusely enhanced after the intravenous injection of gadolinium (D).**

(Fig. 3A). CD71-positive erythroid cells were hyperplastic (Fig. 3B) and the number of CD42b-positive magakaryocytes were also found to have increased and the presence of small mononuclear megakaryocytes was also noted (Fig. 3C). There was no increase in the number of myeloblasts; however, the number of p53-positive cells had increased (Fig. 3D). These findings were similar to those of the BM findings and we diagnosed the mass to be extramedullary hematopoiesis with myelodysplastic features.

Subcutaneous azacitidine was started at 75 mg/m^2 for five days and she was thereafter discharged. Two additional 5-day azacitidine courses were given on an outpatient basis, however, after the third course, she developed complications with septic shock and thus emergently transported to her local hospital and died before any therapeutic effects were noted. A CT scan taken at that time did not show any noticeable changes in the size and shape of the presacral EMH.

Discussion

The most common sites of EMH are the liver and spleen, which are the sites of hematopoiesis during the fetal period and hepatosplenic EMH accounts for 95% of all EMH lesions. The remaining 5% form at non-hepatosplenic sites. While the vertebral column, lymph node, and retroperitoneum are the most common sites of non-hepatopslenic EMH, EMH occurring at various other sites has also been reported (1-3). Among them, presacral EMH is very rare and only thirty cases have been reported in the literature (8-13). Three cases of presacral EMH have been reported to be associated with chronic anemia but presacral EMH accompanying MDS has not been reported. In the present case, the presacral mass was diagnosed to be the extramedullary proliferation of dysplastic bone marrow tissue, and not myeloid sarcoma as there was no increase in the number of myeloblasts (14).

The occurrence of presacral tumors is a rare condition and their frequency is reported to be 1:40,000 patient admissions (15). As they are usually slow-growing and from 26 to 50% of the patients are asymptomatic, many cases of presacral tumors may not draw medical attention unless imaging studies encompassing the pelvic region incidentally detect them, and thus a considerable number of such patients remain unnoticed. Adult presacral EMH masses are a heterogeneous category, with 65% being congenital, 11% neurogenic, 11% osteo-chondral, and 12% other miscellaneous tumors, and, importantly, about half of them are malignant or demonstrate malignant changes (15). However, the differentiation of such masses between benign and malignant presacral tumors based on the clinical findings is difficult and therefore a biopsy of such masses is needed in most instances.

The MRI signals of EMH mostly depend on the composite of the hematopoietic tissue and most cases show iso- to hyper-intensity signals on T1- and T2-weighted MRI imaging due to increased cellularity or the presence of fat tissue in the hematopoietic tissue with a uniform enhancement af-

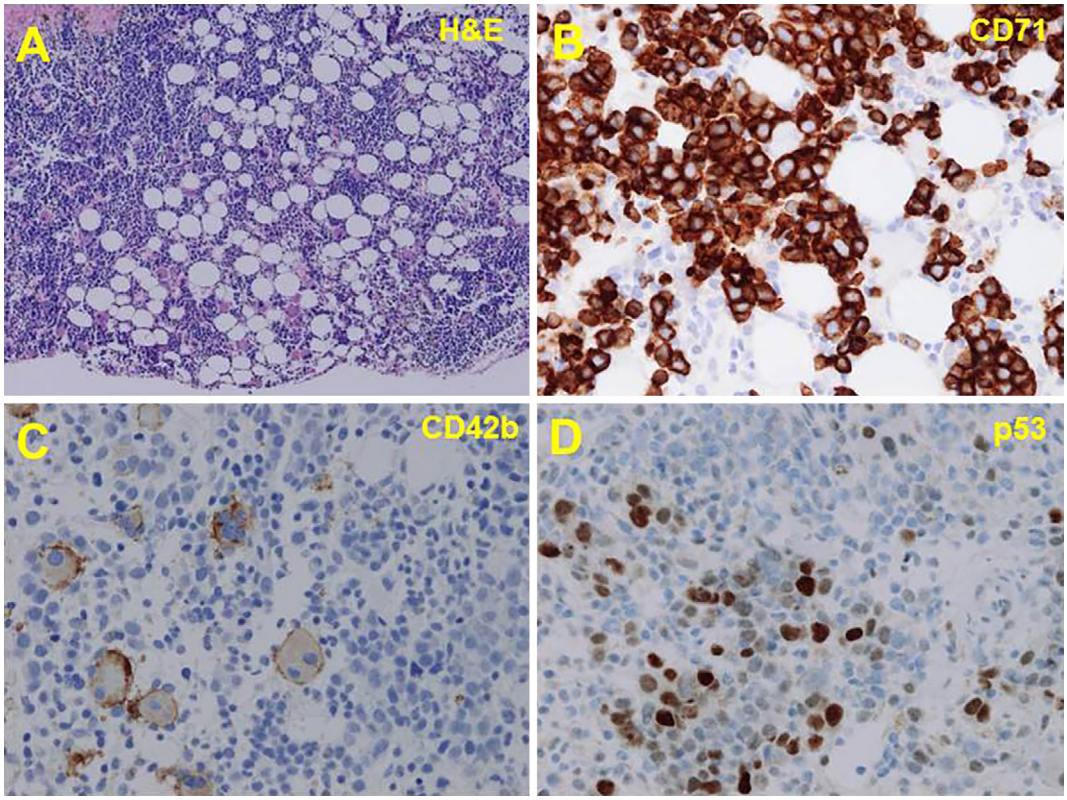

Figure 3. **Computed tomography-guided biopsy of the presacral extramedullary hematopoiesis. (A) A biopsy sample reveals hematopoietic tissue with hyperplasia of the erythroid cells (Hematoxylin and Eosin staining, ×100). (B) Immunostaining shows the number of CD71-positive erythroid cells to have increased (×200). (C) The number of CD42b-positive magakaryocytes also increased and the presence of small mononuclear megakaryocytes and those with widely separated nuclei are observed (×200). (D) An increase in the number of p53-postive cells (×200) is also observed.**

ter gadolinium intravenous injection (2, 3, 7). In the present case, the presacral mass showed a hypo-intensity signal on T2-weighted imaging, which was an atypical characteristic of EMH and thus indicated a diagnosis of EMH to be unlikely before performing a biopsy. We consider that the increased content of iron due to the hyperplastic sideroblasts with a high cellular iron content in the hematopoietic tissue led to the hypo-intensity signal on T2-weighted MRI imaging. Similar hypointensity signals on T2-weighted images of a thoracic epidural EMH mass have been reported in a patient with refractory anemia with ring sideroblasts (4). As the category of RCMD and ringed sideroblasts in the 3rd edition of the World Health Organization (WHO) classification was discarded and was instead included in RCMD according to the 4th edition of the WHO classification (14), a considerable number of RCMD cases had >15% ring sideroblasts in the BM and such RCMD cases might also have an increased iron content in the hematopoietic tissue, which would be sufficient to affect the signal intensities on MRI. In the latest 2016 revision of the WHO classification, RCMD cases with >15% ring sideroblasts have again been separated into a category of MDS with ring sideroblasts and multilineage dysplasia (16). It is therefore expected that studies on the effects of iron content in hematopoietic tissue on imaging studies will be more feasible in MDS patients and the accumulation of pertinent clinical data is awaited.

The mechanism of EMH occurring in the presacral region is considered to be either due to the stimulation of ectopic hematopoietic stem cells in the presacral region, hematogenous emboli, extrusion of proliferative BM into subperiosteal region through a weakened bone cortex, or the spread of proliferative BM due to a sacrum fracture (8). In the present case, we consider that the extrusion of the hematopoietic tissue through the weakened bone cortex to be most likely as she had recently suffered a femoral fracture which is highly suggestive of osteoporosis of the bones. The present case had mild hepatosplenomegaly and it is possible that she also had hepatosplenic EMH; however, unfortunately, this possibility was not studied more in detail. The role of ESA in the formation of the EMH should be mentioned here as Buccisano et al. reported two cases of EMH treated with ESA and thereafter developed epidural EMH masses compressing the spinal cord which subsided readily on ESA withdrawal (17). However, while the present case was treated with ESA and its effect on the formation of EMH cannot be excluded, the ESA was discontinued seven months before the diagnosis of presacral EMH, so we think that the contribution of ESA to EMH formation in this case is unlikely and instead consider that this case exemplifies another case of EMH associated with MDS itself.

Although EMH presenting as a presacral mass is rare and MDS developing presacral EMH is even rarer, MDS should nevertheless be included in the differential diagnosis of EMH. MDS is a heterogeneous entity and dysplastic hematopoietic tissue can present various MRI findings and, thus, care should be taken when interpreting the MRI findings of any masses in patients with MDS.

The authors state that they have no Conflict of Interest (COI).

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