Dear Editor,

Erythropoietic protoporphyria (EPP) is a rare autosomal recessive disease characterized by a deficiency of the enzyme ferrochelatase (FECH), which causes protoporphyrin deposition and photosensitivity. The excess protoporphyrin is excreted by the liver and may induce liver damage. About 20% of patients with EPP develop liver dysfunction, and 2–5% of them progress to cirrhosis and liver failure with a very poor prognosis [1, 2]. No aplastic anemia associated with congenital EPP has been reported to date. Here, we report a case of severe aplastic anemia in a congenital EPP patient. The dosage of cyclosporine A (CsA) is limited for the patient due to EPP associated liver fibrosis and avatrombopag induced complete response of aplastic anemia safely.

In October 2019, a 19-year-old man was admitted to our hospital with liver dysfunction. He had hypersensitivity of skin to sunlight since childhood. Liver function tests demonstrated elevated liver enzymes (alanine aminotransferase, ALT 206U/L, aspartate aminotransferase, AST 81U/L, γ-glutamyl transpeptidase, γ-GT 186U/L, total bilirubin, TBil 19.9 µmol/L, direct bilirubin, DBil 7.6 µmol/L). Magnetic resonance imaging indicated liver fibrosis, broadened portal vein, portal hypertension, and splenomegaly. Liver puncture pathology revealed significant cholestasis of hepatocytes and bile ducts with liver fibrosis, broadened portal vein, portal hypertension, and splenomegaly. Liver puncture pathology revealed significant cholestasis of hepatocytes and bile ducts with liver fibrosis, biliary cast in the capillary bile ducts, and activated Kupffer cells presented as malts cross under polarized light, which is protoporphyrin crystal. Blood testing showed zinc protoporphyrin in erythrocytes was 8.8ug/g Hb (normal, 0–4.7). Total protoporphyrin in erythrocytes was not detected. Urinary porphyrin and uroporphyrinogen were negative. The next generation sequencing (NGS) revealed a double heterozygous FECH mutation (c.1156-1G > A, c.315-48 T > C) inherited from his parents. Otherwise, blood routine showed that leukocyte count (WBC) was 4.72 × 10⁹/L with a normal differential count, hemoglobin concentration (Hb) was 137 g/L, and platelet count (PLT) was 121 × 10⁹/L. This patient was diagnosed with congenital erythropoietic protoporphyria with liver fibrosis. Polyunsaturated phosphatidylcholine and diammonium glycyrrhizinate were provided to protect hepatocytes from toxic damage.

In July 2020, the patient presented with fatigue and low fever for 1 week. Blood routine displayed Hb of 55 g/L and reticulocyte absolute value of 20 × 10⁹/L, with WBC of 2.24 × 10⁹/L and PLT of 18 × 10⁹/L. Bone marrow (BM) punctures of the posterior superior iliac spine were performed twice. Both BM aspirate smears showed hypocellularity, and trephine biopsy showed overly hypoplasia, the bone marrow cavity filled with adipocytes and without any megakaryocytes (Fig. 1A–C). Chromosomal karyotype was 46, XY [20], and no gene mutation associated with AML/MPN/MDS was detected by NGS. The results of liver function tests were within normal limits during the period. Ferritin, folic acid, and vitamin B12 were not deficient. CMV-DNA and EBV-DNA were negative. Paroxysmal nocturnal hemoglobinuria (PNH) clone was detected by flow cytometry. PNH granulocyte clone sizes were 4% and 2% using the FLEAR and CD59-based assays, respectively. PNH erythrocyte clone sizes both were 2% for the CD59 and CD55-based assays, respectively. Severe aplastic anemia (AA) with PNH clone was diagnosed.

The patient had no sibling donor to perform hematopoietic stem cell transplantation (HSCT). Liver fibrosis also placed restrictions on allo-transplantation and intensive immunosuppressive treatment of antithymocyte globulin (ATG). He was started on cyclosporin A (CsA, 75 mg twice daily) with a trough concentration of CsA that was only

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LETTER TO THE EDITOR

Severe aplastic anemia in a patient with erythropoietic protoporphyria successfully treated by avatrombopag

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In October 2019, a 19-year-old man was admitted to our hospital with liver dysfunction. He had hypersensitivity of skin to sunlight since childhood. Liver function tests demonstrated elevated liver enzymes (alanine aminotransferase, ALT 206U/L, aspartate aminotransferase, AST 81U/L, γ-glutamyl transpeptidase, γ-GT 186U/L, total bilirubin, TBil 19.9 µmol/L, direct bilirubin, DBil 7.6 µmol/L). Magnetic resonance imaging indicated liver fibrosis, broadened portal vein, portal hypertension, and splenomegaly. Liver puncture pathology revealed significant cholestasis of hepatocytes and bile ducts with liver fibrosis, biliary cast in the capillary bile ducts, and activated Kupffer cells presented as malts cross under polarized light, which is protoporphyrin crystal. Blood testing showed zinc protoporphyrin in erythrocytes was 8.8ug/g Hb (normal, 0–4.7). Total protoporphyrin in erythrocytes was not detected. Urinary porphyrin and uroporphyrinogen were negative. The next generation sequencing (NGS) revealed a double heterozygous FECH mutation (c.1156-1G > A, c.315-48 T > C) inherited from his parents. Otherwise, blood routine showed that leukocyte count (WBC) was 4.72 × 10⁹/L with a normal differential count, hemoglobin concentration (Hb) was 137 g/L, and platelet count (PLT) was 121 × 10⁹/L. This patient was diagnosed with congenital erythropoietic protoporphyria with liver fibrosis. Polyunsaturated phosphatidylcholine and diammonium glycyrrhizinate were provided to protect hepatocytes from toxic damage.

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The patient had no sibling donor to perform hematopoietic stem cell transplantation (HSCT). Liver fibrosis also placed restrictions on allo-transplantation and intensive immunosuppressive treatment of antithymocyte globulin (ATG). He was started on cyclosporin A (CsA, 75 mg twice daily) with a trough concentration of CsA that was only
34.7 ng/ml. The dosage of CsA was increased to 125 mg twice daily, and the trough concentration of CsA was just 115.2 ng/ml. Limited by the potential hepatotoxicity, it is difficult to increase the CsA dose. Therefore, we initiated avatrombopag therapy (20 mg once daily). After 5 months, his Hb increased to 123 g/L, and platelet counts recovered to $103 \times 10^9$/L (Fig. 2A–B). Avatrombopag was reduced to 20 mg once every other day for 3 months and then stopped.

Fig. 1 The bone marrow aspirate smear. A Bone marrow smear exhibited hypocellular marrow (Wright-Giemsa stain, original magnification, $\times 100$). B The marrow smear showed increased non-hematopoietic cells such as osteoclasts, lymphocytes, and plasma cells (original magnification, $\times 1000$). C The marrow smear showed residual non-hematopoietic stroma (original magnification, $\times 100$)

Fig. 2 Graph of the timeline of platelet counts, hemoglobin level, and liver function tests in response to avatrombopag/cyclosporin A therapy. A–E: HGB, hemoglobin; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin. Dotted line shows lower limits of normal, and solid line showed upper limits of normal.
The patient kept response with a low dose of CsA (75 mg twice daily) and the liver function tests remained stable during the whole course (Fig. 2C–G).

Mild microcytic anemia with low ferritin can be seen in EPP patients even though the mechanism of iron deficiency is unclear [1]. But no aplastic anemia has been described. The patient presented pancytopenia at 20 years old without any deformity of the body. He had no family history of bone marrow failure disease, and no germline gene mutation associated with congenital AA had been detected by next generation sequencing. So, he was diagnosed with acquired AA. The detection of a PNH clone also supported the judgment. T Shirot a [3] reported a case of acquired EPP following myelodysplastic syndrome (MDS) with a 15-year-long history of AA, and stem cell defects of the heme biosynthesis in MDS are thought to lead to the development of EPP. But based on our knowledge, this is the first reported case of AA with congenital EPP. Acquired AA is characterized by pancytopenia and bone marrow hypoplasia, which results from immune-mediated hematopoiesis suppression. No immune injury has been assessed in EPP patients.

The majority of EPP patients manifest as photodermatoses and require sun protection. However, the deposition of protoporphyrin crystals in hepatocytes and bile canaliculi causes progressive liver damage in a minority of patients [4]. The EPP patients of end-stage liver disease should consider liver transplantation or even HSCT to prevent the recurrence of hepatic disease [5].

Treatment options for severe AA include HSCT and immunosuppressive therapy (IST) [6]. Both EPP and severe AA can be cured by HSCT. However, liver fibrosis and lack of sibling donor were hindering him from the transplantation therapy. ATG and the variety of drugs that may be combined also increase the burden on the liver and the risk of infection. Avatrombopag is a thrombopoietin receptor agonist (TPO-RA) that has been approved by the FDA for immune thrombocytopenia (ITP) and periprocedural thrombocytopenia in patients with chronic liver disease [7]. To date, this is the first case report for its use in severe AA. Eltrombopag, the other TPO-RA, showed a beneficial effect on the expansion and maintenance of hematopoietic stem cells and has been used in AA [8]. Eltrombopag has an adverse event of hepatic impairment. With the advantage of absence of hepatotoxicity, avatrombopag is an appropriate option for this patient. Finally, the patient achieved response with two oral drugs of avatrombopag and low-dose CsA sparing HSCT and ATG.

Aplastic anemia with EPP is rare and maybe a mere coincidence. Liver fibrosis associated with EPP affects the prognosis significantly. TPO-RA avatrombopag combined with CsA provides an available therapy for patients with severe aplastic anemia associated with EPP and liver fibrosis.