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CASE REPORT

Romiplostim therapy induces megakaryocyte hyperplasia similar in morphology to a myeloproliferative neoplasm

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Abstract The thrombopoietin analogue romiplostim was recently approved as a therapy for chronic immune thrombocytopenic purpura. It has showed good efficacy in stimulating a transient or sustained increase in platelet count in a majority of patients. Romiplostim's effect on bone marrow morphology has not been fully described, and we report on two patients on romiplostim therapy who underwent bone marrow biopsies. In both marrows, increased numbers of megakaryocytes with hyperplastic morphology, similar to that seen in myeloproliferative neoplasms, were identified. This morphologic finding could create a diagnostic dilemma or pitfall without appropriate clinical information.

Keywords Romiplostim therapy · Megakaryocyte hyperplasia · Myeloproliferative neoplasm

Introduction

Romiplostim was approved by the FDA in 2008 as a therapy for patients with chronic immune thrombocytopenic purpura (ITP). While most ITP therapies are aimed at decreasing platelet destruction, romiplostim stimulates platelet production by binding to the thrombopoietin receptor. As its peptide structure is dissimilar to human thrombopoietin, it is able to increase platelet counts in a majority of ITP patients without stimulating anti-thrombopoietin antibodies [1]. Routine work-up of ITP does not require a bone marrow biopsy either for diagnosis or to monitor response to therapy. As a consequence, few studies describe the bone marrow morphology of patients receiving romiplostim therapy. We recently encountered two such patients on romiplostim that underwent bone marrow biopsy. These biopsies showed atypical megakaryocyte morphology attributable to romiplostim stimulation. Without clinical history including patient therapy, this morphology would be suspicious for a myeloproliferative neoplasm.

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Clinical histories

Case #1 A previously healthy 68-year-old man presented with epistaxis and petechiae. Laboratory findings were platelets of 6,000 mm^3 and an absolute neutrophil count of 0 mm^3. A bone marrow biopsy showed a hypercellular marrow (60–80 %) with increased numbers of megakaryocytes and left-shifted granulopoiesis. Additional work-up revealed an increased immature platelet fraction of 16.7 % (normal 1.1–6.1 %) and a positive anti-neutrophil antibody. Subsequent evaluation included a negative finding for JAK2 mutation. A diagnosis of autoimmune thrombocytopenia and neutropenia was made. Initial therapy included prednisone and intravenous immunoglobulin (IVIG), which resulted in transient improvement of the neutropenia and thrombocytopenia. Additional treatments over the next 5 months included rituximab, G-CSF, cyclosporine, and cyclophosphamide. G-CSF normalized neutrophil counts, but no therapy resulted in sustained elevation of platelets. The patient's bleeding and petechiae resolved, however, and he refused a recommended splenectomy. Romiplostim therapy was initiated at 1 mcg/kg dosing every 2 weeks. Over the ensuing 11 months, the dose of romiplostim varied from 1 to 6 mcg/kg based on the degree of thrombocytopenia, and platelet counts ranged from 10,000 to

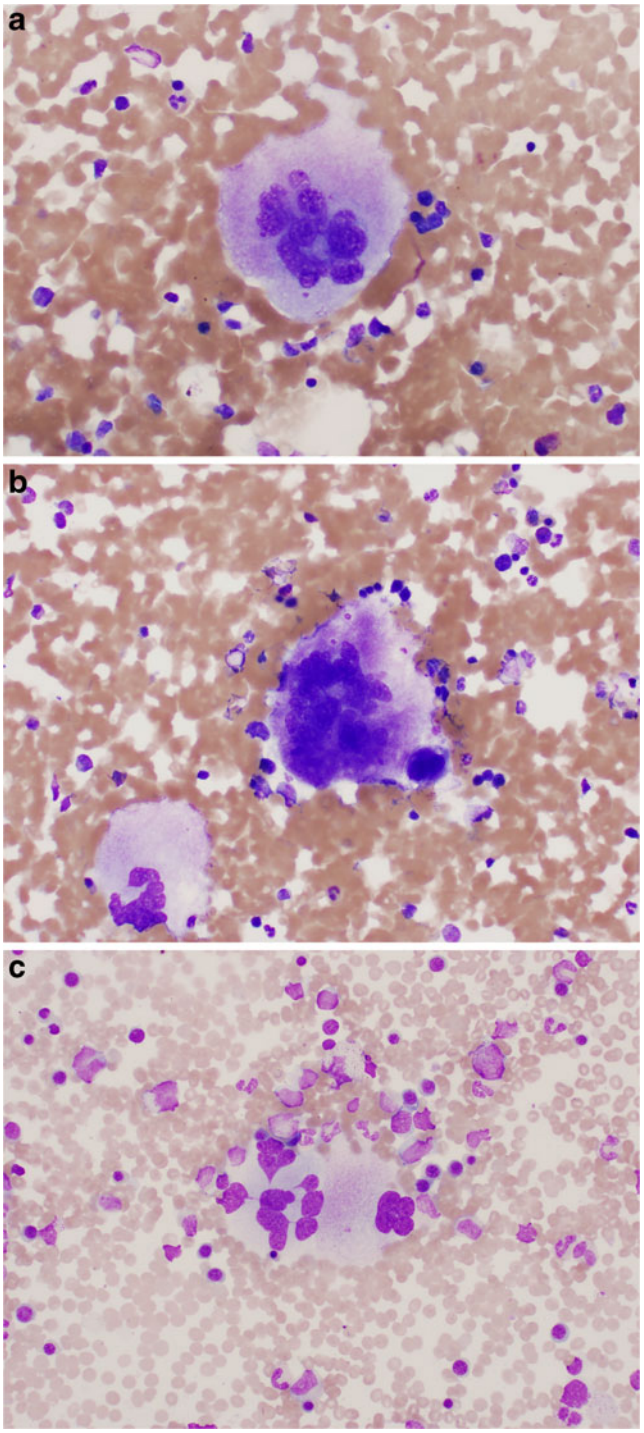

Fig. 1 **a** Aspirate smears show hyperlobate megakaryocytes, **b** megakaryocytes with hyperchromatic nuclei, and **c** megakaryocytes with separate nuclear lobes

200,000 mm^3. After 10 months of therapy, dosing was increased to weekly injections. A bone marrow biopsy was performed 7 days after his most recent dose when a small decrease in hemoglobin raised the possibility of marrow pathology such as myelodysplasia or myeloproliferative neoplasm. The clinical history accompanying the biopsy did not include the romiplostim therapy. The bone marrow showed a hypercellular bone marrow (70 %) with megakaryocyte hyperplasia and increased erythropoiesis.

Case #2 A 50-year-old man presented to the emergency treatment center with a dental infection and was found to have a platelet count of 0 mm^3. He was hospitalized and treated for presumed ITP with a platelet transfusion, solumedrol, and IVIG. He received five doses of romiplostim over the next 20 days, increasing from 1 to 5 mcg/kg. Platelets ranged from 0 to 4,000 mm^3. Eleven days after his last romiplostim dose, a bone marrow biopsy was performed as part of the patient's work-up prior to splenectomy. The clinical history did not include the romiplostim therapy. The bone marrow showed a hypercellular bone marrow (60–70 %) with megakaryocyte hyperplasia and increased erythropoiesis.

Materials and methods

The hematoxylin and eosin and Wright–Giemsa-stained slides were reviewed. The medical records were reviewed for clinical presentation, laboratory data, disease course, and treatment decisions.

Results

In both cases, the bone marrow aspirate smears showed increased numbers of large megakaryocytes with nuclear characteristics that varied from large and hyperchromatic

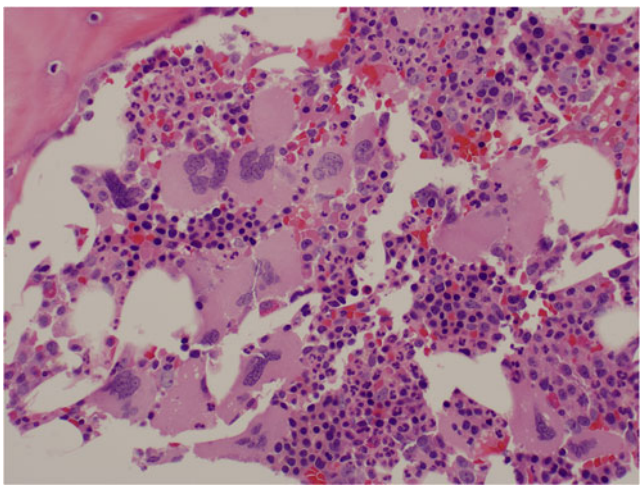

Fig. 2 Bone marrow sections show paratrabecular megakaryocyte clusters

monolobate nuclei to markedly hyperlobate nuclei. Sections of the bone marrow biopsy showed similar morphologic features with paratrabecular clusters of atypical-appearing megakaryocytes (see Figs. 1 and 2).

Discussion

Evaluation of bone marrow biopsy samples is not a routine part of the diagnostic work-up in patients with isolated thrombocytopenia and suspected ITP, and patients placed on romiplostim therapy regimen are also not routinely biopsied [2]. The likely scenario for biopsy in the setting of romiplostim, as in the first case presented, is a bone marrow evaluation as part of a work-up for myeloproliferative neoplasm or myelodysplasia. In this setting, the hyperplastic appearance of megakaryocytes responding to romiplostim stimulation may raise a diagnostic dilemma or potential pitfall, particularly if the clinical history of romiplostim therapy is not reported, as in both of our cases. The prefibrotic phase of primary myelofibrosis is defined in the fourth edition of the *World Health Organization Classification of Haematopoietic and Lymphoid Tissues* by "megakaryocyte proliferation and atypia… accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis [3]." As this definition depends on the sometimes difficult subjective assessment of marrow cellularity in specimens, the finding of atypical-appearing megakaryocytes can be the most concrete evidence for a myeloproliferative neoplasm [4]. Somewhat less confounding is the myelodysplastic syndrome of refractory cytopenia with unilineage dysplasia. In this entity, there is cytopenia (e.g., platelet count of <100) and dysplasia of ≥10 % of the cell lineage in question. In refractory thrombocytopenia, however, the dysplastic megakaryocytes are generally small and hypolobate or have separate nuclear lobes. While essential thrombocythemia is characterized by large and hyperlobated megakaryocytes, it is easily excluded in the patient on romiplostim by a platelet count of less than 450,000 mm^3.

Due to its efficacy, the use of romiplostim therapy is likely to increase. Two multicenter randomized studies in 125 adult patients with chronic ITP refractory to first-line therapies demonstrated a durable platelet response (from <30,000 to >50,000 mm^3 for 6 weeks) in 49 % of participants and a transient platelet increase in an additional 34 %, for an overall 83 % response rate [5]. A follow-up study demonstrated the safety and efficacy of weekly romiplostim therapy over a longer treatment period [6]. While romiplostim has been rarely associated with reticulin fibrosis in animal models and human patients similar to that seen in congenital overexpression of thrombopoietin, the fibrosis recedes with cessation of therapy [7]. Romiplostim has not been associated with therapy-related myeloid neoplasm.

Summary and conclusion

We present here two cases of bone marrow findings in patients on romiplostim therapy. The first patient was diagnosed with autoimmune thrombocytopenia and neutropenia and had received doses ranging from 1 to 6 mcg/kg either every 2 weeks or weekly for 11 months and a bone marrow biopsy 7 days from the last dose. The second patient had a working diagnosis of early ITP and had received five doses ranging from 1 to 5 mcg/kg in 20 days, with a bone marrow biopsy 11 days subsequent to the last dose. In each case, the bone marrow biopsy was hypercellular with markedly increased numbers of large and hyperlobated megakaryocytes, including large clusters on bone marrow sections. As these findings can lead to diagnostic confusion with a myeloproliferative neoplasm or, less likely, myelodysplasia, knowledge of romiplostim therapy is important for accurate bone marrow biopsy evaluation.

Conflict of interest The authors declare that they have no conflict of interest.

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