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Case Report

SPONTANEOUS REGRESSION OF ELTROMBOPAG INDUCED BONE MARROW FIBROSIS, IN A PATIENT WITH CHRONIC IMMUNE THROMBOCYTOPENIA.

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Abstract

Background: Bone marrow fibrosis has been reported in patients receiving thrombopoietin-receptor agonists (TPO-RA), such as Eltrombopag and Romiplostim. These agents have been tested extensively in patients with immune thrombocytopenia (ITP), a condition characterized by autoantibody-mediated platelet destruction and suboptimal platelet production.

Case presentation: Here we describe the case of a 72-year-old female with chronic ITP, who developed grade 2 bone marrow fibrosis (MF-2), during Eltrombopag treatment. Fibrosis was completely reversible after discontinuation of the TPO-RA.

Conclusions: This case confirms that bone marrow fibrosis may be induced by TPO-RA, such as Eltrombopag, and also that fibrosis is mostly spontaneous and normally decreases after discontinuation of medication.

Keywords: Eltrombopag, Immune thrombocytopenia, myelofibrosis, bone marrow histology.

Introduction

Immune thrombocytopenia (ITP) is an autoimmune bleeding disorder that lessens the production of platelets. ITP is a syndrome characterized by: (i) thrombocytopenia (platelet count less than 100,000/mm3); (ii) shortened platelet survival; (iii) presence of antiplatelet antibody in the plasma; (iv) normal or increased megakaryocytes in the bone marrow [1]. Patients are over 60 years of age with no predilection for sex and the chronic form being the most common. Childhood ITP is a clinically distinct condition from adult ITP with a higher likelihood of spontaneous remission.

ITP is a diagnosis of exclusion: an isolated thrombocytopenia without anemia or leukopenia without a clinically apparent cause. The disease is due to IgG antiplatelet autoantibodies, cytotoxic CD8+ T cells and to impaired megakaryocyte function [2]. Spleen is the primary site of platelet clearance in most patients but liver, bone marrow or lymph nodes may also be.

Current consensus supports the first line use of corticosteroids and intravenous immune globulin (IVIG) for ITP. These treatments fail in 60–80% of adult patients [3]. Subsequent treatments include rituximab and the splenectomy that are about 90% effective.

Recent advances in understanding ITP pathogenesis have highlighted the role of dysfunctional platelet reproduction; this led to a new generation of thrombopoietin (TPO)-receptor agonist (TPO-RA) therapies, including Eltrombopag and Romiplostim [4].

TPO-RAs bind to the thrombopoietin receptor c-MPL (TPO-R) on the hematopoietic stem cell leading to stem cell differentiation toward the megakaryocytic lineage. This culminates in stimulation of megakaryocyte proliferation, which results in elevation of platelet counts [5]. Beyond the effect on megakaryopoiesis, the drug also showed a stimulating effect on the hematopoietic stem cell with consistent clinical efficacy in aplastic anemia (AA) and myelodysplastic neoplasms (MDNs).

Early on, concerns were raised regarding possible induction of bone marrow fibrosis as a result of sustained stimulation of megakaryopoiesis by TPO-RAs. Recent clinical trials and reviews indicate that therapeutic doses of TPO-RA may indeed induce bone marrow fibrosis in patients with ITP starting from 6 months to 7 years [6-7].

Here we present a case of myelofibrosis induced by therapy with TPO-RA of a 72-year-old female patient affected by chronic ITP. We would like to focus on histologic findings of bone marrow biopsies performed at diagnosis, during treatment and after cessation of therapy.

Case report

A 72-year-old female patient in follow-up for thrombocytopenia since 1997, was admitted in 2016 for a severe reduction in platelets (12000x109/L) and she was diagnosed as chronic ITP. She received corticosteroids supplemented with intravenous gamma globulin (IVIg). The patient had good improvement and the case was stable for nearly 2 years.

In May 2018, the platelet count dropped and the patient was re-evaluated. Histologically, bone marrow trephine biopsy showed variable cellularity (from 10 to 65%) and megakaryocyte hyperplasia without

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evidence of fibrosis. Eltrombopag was started at 50 mg and after 7 days at 75 mg orally daily and gave a moderate response (plateled count >30x109/L).

After about three years, for gastrointestinal bleeding and worsening thrombocytopenia, the patient underwent a new bone marrow biopsy in April 2021. The pathological report included the following: hypercellularity (60%), dyserythropoiesis , clusters of pleomorphic megakaryocytes and diffuse fibrosis (MF-2) on reticulin staining (Fig. 1). CD34+ myelopoietic precursors were estimated at around 2%. Bone marrow cytogenetic analysis showed normal karyotype. Search for Janus protein tyrosine Kinases (JAK) 2 V617F mutation was performed on peripheral blood, with negative result. Eltrombopag was discontinued.

After three months of discontinuing, bone marrow biopsy was repeated, showing again abnormalities: hyper-cellularity (65%) megakaryocytes in normal numbers and with a tendency to aggregation, reticulin fibrosis grade 1-2. A significant reduction in reticulin fibrosis was finally seen on the biopsy performed six months after stopping treatment (Fig. 2).

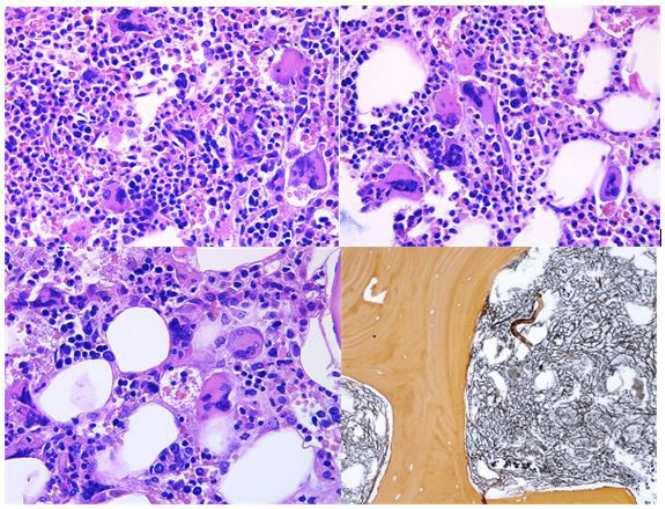

Figure 1: *Hypercellular bone marrow with clusters of pleomorphic megakaryocytes and dyserytropiesis. Grade 2 fibrosis on Gomori's stain.*

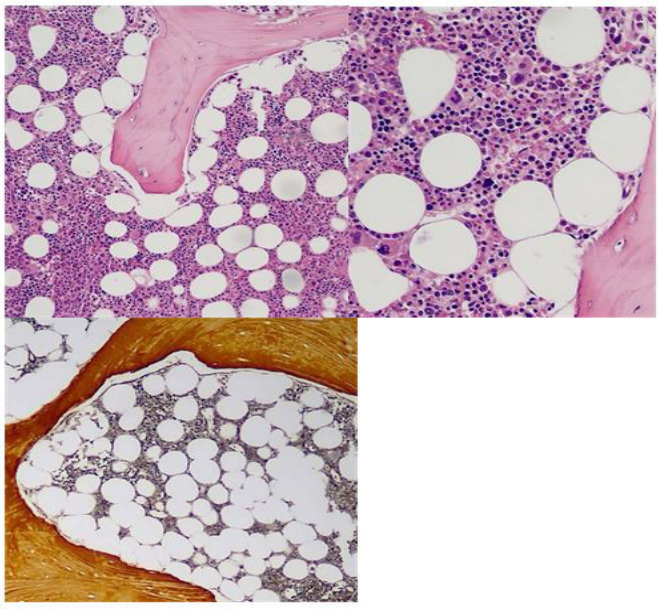

Figure 2: *Reduction of bone marrow cellularity with normal hematopoiesis. Grade 0 fibrosis on Gomori's stain*

Discussion

ITP is a disease caused by autoimmune destruction and which impairs the production of platelets. ITP is distinguished by low platelet count with normal bone marrow and absence of any other causes of thrombocytopenia. Recent advances in the understanding of ITP pathogenesis have highlighted the role of unfunctional platelet reproduction; this led to a new generation of TPO-RA therapies, including Eltrombopag. Eltrombopag induces human megakaryopoiesis binding to the TPO receptor (c-MPL) on stem cell by activating JAK and subsequent downstream signaling leading to differentiation toward the megakaryocytic lineage. Long-term use of Eltrombopag may increase the risk for development or progression of reticulin fiber deposition within the bone marrow. Myelofibrosis considers life-threatening blood problems so the medication must be discontinued if myelofibrosis is established. Here, we report a case of bone marrow fibrosis (MF-2) induced by TPO-RA Eltrombopag, appearing within 36 months following Eltrombopag administration. Six months after discontinuation, we documented disappearance of fibrosis in patient's bone marrow, confirming the non-evolutionary and spontaneously reversible process of TPO-RA-induced fibrosis. These findings are consistent with what is reported in the literature [8]. Our case report adds evidence signifying that myelofibrosis is an adverse effect due to treatment with TPO-RA. Histologic evaluation of bone marrow biopsy reveals atypical megakaryocytes and increased fibrosis. This can lead to diagnostic confusion with a myeloproliferative neoplasm. On-therapy, bone marrow of our patient was hypercellular due to panmyelosis with increased trilineage hematopoiesis. Megakaryocytes were increased in number, with the acquisition of evident pleomorphism and tendency to forming loose clusters. Maturative abnormalities of the erythropoietic series have also been observed and there was a grade 2 thickening of the reticular fibers. The overall picture was characterized by myeloproliferative neoplasm-like features, resembling essential thrombocythemia or early primary myelofibrosis, or myelodysplastic neoplasm with fibrosis.

Development of chronic myelogenous leukemia during treatment with TPO receptor agonist for ITP has also been reported [9]. Eltrombopag has continuous mimetic action on JAK2, MPL, and TPO with long-term administration. This could lead to genetic mutations which cause secondary myeloproliferative/myelodysplastic neoplasms with MF. This possible occurrence complicates, from the histological point of view, the differential diagnosis making it even more difficult.

Conclusion

Long-term use of Eltrombopag causes bone marrow changes, shown by increased reticulin and bone marrow fibrosis. MF is mostly spontaneous and normally decreases after discontinuation of medication, but in a few cases becomes persistent. Any patient on Eltrombopag treatment should be under careful observation and be closely monitored. Trephine bone marrow biopsy plays a key role in detecting increased reticulin and myelofibrosis.

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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