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IM - CASE RECORD

A 29-year-old woman with persistent thrombocytopenia

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Case presentation

Dr. Di Pasquale, Dr. Boscaro: In November 2013, a 29-year-old Moldovan woman was referred to our center with a platelet count of 4×10^9/L and bleeding symptoms such as epistaxis and petechiae. She had been diagnosed with immunethrombocytopenia (ITP) in 2002. Ever since her childhood, her thrombocytopenia had been associated with hemolytic anemia (Evans syndrome) requiring blood transfusions, and complicated by HCV-related hepatitis (anti-HCV antibodies, HCV-RNA 1257491 IU/ml, genotype 1b). Previous therapy for ITP, based on prednisone, intravenous immunoglobulin (IVIg) and azathioprine had been ineffective. In 2006, she underwent splenectomy, and achieved a stable complete remission (CR), maintained with a low daily dose of prednisone (2.5 mg).

She also suffered from Sjögren's syndrome, with severe dry eyes, positive ANA and ENA anti-SSA titers, and monoclonal gammopathy of undetermined significance IgGK without Bence-Jones proteinuria.

Definitive diagnosis

Dr. Vianello: We performed a bone marrow examination, which was normal; platelet-associated autoantibodies against GpIIb/IIIa and GpIb were identified. An abdominal CT scan performed during hospitalization at our center was negative for accessory spleen. A definitive diagnosis of secondary and refractory ITP was established.

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Clinical course

Dr. Bertomoro, Dr. Vianello: As full doses prednisone (1 mg/kg/day) and IVIg (1 g/kg for two days) were ineffective, we introduced romiplostim (1 μg) up to 3.5 mcg/kg) once a week for 26 weeks. A wide fluctuation of platelet count was observed (from 4 to 800 × 109/L). In April 2014 the patient was started on rituximab (375 mg/m^2 × 4 courses), with corticosteroids tapering, obtaining CR with a stable platelet count.

The patient maintained stable remission for one year; then, there was a recurrence of ITP during the 21st week of gestation, with epistaxis, bleeding gums and petechiae (platelet count 3×10^9/L). Therapy with prednisone and IVIg, prompted a transient response. After an unsuccessful course of dexamethasone (40 mg/kg for 4 days), the patient was restarted on romiplostim (1 mcg/kg, increasing the dosage to 10 mcg/kg once a week for 3 weeks), with no response. The patient underwent elective cesarean section at 26 weeks of gestation with prophylactic platelet transfusion. The newborn had no complications and a normal platelet count. In the post-partum period, the patient developed a peri-uterine hematoma, requiring laparotomy for evacuation. After delivery, romiplostim was administered for another 10 weeks without response. We, therefore, switched to eltrombopag, 50 mg daily, which was stopped after 1 week due to severe thrombocytosis (platelet count 2000×10^9/L). The patient was administered a new course of rituximab, obtaining a CR, and low doses of corticosteroids, which were gradually tapered and withdrawn.

In July 2016, following two episodes of infection and flu-like symptoms, ITP relapse was diagnosed. Thrombocytopenia was associated with neutropenia (WBC count 2.66×10^9/L, neutrophil count × 10^9/L), requiring the use of granulocyte colony-stimulating factor, with beneficial effects. Once again, the patient received high dose corticosteroids, IVIg, and eltrombopag, which rapidly raised her platelet count. A diagnosis of multirefractory secondary ITP

was established. During the same year, HCV was successfully eradicated with ledipasvir and sofosbuvir.

Recurrences and further therapies

Dr. Marson: In November 2016, there was a fourth ITP relapse (platelet count 1×10^9/L): prednisone, IVIg, eltrombopag and rituximab failed. The patient received 3 courses of plasma-exchange, with no response. Immunosuppression with cyclosporine A (50 mg × 2 up to 100 mg × 2 daily) was initiated, and the patient underwent 4 courses of immunoadsorption (Ig-Therasorb® system, Miltenyi Biotec, Bergisch Gladbach, Germany), each followed by the use of IVIg. This treatment gradually raised her platelet levels (platelet count 213×10^9/L).

In March 2017, a fifth relapse of symptomatic ITP occurred, which was treated with prednisone, eltrombopag and 3 courses of immunoadsorption, with no response. Cyclosporine A was stopped, and the patient started chemotherapy with 4 courses of cyclophosphamide (1267.5 mg), vincristine (2.366 mg) and prednisone (68 mg) (CVP), every 3 weeks. After the first course, she showed a CR with a platelet count of 400×10^9/L; so eltrombopag and prednisone were tapered, and her platelet count remained stable. The clinical course during the fifth relapse is summarized in Fig. 1. The first course of chemotherapy was complicated by recurrent epistaxis, petechiae and bleeding gums requiring platelet transfusion; a relapse of secondary hemolytic anemia requiring blood transfusion (hemoglobin 68 g/L, hematocrit 25%, reticulocyte count 160×10^9/L); concurrent cytomegalovirus and urinary *E. coli* infections were treated with antiviral and antibiotic therapy. The other three courses of CVP were administered with no complications.

Clinical course

Dr. Di Pasquale, Dr. Bertomoro: Between September and December 2017, the patient had three more relapses. Her treatment included one course of cyclophosphamide (700 mg/m^2), dexamethasone (four courses of 40 mg/day for 4 days, followed by 40 mg every 7 days until it was withdrawn). Mycophenolate mofetil (starting dose 1 gr up to 3 gr daily) and eltrombopag were administered and a stable platelet count was reached (platelet count 398×10^9/L) after 2 months. Eltrombopag was withdrawn and the patient is currently in remission with mycophenolate mofetil 1 g daily.

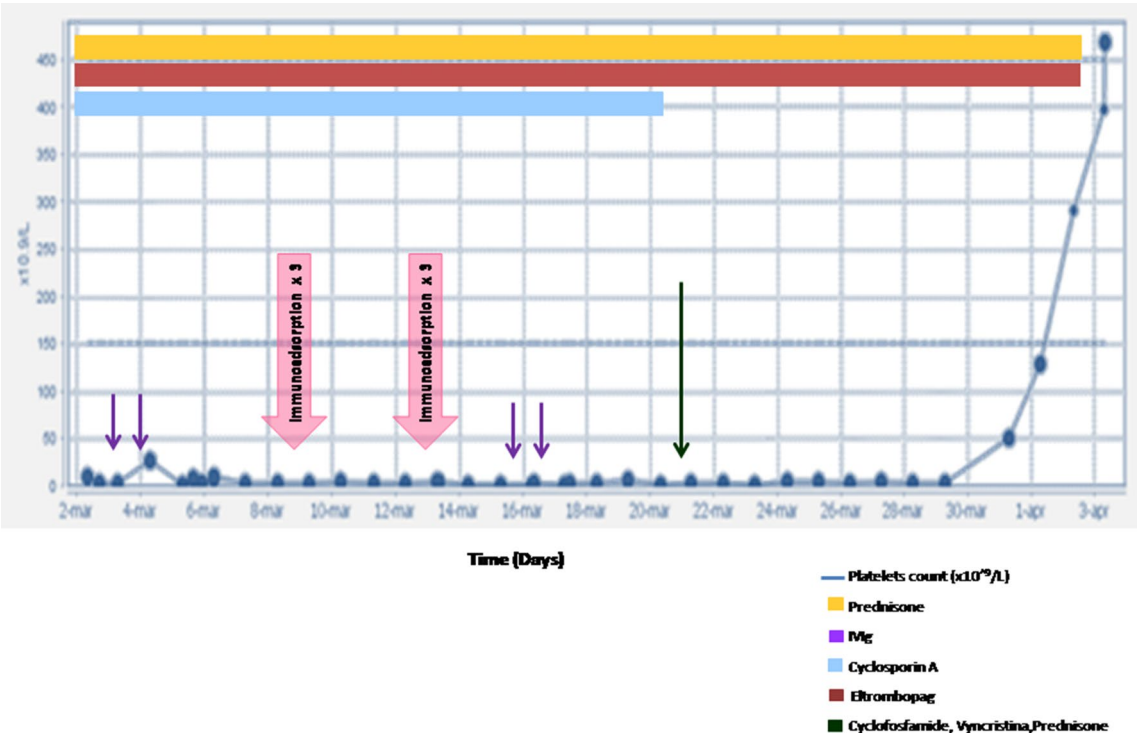

Fig. 1 Clinical course of the patient during the fifth recurrence of ITP in 2017. *CVP* cyclophosphamide, vincristine, prednisone

Discussion

Prof. Fabris: First-line therapy in ITP is based on glucocorticoid and IVIg, while second-line therapy focuses on mechanisms of platelet destruction (splenectomy) and antibody production (immunosuppression). These options may not always be effective in refractory cases, and may have several adverse effects that add to patients' morbidity and mortality [1–3]. Platelet production is controlled mainly by the interactions of thrombopoietin with cMPL [4]. Nowadays, TPO receptor agonists (Tpo-RAs) might represent an important alternative treatment for refractory ITP in adults, proving safe even in the long term [5].

In our patient, response to Tpo-RAs was poor and fluctuating. Even her response to romiplostim fluctuated for a while. Eltrombopag prompted a severe thrombocytosis that made it necessary to stop using this agent. Switching between Tpo-RAs can be helpful, whether it is due to a poor response to the chosen Tpo-RA, to large fluctuations in platelet response, or to problems with the route of administration [6].

A minority of ITP patients are multirefractory to several treatment lines, and no guidelines seem to be available for such cases. An individual approach, combining the agents and balancing the risks and benefits, appears to be the best option [7]. Immunosuppressants have already demonstrated their effectiveness. In a cohort study on 37 patients, Mahevas et al. [8] demonstrated that combining immunosuppressant therapy with Tpo-RAs may be a good strategy for managing ITP patients with severe disease, although some patients remain resistant to all types of medication.

An alternative approach for refractory ITP cases is immunoadsorption, which selectively adsorbs platelet antibodies and circulating immune complexes from plasma, forming complex ligands. Immunoadsorption can exploit protein A columns or immunoglobulin columns, using a polyclonal IgG SHIP directed against the human Ig-kappa and Ig-lambda chains, and against the IgG heavy chain. Given its great capacity for adsorbing all immunoglobulins and subclasses of IgG, there is no need for replacement with fresh frozen plasma, and it is associated with a low incidence of infectious complications. Tauchi et al. treated a case of refractory ITP with a protein A column [9], and found a significant drop in serum platelet autoantibodies just before the clinical response. In two cases of refractory ITP, we had previously obtained a late long-term response to extracorporeal immunoadsorption over a protein-A Sepharose column [10], and the same result was achieved by Kurtoğlu et al. [11] using a tryptophan membrane. The reason for removing circulating platelet autoantibodies in refractory ITP is still being debated, however, since less than 50% of ITP patients have detectable autoantibodies in serum. An immunomodulatory effect of immunoadsorption could be a better explanation for the late response observed.

In our patient, the combined protocol based on immunosuppression, and immunoadsorption on immunoglobulin columns followed by IVIg was effective in obtaining a CR during the fourth relapse, but immunoadsorption was unsuccessful in the fifth recurrence. Since the patient was multirefractory and had bleeding symptoms, and multisystemic autoimmunity, we opted for chemotherapy with CVP, glucocorticoid and eltrombopag, followed by long-term immunosuppression with mycophenolate mofetil, and this approach proved successful. Mycophenolate appears to have good short-term tolerability with a relatively low cost; the immune system returns to normal once the treatment has been stopped, though there may be a delayed response (4–8 weeks) [12]. No randomized clinical trials have bene conducted on mycophenolate mofetil in ITP, but retrospective studies show an approximate 50% response rate in adults with primary ITP [6, 13, 14].

To conclude, our report goes to show that a personalized therapy including multiple agents is warranted for multirefractory ITP patients, based on immunosuppression, immunoadsorption associated with Tpo-RAs. Using cyclophosphamide combined with eltrombopag, mycophenolate mofetil and dexamethasone can help to maintain a safe platelet count without any bleeding episodes, and with mild side effects. New targets for new agents are being studied, however, including the spleen tyrosine kinase (Syk) inhibitor fostamatinib, T-cell co-stimulation with toralizumab and ruplizumab, and FcR binding and signaling [6], and the therapeutic strategies available for patients with multirefractory ITP will soon be enriched with new drugs.

Compliance with ethical standards

Conflicts of interest The authors have no conflicts of interest to disclose.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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