CASE REPORT

Refractory primary immune thrombocytopenia with subsequent del(5q) MDS: complete remission of both after lenalidomide

Thomas Bech Mortensen,¹ Henrik Frederiksen,¹ Claus Werenberg Marcher,¹ Birgitte Preiss²

¹Department of Hematology, Odense Universitetshospital, Odense, Denmark

²Department of Pathology, Odense University Hospital, Odense, Denmark

Correspondence to

Dr Thomas Bech Mortensen, tmdemo@gmail.com

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SUMMARY

A patient with refractory primary immune thrombocytopenia (ITP) characterised by severe skin and mucosal bleedings was treated with several ITP-directed therapies including cyclophosphamide. He later developed therapy-related del(5q) myelodysplastic syndrome with no dysplastic morphological features in bone marrow. He remained severely thrombocytopenic, which suggests ongoing immune mediated platelet destruction. After two 3 week cycles of low-dose lenalidomide, complete cytogenetic remission and complete normalisation of platelet count were observed. This suggests that lenalidomide may be a viable treatment option for ITP in the presence of del(5q) not responding to standard treatments.

BACKGROUND

Primary immune thrombocytopenia (ITP) is characterised by isolated thrombocytopenia with platelet count <100 000 and absence of other initiating or underlying causes of thrombocytopenia. Patients may experience severe haemorrhagic diathesis with serious skin and mucosal bleeding.¹ Evidence indicate that both immune-mediated platelet destruction and an immune-mediated decreased platelet production play a pathophysiological role and the contribution of these distinct mechanisms varies in different patients.² Treatment of ITP can therefore be complex and a large number of different treatment options are available.¹ Treatment of ITP usually needs to be initiated if thrombocytopenia is severe enough to cause bleeding symptoms. Most drugs are immunosuppressants and, due to a large variety of side effects and drug interactions, the treatment should always be individualised.¹

According to the 2016 WHO classification myelodysplastic syndrome (MDS) without excess blasts and isolated deletion of chromosome 5q (del(5q)) is a separate entity in a cytopenic patient regardless of bone marrow morphology.³ The del(5q) syndrome describes the typical findings in patients with del(5q), including thrombocytosis, macrocytic anaemia and hypolobulated megakaryocytes.⁴

Lenalidomide is the preferred treatment for patients with del(5q) MDS.⁴ It has multiple mechanisms of action and works both as an immune modulator and has also been shown to induce ubiquitination and degradation of CK1 α . CK1 α is a negative regulator of p53 and by reducing the intracellular concentration of CK1 α the

activity of p53 is increased, which promotes apoptosis. CK1 α is encoded by a gene (CSNK1a1) within the common deleted region for del(5q) MDS, which means that del(5q) cells are haploinsufficient and, therefore, only express 50% of normal levels of the gene, thus sensitising the del(5q) cells to lenalidomide therapy.⁵

Lenalidomide is a very potent drug for del(5q) MDS but with dose-limiting side effects, including neutropenia and thrombocytopenia that can be challenging in patients with these respective cytopenias.⁴

This patient has both ITP and MDS, which pose a diagnostic and therapeutic challenge. In this case, the treatment with lenalidomide was directed against the MDS but also resulted in complete remission of ITP. This case has been written up because the findings may indicate that lenalidomide could be an effective treatment for patients with refractory ITP in the setting of a del(5q) clone.

CASE PRESENTATION

In 2003, a 54-year-old man presented with thrombocytopenia and haemorrhagic diathesis. He had comorbidity with obesity and type II diabetes but was otherwise healthy. There were no other cytopenias and no underlying conditions were identified that could cause secondary thrombocytopenia. Bone marrow aspiration was performed showing increased number of megakaryocytes but no other abnormalities were found. Cytogenetic analysis was not performed at the time. The patient was diagnosed with immune thrombocytopenia (ITP) and he was initially treated with prednisolone and intravenous immunoglobulins with no effect on symptoms or platelet count. Therefore, four cycles of rituximab were administered followed by cyclosporine resulting in normalisation of platelet count. Cyclosporine was discontinued after a few months because of hypertension. The patient remained in remission until 2007 when he presented with new bleeding symptoms and a platelet count below 10 000. Another four cycles of rituximab were administered again resulting in complete remission through the following year. In 2008, the thrombocytopenia and bleeding symptoms returned and splenectomy was performed again with complete remission lasting until 2011. At relapse, a new bone marrow sample including cytogenetic examination showed a hypercellular bone marrow with increased number of megakaryocytes and a

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stimulated erythropoiesis due to bleeding. However, there were no dysplastic features and no cytogenetic abnormalities. A PET-CT scan showed a minor accessory spleen but was otherwise normal.

Throughout 2011 and 2012 the patient had ongoing severe bleeding symptoms with constant oozing from the gastrointestinal mucosa due to severe thrombocytopenia. He was in need of recurrent admissions to the hospital and needed numerous transfusions with both red blood cells and platelets. During this period, several ITP-directed therapies such as dexamethasone, mycophenolate mofetil, azathioprine, IVIG, danazol, rituximab, romiplostim and eltrombopag alone or in various combinations were unsuccessful. Owing to ongoing need of blood transfusions, he was given two cycles of cyclophosphamide, vincristine and prednisolone in a 'lymphoma schedule'—also without effect.

We were reluctant to use cyclosporine again due to previous severe hypertension, but this was finally reintroduced and after a while, bleeding symptoms regressed and the platelet count slowly rose to normal values. After a year the cyclosporine dosage was slowly tapered to 50 mg OD. Platelet count remained normal until reduction to 25 mg OD where platelet count plummeted to 4000 and bleeding symptoms recurred. The cyclosporine dosage was increased again without effect on platelet counts. The patient was at this time again anaemic due to ongoing bleeding.

In January 2015, a new bone marrow sample and cytogenetic analysis was performed. This now showed a 5q deletion (del(5)(q22q35)), but there were no dysplastic morphological features and there was still increased number of megakaryocytes. Furthermore, there was a stimulated erythropoiesis, and peripheral blood smear showed reticulocytosis confirming the anaemia as being caused by bleeding. The del(5q) was found only in 4 of 25 metaphases, but by definition the patient now had therapy-related MDS. The MDS was attributed to his previous cyclophosphamide treatment. Owing to the 5q deletion, the patient was treated with two cycles of lenalidomide 5 mg daily 21 out of 28 days. Within the first 3 weeks, the platelet count normalised and after 2 months a new bone marrow sample with cytogenetic analysis showed complete remission. After 11 months, the patient relapsed with severe thrombocytopenia and a new cytogenetic analysis showed del(5q) in 3 of 25 metaphases. Lenalidomide was reintroduced and after 4 months the platelet count had normalised but cytogenetic analysis still showed del(5q) in 1 of 25 metaphases.

DISCUSSION

In this case, the patient was initially diagnosed with ITP and subsequently developed an isolated deletion of 5q that was not present at the previous cytogenetic analysis. Owing to previous cyclophosphamide treatment, it was classified as a therapy-related del(5q) MDS. He did not fulfil the diagnostic criteria for del(5q) syndrome since he did not have macrocytic anaemia and thrombocytosis. His anaemia was attributed to the ongoing bleeding and he did not have thrombocytosis but instead had severe thrombocytopenia. It is unclear whether the continued thrombocytopenia was a result of an ongoing immune-mediated destruction of his thrombocytes or whether it was a result of the del(5q) clone, but the absence of dysmegakaryopoiesis and megakaryocyte hyperplasia support ITP as the underlying mechanism of the thrombocytopenia.

To the best of our knowledge only one case, a 55-year-old woman, was described with isolated thrombocytopenia and del

(5q).⁶ The woman, however, had more than 10% of megakaryocytes showing dysmegakaryopoiesis and was, therefore, diagnosed with the MDS subtype RCUD with del(5q).

In this patient, lenalidomide initially resulted in complete cytogenetic remission that has been seen in many instances with del(5q) MDS.⁴ What is particularly interesting is that it also resulted in complete normalisation of platelet count. It seems unlikely that the ITP was an autoimmune association with the del(5q) MDS although this has been described previously.⁷ The immune thrombocytopenia preceded the MDS by 12 years and two bone marrow biopsies did not show morphological signs of MDS and in 2011 cytogenetics did not show del(5q) karyotype. However, when lenalidomide caused clonal remission of MDS, the concurrent ITP resolved. It may be that the immunomodulatory effects of lenalidomide explain a direct effect on the platelet count. Our case report suggests that it would be of interest to evaluate the effect and toxicity of lenalidomide for patients with severe refractory ITP in a clinical trial.

Learning points

- ▶ The treatment of ITP is complex and should always be individualised.
- ▶ There is an association between autoimmune disease and MDS.
- ▶ Lenalidomide may be an effective treatment in refractory ITP cases in the presence of a del(5q) clone.
- ▶ It is possible that the immunomodulatory effects of lenalidomide could be effective in treating severe refractory ITP and it would be of interest to evaluate this in a clinical trial.

Contributors TBM is responsible for formulation of the first draft of the article, reviewing the patient medical files and reviewing existing knowledge on the subject. HF is responsible for revising the article critically for important intellectual content and correction of style and grammar. CWM is responsible for treatment and communication with the patient, and revising the article critically for important intellectual content. BP is responsible for revising the article critically for important intellectual content.

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