Cyclic thrombocytopenia in a patient with polycythaemia vera: a case report

I. Depoortere, MD[1], V. Maertens, MD[2], M. Criel, MD[1], M. Vanden Driessche, MD[3], I. Geerts, MD[1]

SUMMARY

We present a case of a 73-year old patient with polycythaemia vera in whom cyclic thrombocytopenia was diagnosed. Strong fluctuations in platelet count, ranging from 31 to 1334 x $10^3/\mu L$, were noticed after onset of hydroxyurea therapy. We did a literature search to find possible underlying causes of cyclic thrombocytopenia that could guide us towards a fast and appropriate diagnosis and an optimal treatment. In literature, provoked and unprovoked oscillations in platelet numbers have been described. Unprovoked oscillations can most likely be attributed to an unstable haematopoietic stem cell pool, as can be seen in polycythaemia vera. Provoked oscillations could be associated with myelosuppressive agents such as hydroxyurea. In both situations, a decrease in platelet count can be followed by a compensatory thrombopoietin-induced stimulation of megakaryocytes. Frequent hydroxyurea dose adjustments may be carried out in an attempt to control this cyclic pattern but, by contrast, may provoke a bouncing ball effect on platelet count. Certain patients will therefore benefit from maintaining therapy at a constant dose; while certain others require withholding or switching therapy. Cyclic thrombocytopenia is a rare finding and is frequently misdiagnosed as immune thrombocytopenia. If hydroxyurea-treated patients with a chronic myeloproliferative disorder present with thrombocytopenia, cyclic thrombocytopenia should be considered. Intensive follow-up with regular control of platelet count and personalised therapy is mandatory.

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INTRODUCTION

Cyclic thrombocytopenia (CT) is a relatively rare condition characterised by cyclic oscillations of platelet count with periods of thrombocytopenia interspersed with periods of thrombocytosis. CT can be seen in myeloproliferative disorders (MPD) such as polycythaemia vera (PV) and can be related to treatments such as hydroxyurea (HU) but is idiopathic in most of the cases.[1-3] We report a case of a patient who was diagnosed with PV and secondary CT.

CASE DESCRIPTION

A 73-year old woman was presented at the emergency department in June 2013 with a large gluteal haematoma, which she developed immediately after a traumatic injection in another hospital. She didn't take anticoagulants or antiplatelet drugs, and there was no history of increased bleeding tendency or thromboembolic events. Physical examination showed no other particularities.

Laboratory findings were significantly disturbed with a polycythaemia (haematocrit [hct] 52.6%, red blood cells [rbc] 7.33 x $10^6/\mu L$, haemoglobin [hb] 14.8 g/dL) and massive leucocytosis (white blood cells [wbc] 49.2 x $10^3/\mu L$ with 90% mature neutrophils). Blood platelets (bp) were normal (289 x $10^3/\mu L$).

Radiographic findings of the thorax were normal and an echo of the abdomen showed a normal spleen. Further investigation revealed a Janus kinase 2 (JAK2) V617F mutation and a serum erythropoietin (EPO) dosage below 5 U/L. A bone

[1]Laboratory Medicine, Imelda Hospital, Bonheiden, Belgium, [2]Clinical Haematology, Imelda Hospital, Bonheiden, Belgium, [3]Laboratory Medicine, Rode Kruis-Vlaanderen (HILA), Mechelen, Belgium.

Please send all correspondence to: I. Depoortere, MD, Laboratory Medicine, Imelda Hospital, Imeldalaan 9, 2820 Bonheiden, Belgium, tel: 0472/827501, email: iljadepoortere@hotmail.com.

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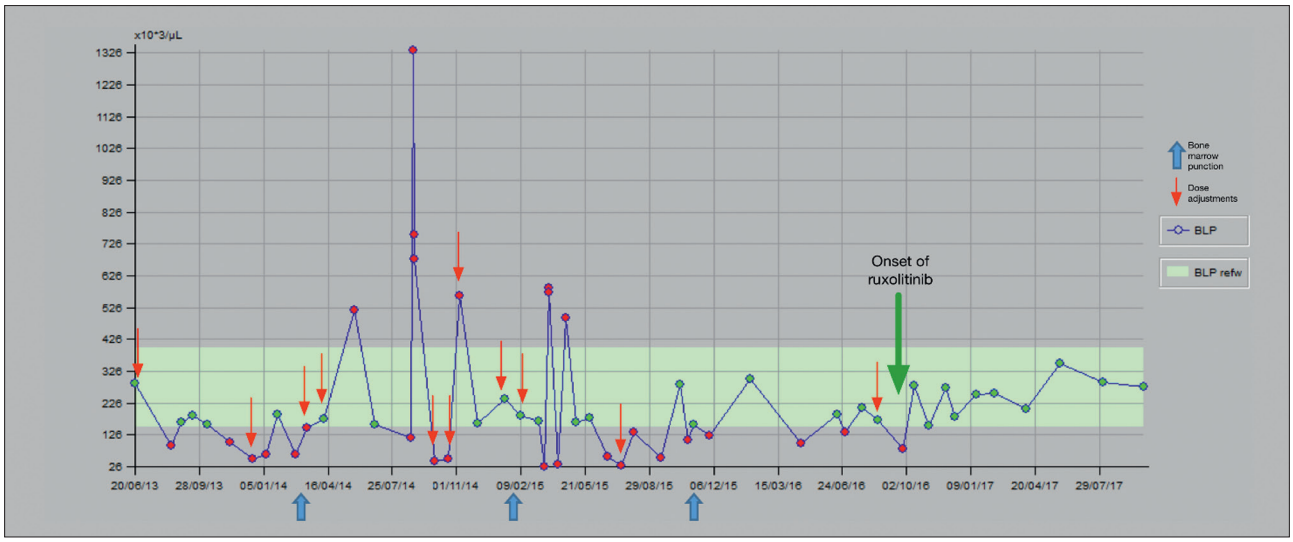

FIGURE 1. Follow-up of blood platelet count. Onset of hydroxyurea and dose adjustments (increase↑ and decrease↓ of dose), onset of ruxolitinib and timing of bone marrow biopsies were marked.

marrow (BM) biopsy was not performed at that moment. PV was diagnosed, and therapy with phlebotomies, aspirin and HU was started.

After two months, laboratory showed a stable polycythaemia (hct: 54.1%, rbc: 7/µL and hb: 15.5 g/dL) and a decrease in wbc (25.3 x 10^3/µL), but bp were now also lowered to 92 x 10^3/µL. Two weeks later, there was a further decrease in wbc (18.9 x 10^3/µL); bp were normal again (165 x 10^3/µL).

During further follow-up, there was a good haematological response with a progressive decrease in haematocrit and leucocytosis, but there was a strong fluctuation of bp ranging from 31 to 1334 x 10^3/µL (*Figure 1*).

Platelet levels were controlled by different methods and analysers in order to exclude analytic faults. Measurements were performed by impedance, fluorescence and optic methods on ethylenediaminetetraacetic acid (EDTA) and sometimes citrated whole blood (XN-3000®, Sysmex). Platelet levels were sometimes confirmed with a manual microscopic count (number of platelets/1000 red blood cells). Aggregates were never seen and pseudo-thrombocytopenia could be excluded. Some measurements were checked on another analyser (DxH®, Beckman Coulter) with concordant results.

During follow-up, three BM biopsies were examined and they all showed a hypercellular BM with normal to strong representation of the megakaryocytic lineage. In September 2016, there was an evolution to myelofibrosis (enlarged spleen, increase in fibrosis and blastosis up to 19% in BM). Because of this evolution, therapy was switched to ruxolitinib, a JAK-inhibitor, and started at a dose of 15 mg 2/d. At the same time, HU was reduced to 1/d in order to stop it six weeks later.

After only two weeks of treatment with ruxolitinib, there was a decrease in spleen size – with a normalisation in August 2017 – and a stabilisation of platelet count within the normal range, though still with minimal fluctuations. During follow-up, the complete blood count was normal with a stable blastosis.

DISCUSSION

PV is the most common chronic MPD with an incidence of 2.5 per 100,000 a year. It usually affects older people, with most patients diagnosed over the age of 55 years. PV is characterised by an increased red cell mass, associated with proliferation of erythroid, granulocytic and megakaryocytic elements of the BM. A specific mutation in a single pluripotential haematopoietic stem cell, JAK2V617F – which results in constitutive JAK2-STAT signalling – is causative for PV in more than 95% of cases.[4] JAK2 exon 12 mutations can be identified in most of the remaining patients.

According to the applicable criteria of the World Health Organization (WHO) 2008, there was enough evidence to diagnose PV in our patient (increased red cell volume, a JAK2V617F mutation and a low EPO level). A BM biopsy was not deemed necessary at that time since – according to those criteria – it was not a mandatory requirement for the diagnosis of PV, and there were, furthermore, insufficient minor criteria to rule out myelofibrosis. However, according to the revised criteria of the WHO 2016, it is now considered necessary to perform a biopsy for the diagnosis of PV and also for the exclusion of myelofibrosis, due to the presence of one minor criterion (leucocytosis) in our patient.[5]

The disease is often treated with HU, a non-alkylating myelo-

KEY MESSAGES FOR CLINICAL PRACTICE

1. Cyclic thrombocytopenia is a rare finding and is frequently misdiagnosed as immune thrombocytopenia.
2. Cyclic thrombocytopenia should be considered in hydroxyurea treated polycythaemia vera patients.
3. Frequent dose adjustments may provoke a bouncing ball effect on platelet count.[1]
4. Some patients benefit from maintaining therapy at a constant dose, others require withholding or switching therapy.[1,3]
5. Intensive follow-up and personalised therapy is mandatory.

suppressive agent that impairs dDNA synthesis. HU is usually well tolerated with limited side effects. Fluctuations in platelet count in our patient started immediately after onset of this therapy. Platelet levels were repeatedly checked with different methods and analysers to exclude analytic faults. The dose of HU was adjusted frequently in an attempt to stabilise platelet count. On the contrary, even stronger fluctuations (ranging from 31 to 1334 x $10^3/\mu L$) were seen, possibly enforced by those multiple dose adjustments. Maintaining a constant dose resulted in a narrower amplitude of the oscillations (*Figure 1*).
Because of the evolution to myelofibrosis, ruxolitinib was started. This JAK1/JAK2 inhibitor is currently approved for clinical use in myelofibrosis and in patients with PV, resistant or intolerant of HU.[4] Since this treatment switch, platelet count finally remained within normal levels, though still with minimal fluctuations.
Most cases of CT are idiopathic and not related with a primary haematological disease.
We restricted our discussion to the occurrence of CT in MPD disorders, such as PV, and explored literature in order to find potential underlying factors.
Unprovoked as well as provoked oscillations in platelet numbers have been described. Unprovoked oscillations can most likely be attributed to an unstable haematopoietic stem cell pool, as can be seen in MPD such as PV, and can lead to cyclic failure of platelet production.[1,2] Provoked oscillations could be associated with myelosuppressive agents such as HU and are usually transient and dose dependent. It is conceivable that the affected patients have a megakaryocyte progenitor pool that is unusually sensitive to HU, resulting in a transient depletion of megakaryocytes. Thrombocytopenia can be followed by a compensatory thrombopoietin (TPO)-induced stimulation of megakaryocytes.[1,2] This normal autoregulatory response is described in some patients, however, in other patients with CT, an out-of-phase variation in serum TPO level was remarked. This suggests a retention of the autoregulatory response or a diminished (endogenous or drug-induced) apoptotic response to high concentrations of TPO.[1] Unfortunately, TPO was never determined in our patient.
An increase in spleen size, which was seen during HU treatment, could also result in platelet sequestration and destruction. During treatment with ruxolitinib, there was a normalisation of platelets, possibly partly due to a reduction in spleen size, which is a major effect of ruxolitinib.[4]
Controlling CT is a challenge because of the described phenomena. Tefferi *et al*. and Burthem *et al* described some HU treated PV patients. They noted that the amplitude of oscillations was narrower when the HU dose was kept constant.[1,3] Withholding treatment with HU resulted in prompt cessation of the cyclic changes, which reappeared with the resumption of HU therapy. An alternative platelet-lowering agent can be tried, though was also not successful in one of the patients.[1]
In our patient, strong fluctuations in platelet count were possibly enforced by multiple dose adjustments with lack of sufficient time for recovery. From the moment CT was diagnosed and a constant dose was maintained, oscillations were less pronounced. They almost disappeared by switching therapy.
Different cycle lengths are described in literature, variating from 14-50 days.[1-3,6] In our patient, cycle lengths could be difficultly determined as a result of frequent dose adjustments and irregular timing of platelet analysis.
It is also important to note that CT is often misdiagnosed as immune thrombocytopenia (ITP). Standard treatment with steroids fails and such patients are frequently mislabelled as 'steroid refractory'. In some patients, a 'rebound thrombocytosis' attributable to CT could falsely be interpreted as a

successful response to steroid therapy. Other ITP treatments such as intravenous immunoglobulin and splenectomy are often tried but are also unsuccessful.[6,7] For those reasons, it seems to be more appropriate to observe any new-onset thrombocytopenia for several weeks if symptoms permit.

CONCLUSION

CT in HU treated PV patients is a relatively rare condition and is characterised by cyclic oscillations of platelet count, with periods of thrombocytopenia interspersed with periods of thrombocytosis. CT can be provoked and unprovoked. The complex interaction of the described phenomena may account for the difficulty in controlling platelet count.[1] The best approach is to maintain therapy at a constant dose or – if response is inadequate – to withhold or switch therapy.

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