CASE REPORT

Spontaneously recovered severe thrombocytopaenia following zoledronic acid infusion for osteoporosis

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SUMMARY

Zoledronic acid is widely used for the treatment of various skeletal disorders. While acute phase reactions are commonly seen, hypocalcaemia, femoral shaft fractures, osteonecrosis of the jaw and renal failure are rare. Two cases of fatal thrombocytopaenic purpura have been reported following zoledronic acid infusion. We report a case of non-fatal thrombocytopaenia with spontaneous recovery. A 70-year woman with osteoporosis participated in a research study. Complete blood and platelet counts prior to zoledronic acid infusion were normal (138 000/ μ L), but had declined slightly from 185 000/ μ L 2 years ago. One year after the first zoledronic acid infusion, her platelet count declined to 50 000/ μ L without any clinical manifestations, and rose slowly returning to normal (156 000/ μ L) over the next 1 year. Extensive evaluation did not reveal any specific abnormalities, and the pathogenesis of her transient severe thrombocytopaenia after two infusions of zoledronic acid remains unclear.

2011. She underwent her first trans-iliac bone biopsy in August 2010 and a second one in February 2012, each preceded by in vivo tetracycline labelling (500 mg three times/day for 3 days on two occasions separated by 11 days) in preparation for detailed bone histomorphometry as required by the research study protocol.⁸

The platelet counts before the first zoledronic acid infusion and immediately before the first bone biopsy were within the reference range (figure 1). The patient began to develop thrombocytopaenia 5 months later, reaching a nadir of 50 000/ μ L in December 2011. In May 2012, her platelet count began to rise steadily and returned to normal a year later at 156 000/ μ L, without any intervention. She did not manifest any clinical or laboratory findings of thrombotic thrombocytopaenic purpura. Serum alkaline phosphatase and N-terminal telopeptide were both low in February 2013, and remained low throughout the study.

BACKGROUND

Zoledronic acid, a potent bisphosphonate, is widely used in clinical practice for the treatment of osteoporosis, various other metabolic bone disorders and malignancies. It is generally safe and well tolerated, but associated with several adverse reactions.¹ While acute phase reactions are more commonly seen, hypocalcaemia,² femoral shaft fractures,³ osteonecrosis of the jaw⁴ and renal failure⁵ are uncommon. Only two cases of thrombotic thrombocytopaenic purpura have been reported following intravenous infusion of zoledronic acid and, unfortunately, both were fatal.^{6 7} We report a case of non-fatal severe thrombocytopaenia with spontaneous full recovery following intravenous zoledronic acid administration.

CASE PRESENTATION

A 70-year-old woman with osteoporosis, manifested primarily by low bone mineral density (T-scores of -4.0 SD and -2.1 SD at the lumbar spine and femoral neck respectively), participated in a clinical research study comparing the skeletal effects of zoledronic acid and teriparatide. Her only medications prior to participating in the study included: calcium carbonate (1000 mg) with cholecalciferol (1000 IU) twice daily for osteoporosis, simvastatin 40 mg/day for dyslipidaemia and ibuprofen 800 mg as needed for osteoarthritis pain. She received two intravenous zoledronic acid (with mannitol as incipient) infusions of 5 mg each in 100 mL on 11 February 2010 and 24 February

INVESTIGATIONS

Serial complete blood counts showed progressive decline in platelets from 185 000/ μ L to a range of 50 000–60 000/ μ L over the next 2 years and 3 months. Prior to the zoledronic acid infusion, the patient's platelet counts were within the reference range (~185 000/ μ L). However, approximately 5 months after the first infusion of zoledronic acid, the platelet count dropped to 138 000/ μ L. A second zoledronic acid infusion was given a year later, in May 2011, as required by the protocol. The platelet counts dropped further to 50 000/ μ L and remained low for approximately a year, ranging between 50 000/ μ L and 60 000/ μ L. In May 2012, the platelet count was 72 000/ μ L, began to rise steadily thereafter and returned to normal 1 year later (May 2013) at 156 000/ μ L (figure 1).

A bone marrow biopsy, performed in February 2012, was negative for obvious neoplasm, with adequate megakaryocytes. In addition, minute lymphocytic clusters were seen and flow cytometry revealed a slight increase in CD57 and decrease in CD26, relevance of which is unclear.

However, the patient's haemoglobin and haematocrit remained stable over the course of the study, ranging between 12.6 and 13.4 g/dL.

DIFFERENTIAL DIAGNOSIS

Many drugs are known to cause thrombocytopaenia,⁹ and the only drugs that our patient was exposed to included simvastatin, ibuprofen, zoledronic acid in mannitol, and tetracycline.

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Figure 1 Serial platelet count before, during and after zoledronic acid infusions.

Simvastatin has, rarely, been implicated in thrombocytopaenia, but is dose and time dependent.¹⁰ Apart from a gradually declining platelet count, no other similarities could be found between our patient and those in the reported studies. Additionally, our patient had been on simvastatin for 4 years prior to the administration of intravenous zoledronic acid, and remained on it throughout the study, thus eliminating simvastatin as a potential cause of our patient's thrombocytopaenia.

Thrombocytopaenia is also reported to be associated with the use of a variety of non-steroidal anti-inflammatory drugs. Several cases of non-steroidal anti-inflammatory drug-induced and two cases of ibuprofen-related thrombocytopaenia have been reported.⁹ Our patient was intermittently on 800 mg of ibuprofen, as needed, for osteoarthritic pain. Owing to the irregular nature of administration, a causal relationship between ibuprofen and gradual decline in platelet count was not established. A case of reversible thrombocytopaenia has been reported in association with diclofenac therapy.¹¹

Tetracyclines were used in our patient as a tracer prior to the bone biopsies in 2010 and 2011 (total dose of 12 g in 4 sessions). Two cases of probable tetracycline and one case of minocycline-induced thrombocytopaenia have been reported.^{9 12} Our patient was neither exposed to minocycline nor did she develop purpura. The lack of purpura, more gradual decline in platelet count and its spontaneous recovery, steers against tetracyclines as a probable cause of her thrombocytopaenia.¹²

We recognise that isolated thrombocytopaenia can suggest idiopathic thrombocytopaenic purpura (ITP), which is largely a diagnosis of exclusion. In addition, absence of clinical manifestations and spontaneous resolution with time makes ITP unlikely. Any drug-related ITP was excluded by careful review of medication exposure history. Other known causes of ITP were excluded by relevant tests and bone marrow examination.¹³

Other potential causes of thrombocytopaenia such as HIV and hepatitis C virus infection were excluded by relevant tests.¹⁴ Finally, an extensive literature search did not reveal any reports of thrombocytopaenia related to mannitol. Thus zoledronic acid appears to be the most proximate cause of this patient's thrombocytopaenia.

OUTCOME AND FOLLOW-UP

Our patient recovered spontaneously with no intervention and no drug therapy for her thrombocytopaenia, over a period of 2.5 years. The temporal relationship between zoledronic acid administration and the development of thrombocytopaenia implies that she developed drug-induced thrombocytopaenia by some unknown mechanism. The prolonged thrombocytopaenia suggests that the effect of zoledronic acid may be long lasting. Slow, but complete recovery, implies that the most likely mechanism is immune mediated. Although our patient did not develop manifest thrombotic thrombocytopaenia purpura, it is worth investigating, since two fatal cases of thrombotic thrombocytopaenic purpura following zoledronic acid infusion have been reported.^{6 7}

DISCUSSION

Multiple mechanisms have been proposed to explain the thrombocytopaenia associated with zoledronic acid. One mechanism involves mesenchymal stem cell apoptosis. Another possibility is suppression of T_{reg} levels by zoledronic acid in peripheral blood while increasing the levels of γδ T cells and interleukin-17.¹⁵ This suggests that bisphosphonates can affect the function of cells in innate and acquired immune pathways. However, it is unclear whether these proposed mechanisms explain our patient's thrombocytopaenia.¹⁵

This case report highlights a potential serious adverse reaction to zoledronic acid, admittedly very rare. Considering the at risk

population likely to be exposed to zoledronic acid, it may not be trivial. Although we did not conclusively establish a causal relationship between zoledronic acid and thrombocytopaenia, clinicians should be aware of this adverse effect of zoledronic acid, as two cases of fatal thrombocytopaenia following zoledronic acid administration have been reported.^{6 7}

Learning points

- ▶ Zoledronic acid is generally well tolerated, but can be associated with several adverse events.
- ▶ Although thrombocytopaenia in our patient was asymptomatic and resolved spontaneously, it was severe and long lasting. Clinicians should be aware of this potential complication during long-term therapy of osteoporosis with zoledronic acid.
- ▶ The temporal relationship between zoledronic acid administration and the duration of thrombocytopaenia implies that it is most likely immune mediated and further exposure to this drug should be avoided.

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Competing interests None declared.

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