CASE REPORT

Treatment of immune thrombocytopenic purpura associated with cytomegalovirus infection in a child with pre-B cell acute lymphoblastic leukaemia after central nervous system relapse

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SUMMARY

A 13-year-old male patient with a history of pre-B cell acute lymphoblastic leukaemia (ALL) with isolated central nervous system relapse on maintenance chemotherapy presented with severe thrombocytopenia refractory to platelet transfusions. The patient showed only modest responses to two courses of intravenous immunoglobulin and steroids. He was found to be positive for cytomegalovirus (CMV) with modest viral load. His thrombocytopenia normalised with rituximab therapy and CMV treatment supporting the diagnosis of CMV-associated immune thrombocytopenic purpura (ITP). Following treatment, the patient continued to have a stable platelet count well above the threshold for transfusions. He continued to be intermittently treated for CMV when viral loads became detectable. This report discusses the unique management considerations of ITP in a patient undergoing therapy for ALL with a review of previously reported cases and discusses the possibility of CMV viraemia as a modulating factor.

BACKGROUND

Immune thrombocytopenic purpura (ITP), the most common bleeding disorder in childhood, is classically an isolated severe thrombocytopenia reported in otherwise healthy school-age children, often following a viral illness. ITP has been associated with haematological malignancies like chronic lymphocytic leukaemia, Hodgkin's lymphoma and non-Hodgkin's lymphoma.¹ However, the presence of ITP in children with acute lymphoblastic leukaemia (ALL) is rare and not well described in the literature.² Cytomegalovirus (CMV) can be associated with ITP in the general population. Immunosuppressed patients, such as those receiving chemotherapy, are at increased risk for clinically significant CMV infections. This case report describes the presentation and treatment of ITP associated with CMV infection in a 13-year-old male patient with pre-B ALL receiving maintenance chemotherapy for isolated central nervous system (CNS) relapse.

CASE PRESENTATION

A 13-year-old male patient with a diagnosis of pre-B ALL presented to the oncology service during maintenance chemotherapy for evaluation of the

new onset of gross haematuria and petechiae. The patient was initially diagnosed with ALL at 10 years of age. He received high-risk chemotherapy for pre-B ALL, but suffered an isolated CNS relapse at age 12 during maintenance chemotherapy. He went into remission with reinduction chemotherapy and at the time of presentation with petechiae he was undergoing maintenance chemotherapy on Children's Oncology Group protocol AALL1331, low-risk arm. He had been randomly assigned to the arm that did not receive blinatumomab, which is a bispecific T cell engager that targets the CD19 surface antigen on B lymphocytes.

On evaluation for the new onset of petechiae, the patient had a platelet count of $3 \times 10^9/L$. His physical examination was unremarkable to the evaluation of thrombocytopenia. In particular, he had petechiae and small bruises, but no deep vein thromboses, lymphadenopathy, hepatomegaly or splenomegaly. The platelet count remained refractory to multiple platelet transfusions and decreased to a nadir of $1 \times 10^9/L$ during the hospitalisation.

INVESTIGATIONS

An indirect anti-platelet antibody screen was obtained and was negative for antibodies against glycoprotein (GP) IIB/IIIA, GP IA/IIA, GP IB/IX and human leucocyte antigen class I. Direct platelet antibody testing via flow cytometry was unable to be performed due to the patient's severe thrombocytopenia. A bone marrow aspirate was obtained and was normocellular, negative for malignant cells and positive for megakaryocytes.

DIFFERENTIAL DIAGNOSIS

1. ITP
2. Myelosuppression due to chemotherapy
3. Myelosuppression due to viral infection
4. Bone marrow relapse of pre-B ALL
5. Secondary haematologic malignancy
6. Microangiopathic consumption of platelets
7. Hypersplenism

TREATMENT

The evaluation of the bone marrow described above supported a peripheral consumption of platelets, such as ITP, rather than insufficient platelet production as the cause of the

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thrombocytopenia. Splenic sequestration was ruled out due to his normal splenic size. The patient's platelet count improved slightly with two courses of intravenous immunoglobulin (IVIG) and steroids, further supporting the diagnosis of ITP; however, this response was not long lasting. The first dose of IVIG (750 mg/kg) was given with no significant change in the platelet count, which rose from $3 \times 10^9/L$ to $9 \times 10^9/L$ 2 days later, but fell back to $1 \times 10^9/L$ 2 days afterwards. A second dose of IVIG (830 mg/kg) with methylprednisolone (5 mg/kg) was given 4 days after the first dose, and the platelet count rose from $1 \times 10^9/L$ to $37 \times 10^9/L$ 2 days later, but fell back to $10 \times 10^9/L$ 2 days afterwards.

During his hospitalisation, the patient was found to have a positive qualitative CMV DNA PCR raising the suspicion of CMV-associated ITP. However, his viral load was low (7767 copies/mL) so its significance was unclear. He completed a treatment course of valganciclovir with a subsequent undetectable CMV count. Five days after the second dose of IVIG, the patient's platelet count was stable at $10 \times 10^9/L$, he was without signs of active bleeding and he was discharged home.

He restarted maintenance chemotherapy dexamethasone pulse (3 mg/m^2 twice a day for 5 days) with vincristine 1 day after discharge, but the platelet count was still $10 \times 10^9/L$. A third dose of IVIG (800 mg/kg) was given 5 days later without a significant impact on the platelet count. The patient's myelosuppressive chemotherapy (mercaptopurine and methotrexate) had been held on admission due to thrombocytopenia but was restarted after the diagnosis of ITP was confirmed as it was anticipated that the immunosuppression from chemotherapy would help improve platelet counts. CNS radiation, initially planned for the current cycle of maintenance chemotherapy, was held due to persistent thrombocytopenia and the risk for intracranial haemorrhage.

The patient continued maintenance chemotherapy as an outpatient. The platelet counts fluctuated between $9 \times 10^9/L$ and $22 \times 10^9/L$ over the next 2 weeks.

OUTCOME AND FOLLOW-UP

Due to the persistent thrombocytopenia and the need for higher platelet counts to continue his chemotherapy and radiation therapy treatment, the patient was treated with 4 weeks of the anti-CD20 antibody rituximab with his platelet counts improving dramatically. After the rituximab treatment, his platelet counts ranged from $94 \times 10^9/L$ to $154 \times 10^9/L$. No platelet transfusions were required subsequently, and the patient has been asymptomatic from a thrombocytopenia standpoint. CNS radiation was restarted after the thrombocytopenia improved. Due to the potential for hypogammaglobulinaemia after rituximab, IgG levels were monitored monthly after the rituximab treatment was completed. He received IVIG infusions at 2, 4, 6 and 8 months after completing the rituximab infusions for IgG levels less than 400 mg/dL. Unfortunately, the patient had a second isolated CNS relapse while on maintenance chemotherapy 6 months after completing the rituximab treatment. The patient received retrieval chemotherapy and chimeric antigen receptor T cell therapy, and is preparing for haematopoietic stem cell transplant at the time of publication. The patient was intermittently restarted on valganciclovir to maintain CMV viral loads $<500 \text{ IU/mL}$ and has since been placed on valganciclovir indefinitely given the repeat CNS relapse. His platelet count has remained stable, generally above $100 \times 10^9/L$.

DISCUSSION

ITP remains the most common bleeding disorder in childhood. Standard first-line therapies include IVIG and corticosteroids. Second-line therapies include thrombopoietin (TPO) mimetics such as eltrombopag and romiplostim as well as the anti-CD20 antibody rituximab. In severe, treatment-refractory ITP, splenectomy is reserved as a last resort therapy. Treatment of ITP in a patient who is actively on therapy for a haematological malignancy such as leukaemia has unique challenges. For example, while IVIG and steroids were able to maintain our patient's platelet count around $10 \times 10^9/L$ and relieved his symptoms of thrombocytopenia, his platelets remained too low to resume craniospinal radiation safely. Additionally, the use of TPO mimetics is not well studied in the population of patients with haematological malignancy as they are generally avoided in this patient population. TPO receptors are also present on haematopoietic stem cells, thus there is concern for secondarily activated malignant cells with TPO mimetics.

While rare, ITP has been reported in patients receiving chemotherapy for ALL, which is somewhat unexpected given the immunosuppression that chemotherapy causes. Standard first-line therapies for ITP remain corticosteroids and IVIG.³ A previous case report describes persistent thrombocytopenia responding to immunoglobulin and steroids in a 13-year-old male patient with T cell lymphoblastic lymphoma on methotrexate and mercaptopurine.¹ Another case report describes chronic ITP in a 7-year-old patient with ALL undergoing early intensification therapy.² That patient's thrombocytopenia was unresponsive to typical treatments of ITP (steroids and IVIG) as well as to anti-D antibody, vincristine and rituximab. The patient was eventually treated with splenectomy. With IVIG after the splenectomy, the patient was able to maintain platelet levels sufficient to continue maintenance chemotherapy. Consecutive doses of high-dose IVIG (1 g/kg daily for 2 days for a total of 2 g/kg) can potentially be used to treat ITP that is resistant to lower doses of IVIG.⁴ In our patient's situation, higher dosing of IVIG was not pursued due to the increased risk of haemolysis with higher doses of IVIG as he was already mildly anaemic from his chemotherapy treatment.

Case reports have demonstrated active CMV infection in immunocompetent paediatric and adult patients with severe and refractory ITP.^{5,6} Platelet counts worsened with treatment with corticosteroids then improved with steroid taper and initiation of intravenous CMV immune globulin and ganciclovir.⁵ These and other similar case reports suggest a role for evaluating and treating CMV infection in cases of refractory, symptomatic and severe ITP especially prior to pursuing radical interventions like splenectomy. To our knowledge, there are no other published case reports of CMV-associated ITP in a paediatric patient with ALL.

In our case, the patient's ITP resolved with a 4-week course of rituximab with concomitant CMV treatment with ganciclovir, and his platelet count was much improved thereafter allowing for resumption of his chemotherapy and radiation therapy. Given rituximab's mechanism of action being the removal of B lymphocytes as an anti-CD20 antibody, hypogammaglobulinaemia is a known side effect of treatment.⁷ As patients with ALL receiving chemotherapy are already immunocompromised, treatment with rituximab can cause a further decrease in the IgG levels. In our patient, the hypogammaglobulinaemia required IVIG infusions every 2 months afterwards to keep his IgG level $>400 \text{ mg/dL}$.

Learning points

- ▶ Although uncommon, immune thrombocytopenic purpura (ITP) can be seen while on treatment for pre-B acute lymphoblastic leukaemia (ALL).
- ▶ ITP in ALL can respond to the typical first-line treatments of corticosteroids and intravenous immunoglobulin but may require immune-modulating agents like rituximab.
- ▶ Rituximab can be associated with transient or prolonged hypogammaglobulinaemia, so IgG levels should be monitored after rituximab therapy to detect the possible need for immunoglobulin supplementation.
- ▶ Consider cytomegalovirus (CMV) testing and treatment in immunocompromised patients with refractory or severe ITP. Treatment of the CMV infection may facilitate the treatment of the ITP.

Contributors All the authors (ARM, MRP and DJK) contributed to the care of the patient, and the conception, writing and editing of the manuscript.

Competing interests None declared.

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REFERENCES

- 1 Tokeji K, Sakaguchi S, Kurimoto T, *et al.* Immune Thrombocytopenia in a Child with T Cell Lymphoblastic Lymphoma. *Case Rep Hematol* 2016;2016:1–2.
- 2 Horino S, Rikiishi T, Niizuma H, *et al.* Refractory chronic immune thrombocytopenic purpura in a child with acute lymphoblastic leukemia. *Int J Hematol* 2009;90:483–5.
- 3 Pruemer J. Epidemiology, pathophysiology, and initial management of chronic immune thrombocytopenic purpura. *Am J Health Syst Pharm* 2009;66:S4–S10.
- 4 Benesch M, Kerbl R, Lackner H, *et al.* Low-dose versus high-dose immunoglobulin for primary treatment of acute immune thrombocytopenic purpura in children: results of a prospective, randomized single-center trial. *J Pediatr Hematol Oncol* 2003;25:797–800.
- 5 DiMaggio D, Anderson A, Bussell JB. Cytomegalovirus can make immune thrombocytopenic purpura refractory. *Br J Haematol* 2009;146:104–12.
- 6 Shimanovsky A, Patel D, Wasser J. Refractory Immune Thrombocytopenic Purpura and Cytomegalovirus Infection: A Call for a Change in the Current Guidelines. *Mediterr J Hematol Infect Dis* 2016;8:2016010.
- 7 Casulo C, Maragulia J, Zelenetz AD. Incidence of hypogammaglobulinemia in patients receiving rituximab and the use of intravenous immunoglobulin for recurrent infections. *Clin Lymphoma Myeloma Leuk* 2013;13:106–11.

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