CASE REPORT

Vaccine-induced immune thrombocytopaenia purpura in autologous haematopoietic stem cell transplantation

Wan Jamaludin WF, MRCP[1], Kok WH, MBBS[2], Loong L, MSc[3], Palaniappan SK, Master Int Med[2], Zakaria MZ, MRCP[4], Ong TC, MRCP[5], Abdul Wahid SF, PhD[1]

[1]Cell Therapy Centre, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia, [2]Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur Malaysia, [3]Department of Pharmacy, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia, [4]Prince Court Medical Centre, Kuala Lumpur, Malaysia, [5]Department of Haematology, Hospital Ampang, Pandan Mewah, Selangor, Malaysia

SUMMARY

Immune Thrombocytopenia Purpura (ITP) secondary to vaccinations is rare, especially after autologous hematopoietic stem cell transplantation (HSCT). A 31-year-old female received autologous HSCT for relapsed Hodgkin Disease, with platelet engraftment at Day+14. One week after receiving second scheduled vaccinations, she developed severe thrombocytopenia ($3x10^9$/L) associated with pharyngeal hematoma. Bone marrow (BM) examinations were consistent with ITP, possibly secondary to Influenza vaccine. Platelet increment was poor despite high dose corticosteroids, intravenous immunoglobulin (IVIG), Danazol and Eltrombopag. A repeated BM biopsy was in agreement with ITP. Re-treatment with tapering doses of prednisolone resulted in stable platelet counts at $120x10^9$/L a year later.

INTRODUCTION

Scheduled vaccinations are an important strategy to prevent infections in haematopoietic stem cell transplantation (HSCT) recipients. However, vaccines may be associated with adverse side effects including severe thrombocytopaenia. We describe a case of immune thrombocytopaenia purpura (ITP) in adult autologous HSCT recipient after receiving scheduled vaccinations including Influenza vaccine.

CASE REPORT

A 31-year-old female had relapsed Hodgkin Lymphoma twelve years after initial remission. Following salvage chemotherapy, she received autologous HSCT with $CD34^+$ dose of $4.7x10^6$/kg with platelet engraftment at Day+14. Positron Emission Tomography scan after HSCT confirmed second remission.

She received first scheduled vaccinations at 14 months after HSCT uneventfully, consisted of Diphtheria/ Tetanus/ Pertussis/ Inactivated Polio/ Hemophilus B Vaccines (DTP/Polio/Hib) Pneumococcal Polysaccharide 23-Valent Vaccine and Hepatitis B. Two months later, second doses of DTP/Polio/Hib, Hepatitis B and first dose of Influenza vaccines (quadrivalent influenzae vaccine for Type A and B subvirion) were administered. After one week, she noticed spontaneous bruises, petechiae and buccal haematoma. She denied preceding infective illnesses or traditional medications. Systemic examinations were unremarkable except for moderate peripheral bruises.

The platelet counts were $203x10^9$/L which dramatically dropped to $3x10^9$/L after the second vaccinations. Peripheral blood morphology showed true thrombocytopaenia. Viral infections, pregnancy, connective tissue diseases and autoimmune disorders were excluded. Endoscopic *Helicobacter pylori* urease test was deemed risky due to severe thrombocytopaenia. Urea breath test was limited by concurrent Esomeprazole therapy. Anti-human platelet antibody and anti-glycoprotein IIb/IIIa assay was negative. She was diagnosed with ITP secondary to vaccines and received oral Dexamethasone 40mg for four days. Two weeks later, the platelets remained in single digit. High doses of Methylprednisolone, intravenous immunoglobulin (IVIG) and Danazol were administered with persistently poor clinical response. Bone marrow (BM) biopsy at this point showed hypo-normocellularity, adequate megakaryocytopoiesis without lymphomatous relapse or dysplasia, supportive of ITP. Splenectomy was unsuitable given the high intra-operative haemorrhagic risks. Off-label use of Rituximab was considered but not administered due to intercurrent bacteraemia.

Thrombopoietin receptor agonist (Eltrombopag) was administered later but the platelet counts remained $<10x10^9$/L. One month into Eltrombopag, she developed dysphagia and laryngoscopy revealed haematoma with dried clots at the arytenoid, inter-arytenoid and hypopharynx regions. The vocal cords were mobile without airway obstruction. She received platelet transfusions and IVIG. Finally, the pharyngeal haematoma resolved with nebulised adrenaline, menthol inhalation, ice gargle and parenteral feeding.

A second opinion from another institution was sought, and a repeated BM biopsy there was in agreement with ITP. She was restarted on corticosteroids with a slow tapering course of prednisolone. Six months later, she had a protracted platelets recovery of $34x10^9$/L. A year later, prednisolone was successfully stopped with stable platelet counts of $120x10^9$/L (Figure 1).

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Corresponding Author: Wan Fariza Wan Jamaludin
Email: Wan Fariza Wan Jamaludin

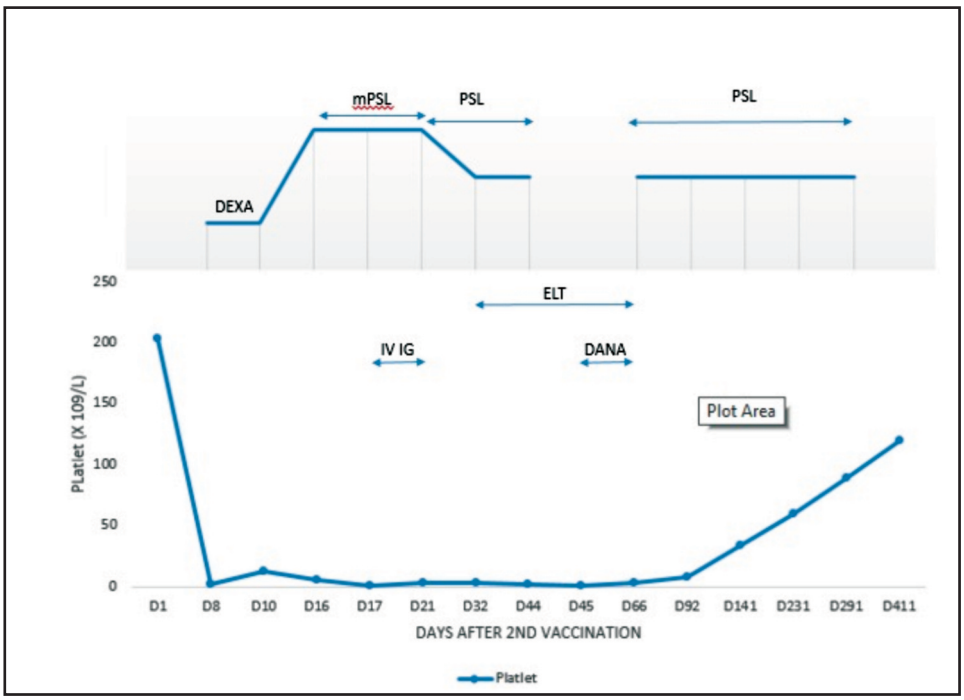

Fig. 1: Platelets response to medical therapies, following severe thrombocytopaenia after the second scheduled vaccinations. Vertical axis: platelets level; horizontal axis: days after vaccinations.

DISCUSSION

To the best of our knowledge, this is the second reported case of vaccine-induced ITP in HSCT recipients. The first case was reported in a 19-year-old haplo-identical recipient, who received the first Influenza vaccine at Day +388 (A/New Caledonia/20/99 [H1N1], A/New York/55/2004 [H3N2],B/Shanghai/361/2002).[1] The normal baseline platelets count dropped to $10x10^9$/L two weeks after vaccination. The anti-IIb/IIIa antibody enzyme-linked immunosorbent assay (ELISA) test was positive and the patient responded to corticosteroids and IVIG within 33 days. Our patient had a stable platelet engraftment which dropped one week after the second vaccinations, therefore we postulated that the ITP was secondary to vaccines rather than to HSCT itself. She received DTP/Polio/Hib and Hepatitis B vaccines during both scheduled vaccinations, with Influenza being the only new vaccine introduced during the second round (A/California/07/2009X-179A; A/HongKong/4801/2014X263B; B/Phuket/3073/2013; B/Brisbane/60/2008). Hence, we also postulated that the ITP was caused by Influenza vaccine. The incidence of Influenza vaccine- induced ITP varied between two in 38 million doses and two in 61 paediatric admissions for post-vaccination thrombocytopaenia.[2] The onset of thrombocytopaenia ranged between 4-26 days and most patients responded to corticosteroids, IVIG and immunosuppressants (reviewed in 2 and 3). Influenza vaccination may cause fourfold increased risk of ITP.[4]

In vaccine-induced ITP, autoimmunity may result from molecular mimicry, where the vaccines epitopes share similar antigen structure with recipient's platelets. Here, the target of molecular mimicry probably involves hemagglutinin (HA). HA binds platelets, and the platelet-bound HA are recognised by anti-HA antibodies, activates complement cascade which induces platelet lysis and thrombocytopaenia.[3] Vaccine constituents e.g. yeast proteins and preservatives may increase autoimmunity.[3] were identified in these cases. However, ELISA test against autoantibodies e.g., platelet IIb/IIIa receptor antibodies was reported to have low sensitivity and is positive in only 60% of ITP patients.[5] Therefore, autoantibodies hypothesis alone is insufficient to explain all of the underlying pathogenesis of ITP. T-cell dysregulation with increased pro-inflammatory cytokines and chemokines e.g., interferon gamma, tumour necrosis factor and C-X-C motif chemokine 10 (CXCL10) has been proposed, especially in anti-platelet antibody-negative cases.[3]

CONCLUSION

Scheduled vaccinations for HSCT recipients are routinely given at 6-12 months after transplantation. Annual Influenza vaccinations are also recommended as Influenza infections can be life threatening in HSCT recipients. Although vaccine-induced ITP is rare, platelet counts should be monitored within 1-2 weeks after administration. If thrombocytopaenia develops, other secondary causes for ITP should be excluded. During therapy, the platelets count must be carefully monitored, and major bleeding signs elicited. Unfortunately, there is limited evidence on the safety to re-vaccinate patients with vaccine-induced ITP. Some reports recommend delaying subsequent vaccinations during resolution of ITP and to resume it once ITP is stable or in remission. Our patient declined further vaccinations after

weighing the benefits of vaccines and possibility of ITP recurrence, and received thorough counselling on other infection preventative steps instead such as hygiene, personal protective equipment and avoidance of environmental exposures.

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