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Case Report

Hypersensitive reactions to platelet transfusion: A case report of urticarial hives and pre-septal cellulitis in the context of a patient with Pre-B acute lymphoblastic leukaemia patient

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ABSTRACT

Background and Aims: Adverse transfusion reactions (ADR), such as fever, chills, and urticarial rashes, are significant in clinical practice, particularly in patients with complex histories. Urticarial reactions, characterised by red, itchy welts, are hypersensitivity reactions, whereas cellulitis, a bacterial infection, differs in aetiology and treatment. This study contributes to a better understanding of hypersensitivity in platelet transfusion and improves clinical management strategies for similar cases in the future. In a contemporary case, a 13-year-old man with pre-B ALL receiving chemotherapy developed widespread urticarial rashes, eye redness, and swelling after receiving four units of random donor platelets. Symptoms were successfully managed with symptomatic treatment after consultations with an ophthalmologist and dermatologist.

Materials and Methods: The methodology involves a systematic approach using the Naranjo ADR Probability Scale, Hartwig Severity Scale, and Shumock and Thornton Preventability Scale. These scales comprehensively evaluate different aspects of the case, including the likelihood, severity, and preventability of adverse drug reactions.

Results: Platelet transfusion causes urticarial hives and pre-septal cellulitis. The Naranjo ADR Causality Assessment scored it as 8 ('probable'). The Hartwig Severity Scale classified it as Level 3 ('Moderate'), and the Shumock and Thornton Scale deemed it 'Probably Preventable', emphasising the need for preventive measures.

Conclusion: This case underscores the complexities of managing transfusion responses in pre-B ALL patients, emphasising the need for close monitoring, timely intervention, and the use of structured adverse drug reaction (ADR) evaluation tools to effectively minimise the risks associated with blood transfusions.

Keywords: Urticarial, Hives, Cellulitis, Transfusion reaction, Platelet transfusion, Leukaemia

INTRODUCTION

The act of transfusing blood has evolved since the first effort in the 17th century, beginning with the use of whole blood and its components for specific uses, such as Red blood cells, platelets, White blood cells, frozen plasma, and plasma derivative products. Platelets are essential for haemostasis because they respond to vascular injury. When the serious and deadly haemorrhagic side effects of chemotherapy in leukaemia were studied in the 1950s and 1960s, the necessity of platelet component therapy was widely recognised (Freireich, 2011). Blood was first collected in glass bottles in the mid-twentieth century, causing platelets to degrade over time. The invention of plastic bags altered blood storage at the same time. To store their short shelf life of 5 days (Askari, Nollet, Debol, Brunstein, & Eastlund, 2002).

Platelet transfusions can cause allergic and anaphylactic reactions, with between 0.09% and 21% of individuals at risk. The severity of these reactions varies greatly, with isolated pruritus and urticarial infection being the only cutaneous manifestations (Behnke, 1970). Systemic effects include bronchitis, hypotensive response, and shock. Only 5% of allergic reactions are linked to temperature increases of one degree or higher.(Behnke, 1970).

Transfusion reactions are adverse reactions to the transfusion of complete blood or one of its components and can be minor to life-threatening in intensity (Behnke, 1970). Acute reactions

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can occur immediately after transfusion, whereas delayed reactions may occur from days to weeks later. Pathophysiology varies according to the transfusion reaction (Jacquot & Delaney, 2018)

Acute reactions include mild allergic, febrile non-haemolytic, septic, acute haemolytic transfusion reactions, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload and anaphylactic reactions (TACO). Anaphylactic reactions have more serious outcomes, such as the development of antibodies against IgA in patients with IgA deficiency. Delayed reactions and transfusion-associated graft-versus-host disease are also possible (Suddock & Crookston, 2024).

In cases of suspicious reactions, transfusions should be immediately withdrawn, and the blood bank and treating physician should be informed (Siddon, Kenney, Hendrickson, & Tormey, 2018). This report serves as a reminder to physicians of the therapeutic consequences of transfused blood products in such patients and the possibility of urticarial hives and cellulitis in patients allergic to blood products (Tariket et al., 2018; Margo, 1999).

MATERIALS AND METHODS

Study design

A detailed case study involving a patient with pre-B acute lymphoblastic leukaemia who experienced hypersensitive reactions, including urticarial hives and pre-septal cellulitis, following platelet transfusion was conducted. The patient's comprehensive medical history, presenting signs and symptoms, and treatment regimen were meticulously reviewed and documented.

Ethical clearance for this study was obtained from the Institutional Ethics Committee of KLE College of Pharmacy. Approval was granted on February 23, 2023, with reference number KLE/COP/EC/135/2023-2024, under the study title "Hypersensitive Reactions to Platelet Transfusion: A Case Report on Urticarial Hives and Pre-Septal Cellulitis in the Context of a Pre-B Acute Lymphoblastic Leukaemia Patient."

Following ethical approval, further actions included detailed monitoring of the patient's response to treatment, comprehensive data collection, analysis of incidence using ADR scales, and management of hypersensitive reactions.

Adverse drug reaction (ADR) scales such as the Naranjo Algorithm adverse drug reaction assessment tool, Hartwig's Severity Assessment Scale, and Schumock & Thronton Preventable Scale are employed to systematically assess the likelihood that a drug or transfusion reaction is due to a specific medication or component. These scales utilise a series of questions to evaluate various factors, including the temporal relationship between drug administration and adverse events, alternative causes, drug levels, patient history, and outcomes following de-challenge and re-challenge. Utilising these scales helps ensure a standardised approach to identify and manage ADRs, enhance patient safety, and guide clinical decision-making. In the context of this study, applying ADR scales allows for a rigorous evaluation of the hypersensitive reactions observed, ensuring that the findings are robust and actionable (Figure 1).

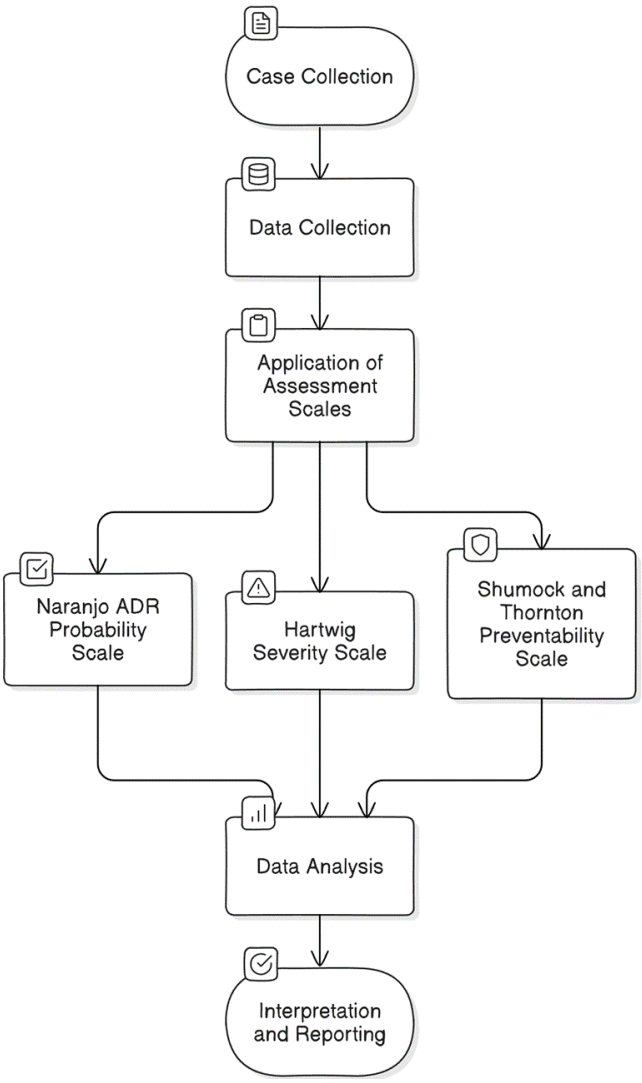

Figure 1. Methodology

Patient Characteristics

A 13-year-old boy who had previously experienced pre-ball came to the emergency room complaining of three episodes of loose stools with a yellowish consistency, as well as a cough that began slowly but was not associated with expectoration. In addition, there had been one episode of vomiting food particles, followed by nausea and facial petechiae for a day. All these signs were subtle. Laboratory results revealed abnormalities, including thrombocytopenia (96 x 103/μL), decreased lymphocyte counts (14%), elevated neutrophil counts (76% of the

manual leukocyte differential count), and no eosinophil counts. The red cell count, packed cell volume, reticulocyte count, and haemoglobin levels were 3.38 x 106/cm3, 10.5% g/dL, and 32.1%, respectively. Bilateral crept into the infra-capsular and infra-axillary regions, according to a systemic review.

The child was admitted to a paediatric emergency ward with a history of lower respiratory tract infection and Pre-B-ALL for 10 years. No family history of Pre-B-ALL was found. The patient was subsequently directed to an ENT specialist for treating laryngitis (lower respiratory tract infection). He complained of a foreign body sensation and a dull, throbbing pain in his throat that had been there for five days. The pain was subtle at first but gradually worsened and was accompanied by trouble swallowing foods and drinks. Due to a history of nasal obstruction for the past 3 days, the patient was advised to take medication in the form of nasal drops, i.e., Otrivin (xylomethazoline) nasal spray. Local examination of the Eyes, Nose &Throat indicated the following:

1. Oral throat cavity is normal.
2. Oropharynx: Grade 3 tonsil hypertrophy (+); posterior pharyngeal wall: postnasal dry (+).
3. Nose: ala vestibule (+), crusting (+), bilateral nasal cavity crusting (+), no para-nasal sinus tenderness.

The final diagnosis of LRTI was grade 3 tonsillitis. This was managed using the following treatments: saline nasal drops (2 drops thrice a day), Otrivin-P (Xylometazoline Hydrochloride and Sorbitol) nasal spray (2 drops thrice a day), Syrup Mucolite (Ambroxol) 5 ml BD, Alex lozenges (Dextromethorphan Hydrobromide) BD, Tab. Paracetamol (Acetaminophen) to treat pain and betadine (Povidone iodine) gargle. The patient was further managed with antibiotics (Piperacillin/Tazobactam, Amikacin, Azithromycin, Ciprofloxacin/Tinidazole) and started on i.v. fluids (Sodium chloride), and shifted to the paediatric haematology-oncology ward for further management of Pre-B-All. On the 14th day of hospitalisation, after the LRTI symptoms had been suppressed, he was transfused with 2 points of packed cell volume due to a considerable reduction in haemoglobin to 6.4%, which was 9.5% after receiving 2 pints of PCV. On the 16th day of his stay, he received a 4-pint random donor platelet (RDP) transfusion due to thrombocytopenia (28x103/µL) (see Table 1). His grandfather's records revealed that he developed rashes all over his body with itching immediately after receiving a platelet transfusion in less than ten minutes—and that within 2 days that is 48 hrs, he noticed redness in his eyes with swelling and pus production. These symptoms were initially insignificant but were eventually intensified. He had received an Avil injection (Pheniramine Maleate) and a Cetirizine tablet (Cetirizine Hydrochloride) after consultation with dermatologists and ophthalmologists. Subsequently, ophthalmologists discussed local examinations and noted conditions such as erythema (+), lid oedema (+), inflammation symptoms (+), conjunctional congestion (+), and watery discharge linked to pus (+), which led to the diagnosis of pseudo-septal cellulitis. To address this, he was prescribed an eye drop called moxiflox (moxifloxacin) and was advised to take antibiotics. The dermatologist reported an itchy rash with hypopigmentation all over the body. After performing local examinations, the condition was ultimately determined to be urticarial hives, for which the patient was prescribed cetirizine tablets to be taken orally and Calamine lotion to be administered topically. The patient's rashes were improving, and the puffiness in his eye decreased after receiving anaphylactic treatment. As indicated in Table 2, the Naranjo Score of "08" so the adverse medication reaction can be categorised as probable. (causality assessment). The ADR was categorised as moderate in severity by Hartwig's severity evaluation scale (Table 3) and probably preventable by Schumock and Thornton's Preventability Scale (Table 4). All the evaluation findings were combined into an ADR analysis, which is described in Table 5. The results of all evaluations were compiled into an ADR analysis, as shown in Table 2.

- **Annotation:** According to **Naranjo's Adverse Drug Reaction Causality Assessment**, a score of 8 indicates that an adverse drug reaction (ADR) is probable, indicating a strong likelihood that the drug caused the reaction, although other factors might be involved. This score reflects a high level of evidence supporting the drug's role in the reaction, based on criteria such as timing, de-challenge, and re-challenge.
- Hartwig's Severity Assessment Scale assigns a severity level of 3, indicating moderate severity. This rating indicates that ADR had a significant impact on patient health but did not present an immediate threat to life or require urgent care.
- The **Schumock and Thornton Preventability Scale** classifies ADR as probably preventable. This suggests that proper premedication, monitoring, and alternative transfusion strategies could potentially prevent hypersensitivity reactions—urticarial hives and pre-septal cellulitis—could have potentially been avoided, thus enhancing patient safety (Table 2).

DISCUSSION

Urticarial hives, one of the most common ADRs, can cause severe hypersensitivity reactions in people with low immunoglobulin A if therapy is delayed and is considered a Type I (immediate) hypersensitivity reaction, typically triggered by allergens, medications, or infections, leading to the release of histamine and other inflammatory mediators (Freireich, 2011; Behnke, 1970). Hypersensitivity reactions are defined as an exaggerated or inappropriate immune response to a substance that is harmless to most people (Freireich, 2011; Tariket et al., 2018). Cellulites are likely to cause a strong urticarial hypersensitivity reaction to abnormal stimuli. Studies have indicated that cellulitis can develop within 24 hours of a tender rash on the body (Choi et al., 2021; Ramanathan, Triulzi,

Table 1. Complete blood count (CBC) laboratory investigations before and after platelet transfusion

	30/01	**03/02**	**11/02**	**18/02**	**24/02**	**01/03**
HAEMOGLOBIN (13-16 %)	10.9	8.3	7.1	8.3	10.1	10.2
RED BLOOD CELL (4.5-6.5 million/cmm)	3.38	2.81	2.44	2.84	4.17	4.07
PLATELETS (1.5-4.5lakhs/cmm)	96000	1.14	22000	34000	34000	2.02
WHITE BLOOD CELL (4000-11000)	5.5	11.3	1200	1000	2100	4900
NEUTROPHILS (40-70%)	76	76	65	44	46	56
LYMPHOCYTES (20-40%)	14	15	21	34	20	20
EOSINOPHILS (1-8%)	0	0	2	15	26	22
MONOCYTES (2-10%)	10	9	12	7	9	1
BASOPHILS (1-10%)		0	0	0		
ABSOLUTE NEUTROPHIL COUNT (2500-6000 /µL of blood)			0.8	400	900	1000
ABSOLUTE LYMPHOCYTE COUNT (1000-4800 /µL of blood)			0.3	400	400	2700

Table 2. Analysis of platelet transfusion-related adverse reactions using different ADR assessment scales.

Adverse Drug Reaction Assessment Scale						
Drug	**Adverse drug Reaction caused**	**Naranjo 's ADR casuality assessment**		**Hartwig severity assessment scale**		**Schumock–Thronton preventable scale**
		Score	**The type of ADR**	**Level**	**The type of ADR**	
Platelet transfusion	Urticarial hives and pre-septal cellulitis	8	Probable	3	Moderate	Probably preventable

& Logan, 1997). Most cases in the study included subjects of all sexes and ages with clinical symptoms of hypotension, chest pain, dyspnoea, severe cyanosis, and transient diffused pulmonary infiltrates, with a history of Hodgkin's lymphoma, acute melody leukaemia, Chronic Obstructive Pulmonary Disease and Diabetes, wherein the condition was managed by either withdrawing platelet transfusion or by administering corticosteroids and histamines (Nevala-Plagemann, Powers, Mir-Kasimov, & Rose, 2019). This study presents a 13-year-old male patient with a complaint of loose stools and a cough yellow in colour. To treat thrombocytopenia, platelet transfusion was routinely performed on examination of unusual reports along with other medications, such as antibiotics (Injection Pipzo (Piperacillin/Tazobactum) 2.5 mg IV TID, Injection Akmin (Amikacin) 375 mg IV OD, Injection Targocid (Teicoplanin) 250 mg IV BD, Tablet Azee (Azithromycin) 250 mg OD), Injection Paracetamol 375 mg IV SoS in the event of a fever spike, and supportive treatment for tonsillitis and LRTI. Numerous case studies and reviews have demonstrated that hypersensitive reactions are more frequently linked to platelet transfusion (Zaki, 2011). Although platelet transfusion is effective in treating urticarial hives in several studies and publications, this incidence continues to occur, most likely because of a lack of awareness among some populations regarding the possibility of adverse drug reactions. If such reactions are to be prevented in the future, concerns regarding targeted therapy and drug reaction monitoring during transfusions in a specific population must be addressed. In the present study, the assessment of adverse reactions was performed using the ADR causality assessment scale, the Naranjo scale, where the total score was calculated as 8 (Zaik, 2011), the Hartwig severity assessment scale (Askari et al., 2002), and the Schumock and Thornton preventability scale (Blieden et al., 2014).

The Naranjo ADR Causality Assessment scored the reaction as 8 ('probable'). The Hartwig Severity Scale classified it as Level 3 ('Moderate'), and the Shumock and Thornton Scale deemed it 'Probably Preventable,', emphasising the need for preventive measures (Nevala-Plagemann et al., 2019)

Table 3. Comparison of pertinent articles focusing the shared and contrasting aspects of case reports.

References (Author names)	Age/ gender	Clinical features	Onset of symptoms	Laboratory investigation	Patient history	Treatment
Eche et al., 2019	43-year-old male	Right scrotal mass and elevated human chorionic gonadotropin and lactate dehydrogenase.	20 min	Chest tightness followed by mild dyspnea and dry cough.	Cell tumour, comprised of seminoma (40%), choriocarcinoma (20%)	IV 100 mg of hydrocortisone, 25 mg of diphenhydramine, and 20 mg of famotidine
Margo, 1999	A 67-year-old woman	----------	immediately	bilateral turgescence and redness of the conjunctiva and eyelids	----------	----------
Blieden et al., 2014	A 59 year-old male	hypotension (blood pressure 77/40mmHg), diaphoresis, respiratory distress, and atrial fibrillation with rapid ventricular response (heart rate 200 beats per minute)	10 min after blood transfusion	elevated white blood count ($37\times10^3/\mu L$) with markedly increased eosinophilia (46% of manual leukocyte differential cell count) and thrombocytopenia ($17\times10^3/\mu L$). Hemoglobin was 11.5g/dL and hematocrit was 34.3%	atrial fibrillation	methylprednisolone sodium (for 3 days) and immunoglobulin (400 mg/day for 5 days), followed by oral PSL (50 mg/day).
Freireich, 2011	An 88-year-old female	red, swollen, and intense, macular erythema of the palms and soles	immediately after transfusion	fever, acral tingling, pruritis, burning sensation, and pain followed by a rash in the acral area, pancytopenia with a platelet count of 13,000, and neutropenia with a white blood cell count of 1,200	Myelodysplastic syndrome (MDS)	cool water soaks and 1% hydrocortisone cream
Ling, Shi, & Chen, 2017	73-year-old female	abdominal pain that had persisted for 1 week and melena for 5 days Furthermore, diagnosed as antral gastric mucosa exhibited chronic active inflammation	immediately	----------	----------	amoxicillin, clarithromycin, pantoprazole, and colloidal bismuth pectin
The current case study	13-year-old boy	rashes all over his body, redness in his eyes, and swelling and pus secretion	immediately after transfusion	decrease in haemoglobin to 6.4% and 9.5%	LRTI and PRE-B -ALL	Inj. Avil (Pheniramine Maleate) stat, Moxifloxacin, Tab Cetirizine to be taken orally, and calamine lotion

CONCLUSION

Severe reactions, such as urticarial hives and pre-septal cellulitis, can be caused by commonly performed platelet transfusions. To avoid the development of such events in the future, a proper risk assessment using a history-taking process, previous transfusion reactions, and concurrent medications that may interact with blood transfusion is necessary. Pharmacists play a key role in reporting adverse events correlated with platelet transfusions to hemovigilance systems.

Healthcare providers play a multifaceted role in hemovigilance activities related to blood transfusions, including education, risk assessment, individualised treatment planning, monitoring, adverse event reporting, and quality improvement initiatives. By actively engaging in these activities, pharmacists, as healthcare provider team members, can contribute to enhancing the safety and quality of blood transfusion practises and minimising the risk of adverse reactions for patients. Preventive measures include pre-transfusion medication protocols for patients with known allergies, strict adherence to aseptic techniques to prevent infections, close monitoring during and after transfusions, and ensuring that patients are well hydrated to mitigate the risk of transfusion-associated circulatory overload (TACO). Additionally, thorough donor screening and matching, along with robust training for caregivers and healthcare staff, are crucial steps in safeguarding paediatric patients undergoing platelet transfusions.

Ethics Committee Approval: Ethical clearance for this study was obtained from the Institutional Ethics Committee of KLE College of Pharmacy. Approval was granted on February 23, 2023, with reference number KLE/COP/EC/135/2023-2024

Informed Consent: Informed consent was obtained from the participants

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study: M.G., A.J., A.S.; Data Acquisition: M.G., A.J., A.L.; Data Analysis/Interpretation: M.G., A.S., M.S.G.; Drafting Manuscript: M.G., A.L., A.J.; Critical Revision of Manuscript: M.G., A.S., M.S.G.; Final Approval and Accountability : M.G., A.S., M.S.G., A.L., A.J.

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