CASE REPORT

Co-occurrence of Autoimmune Haemolytic Anaemia and B-thalassaemia Major in an Infant: A Case Report and Updated Pathogenic Insight

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ABSTRACT

Thalassaemia, a common inherited blood disorder, involves defective globin production leading to premature erythrocyte destruction. Autoimmune haemolytic anaemia (AIHA), a rare complication in thalassaemia, is characterised by autoantibody production against erythrocytes. We present a case of a 7-month-old boy diagnosed with β-thalassaemia major (BTM), complicated by AIHA six weeks after initiating blood transfusions. Despite daily transfusions and oral Prednisolone, the haemoglobin (Hb) level dropped to a life-threatening level (2.5g/dl). High-dose IV Methylprednisolone and Rituximab were administered, resulting in Hb improvement to 11.9 g/dL. AIHA resolution was indicated by negative C3d and reduced IgG on repeated testing. Recognition of AIHA in BTM is vital for effective management, including immunosuppressive therapy, leucodepleted transfusions, and potential splenectomy or haematopoietic stem cell transplant. Early intervention is crucial to reduce the mortality associated with AIHA in children.
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INTRODUCTION

Thalassaemia, a prevalent inherited blood disorder in Malaysia, involves defective globin production causing premature red blood cell (RBC) destruction. Although haematopoietic stem cell transplantation (HSCT) is a curative option for β-thalassaemia major (BTM), limitations lead to reliance on transfusion therapy (TT) with associated risks. Chronic transfusions pose threats like viral infections, iron overload, and autoimmunisation, where up to 40% of patients develop autoantibodies (1). AIHA accelerates RBC destruction, increasing transfusion needs and complications, and affecting blood compatibility testing. About half of AIHA cases are primary, and the rest are secondary. While autoimmunisation is a recognised complication in BTM patients, the occurrence of overt AIHA in this population is relatively rare (2), highlighting the unique clinical significance of such cases. Management includes immunosuppressive therapies (IST) like steroids, intravenous immunoglobulin (IVIG), and Rituximab. Effectively addressing AIHA in BTM patients remains a significant challenge with implications for treatment effectiveness and safety.

CASE REPORT

We present a case of 7-month-old boy with strong family history of β-thalassaemia (Figure 1) who was diagnosed at 6 months old and developed AIHA about six week after starting TT. He presented with poor weight gain, reduced oral intake, decreased activity, and pallor with haemoglobin (Hb) of 3.4 g/dL. Physical examination revealed significant hepatosplenomegaly. Tachypnoea was also noted, suggesting possible bronchopneumonia. Hb analysis revealed undetectable HbA, elevated HbF (96.2%), and HbA_2 (3.8%), confirmed by gel electrophoresis to be BTM. His blood group was O RhD positive and initial pretransfusion testing was unremarkable. Pre-transfusion extended RBC phenotyping showed R1R2 (CDe/cDE), Jk(a-b+),

Fy(a+b-), ss, kk, NN, Le(a-b-). He received 5 crossmatch-compatible, leucodepleted packed RBC transfusions and antibiotics for bronchopneumonia throughout 10 days of hospitalisation, responding well with discharge Hb of 10.6 g/dL.

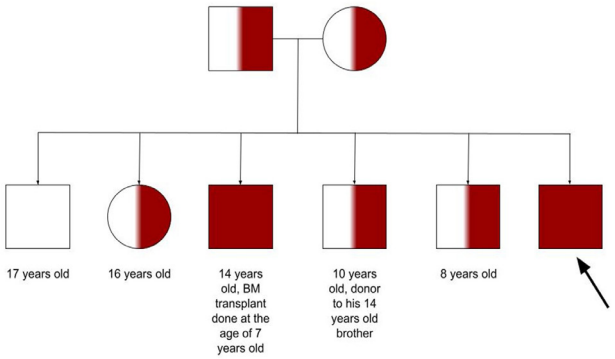

Figure 1: Family pedigree of the case. Carriers are β-thalassemia trait, affected members are β-thalassemia major.

Two weeks later, he presented with pallor, lethargy, and fever. Hb was 4.6 g/dL with normal pretransfusion workup. He received five crossmatch-compatible, leucodepleted packed RBCs and IV antibiotics over eight days and was discharged with Hb of 11.5 g/dL.

He presented again, one week later with fever, tachypnoea, lethargy, worsening hepatosplenomegaly, and severe anaemia (Hb 4.6 g/dL). Pretransfusion testing showed: positive antibody screen (1+) with all cells; positive direct antiglobulin test (DAT) with IgG (3+) and C3d (3+); pan-positive antibody identification at saline (1+) and enzyme phase (4+) and pan-agglutination reaction after elution. Alloadsorption study was negative. Findings indicated warm IgG and cold autoantibodies, without clinically significant alloantibodies. Laboratory investigations showed evidence of haemolysis with high reticulocytes, lactate dehydrogenase and indirect bilirubin levels. Peripheral smear showed spherocytes and agglutination (Figure 2).

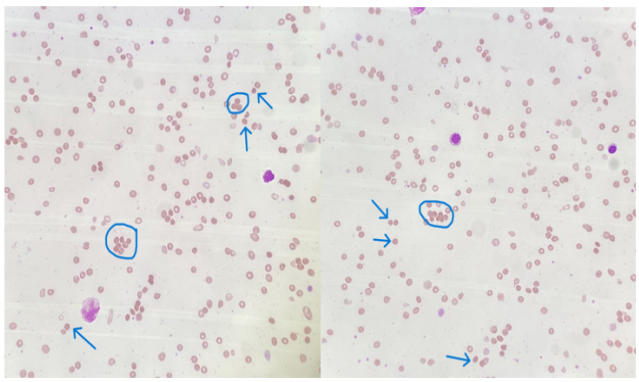

Figure 2: Peripheral blood smears show severe anaemia with presence of spherocytes (arrow) and red cell agglutinations (circle).

He received frequent leucodepleted, phenotype-matched packed RBC transfusions along with oral prednisolone 2 mg/kg/day. Despite this initial treatment, Hb dropped to 2.5 g/dL. IV methylprednisolone 10 mg/kg/day was initiated on day 8 for poor Hb recovery. However , Hb was persistently low at 3-4 g/dL then methylprednisolone was escalated to 30 mg/kg/day on day 10 to enhance immunosuppression. He was also given IVIG 1 g/kg/day on days 9 and 10 concurrently, aiming to suppress hemolysis. When these measures proved insufficient, IV rituximab was started on day 16 in a tertiary centre resulting in improved Hb to 11.9 g/dl. He was also treated with oxygen and antibiotics for RSV pneumonia after tested positive for RSV antigen. No positive cultures or Mycoplasma pneumoniae serology test was reported. Repeated DAT was negative for C3d and 2+ for IgG, indicating AIHA resolution. He was discharged at day 21 on tapering oral prednisolone dosage and TT every 3-4 weeks as per his BTM management. DAT remained positive for six months without evidence of haemolysis. His clinical course is summarised in Table I and Figure 3.

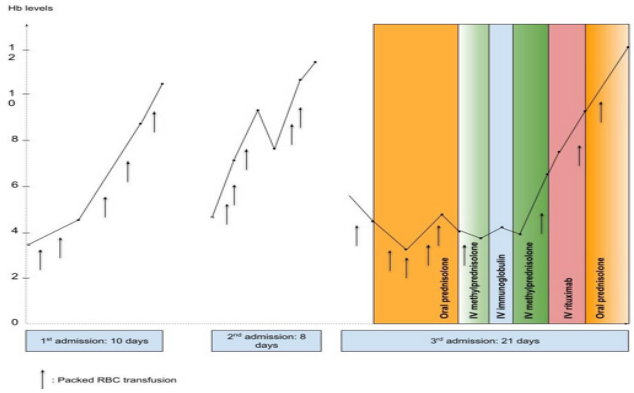

Figure 3: Summary of the patient's admissions, management and haemoglobin levels recovery.

Table I : Summary of the patient's admissions, management and haemoglobin levels recovery.

	1st admission (6 months old)	2nd admission (3 weeks after 1st admission)	3rd admission (1 week after 2nd admission)
Total duration of hospital stays (day)	10	8	21
Hb on arrival (g/dL)	3.4	4.6	4.6
Hb upon discharge (g/dL)	10.6	11.5	11.9
Coombs test	N/A	N/A	IgG: 3+ C3d: 3+
Antibody screening	Negative	Negative	Cell I: 1+ Cell II: 1+ Cell III: 1+
Further serological testing	N/A	N/A	Elution: Panagglutination Alloadsorption: Negative

CONTINUE

Table I : Summary of the patient's admissions, management and haemoglobin levels recovery. (CONT.)

	Ist admission (6 months old)	2nd admission (3 weeks after 1st admission)	3rd admission (1 week after 2nd admission)
Packed RBC transfusion (unit (cc/kg))	5 (10)	5 (15)	15 (5-10)
Other treatment / medication	IV Cefuroxime IV Ceftriaxone PO Cefuroxime	IV Ampicillin	IV Tazocin PO Azithro-mycin PO Predniso-lone IV Methylpred-nisolone IV Immunoglob-ulin IV Rituximab

DISCUSSION

We described a case of an infant with β-thalassemia major (BTM) who developed mixed-type AIHA approximately six weeks after initiating TT. AIHA poses challenges in BTM, potentially causing severe hemolysis and increased transfusion needs.

Studies show variable autoimmunization rates in BTM, with AIHA incidence ranging from < 1% to 21% (2) . Risk factors include older age, higher transfusion burden, splenectomy history, intermediate thalassemia phenotype, family AIHA history, prior alloimmunization, IgG+ complement DAT, and increased risk during the first 72 transfusion events (2).

Childhood AIHA affects 1 in 80,000 live births, with higher prevalence in infants (21%). It can be primary or secondary to infections, drugs, autoimmunity, or malignancy (3). Our patient's suspected bronchopneumonia during initial presentations may explain the development of secondary AIHA.

Despite generally immature immune systems and their tendancy towards tolerance, infants can still develop autoimmune disorders (AID). This is likely involves a complex of genetic, environmental, epigenetic, and hormonal factors. In neonatal autoimmunity, maternal autoantibodies transferred through the placenta play a significant role, but other mechanisms such as dysregulation in apoptosis, molecular mimicry, bystander activation, and environmental triggers are also proposed. Persistent maternal microchimerism in the baby's circulation is suggested to contribute to chronic inflammation and autoimmunity. However, our understanding of these processes remains incomplete (4).

Research, including animal studies, reveals insights into the pathogenesis of AIHA It involves genetic predisposition and environmental factors, affecting various immune system components including autoantibodies, cytokines, complement systems, phagocytes, B and T lymphocytes, and natural killer cells. It's linked to dysregulated self-tolerance mechanisms and autoreactive T and B cells targeting self-antigens (4) . Patients with AIHA show elevated Th17 cells and expanded CD8+ T cell clones. Evidence also suggests the role of reactive oxygen species in triggering autoantibody production, which is shown to be suppressed by antioxidants. This supports the oxidative stress theory in AIHA pathogenesis (5).

AIHA can also be triggered by red blood cells' exposure to high shear stress, leading to increased IgG binding and epitope exposure. Genetic studies reveal associations with HLA-B locus, specifically HLA-B8 and BW6 alleles (5)

In BTM, proposed mechanisms for AIHA include constant immune stimulation activating monocytes to clear excess alpha-globin chains, exposure of hidden epitopes triggering the complement cascade, and a higher frequency of CD4bright and CD8dim T-lymphocyte subsets associated with AID (2,5) . BTM's association with AID may stem from the proximity of the β-chain locus (11p15.5) to immune regulation genes such as STIM1, CD151, TC21/RRAS2, SIGIRR/TOLL/IL1R8, pp52/LSP1, TRIM21, TOLLIP, and SLEN3 (2).

Our patient developed AIHA after multiple transfusions. While continuous exposure to foreign antigens can disrupt immune self-tolerance, paradoxically, research indicates a lower AIHA risk with prolonged blood exposure in BTM patients, possibly due to increased T-regulatory cells causing immune activation suppresion (2).

Managing AIHA in children typically involves glucocorticoids as first-line treatment, with or without IVIG. Second-line options include cyclosporine and rituximab. Plasmapheresis is considered in a reftractory life-threatening AIHA . While studies show a high response rate to steroids, some cases, including ours, may require IVIG and rituximab . This could be due to the mixed type AIHA and other factors such as primary immunodeficiency (3). IVIG is effective, particularly for severe disease, and rituximab is considered the best second-line therapy, with other options like Azathioprine, Danazol, and Cyclosporine. Our patient responded well to IVIG and rituximab, leading to remission. At the same time, concurrent antimicrobial treatment addresses underlying infections that potentially contributing to AIHA development.

RBC transfusions are often necessary for AIHA, considering overall health, disease severity, anemia

progression, and hemolysis indicators. Extended RBC phenotyping and leucodepleted phenotype-matched RBC transfusions help protect against autoimmunization in BTM patients (2) .

Clinicians managing BTM patients should remain vigilant for AIHA, particularly in cases of unusual anemia or hemolytic crisis. Preventive strategies include monitoring DAT positivity, implementing restrictive transfusion regimes, considering immunosuppressive therapy, and evaluating the risk-benefit balance of interventions like splenectomy and hematopoietic stem cell transplantation.

Future research on AIHA in BTM should focus on understanding how genetic factors and immune system irregularities interact to cause the condition. Key priorities include identifying predictive biomarkers, optimizing personalized treatment protocols, and exploring novel therapies. Studies should also investigate the long-term effects of AIHA on BTM patients and evaluate preventive strategies, such as tailored transfusion regimes. By addressing these areas, researchers aim to improve early detection, treatment effectiveness, and overall outcomes for BTM patients at risk of developing AIHA.

CONCLUSION

This case underscores the complexity of AIHA in BTM revealing challenges in diagnosis and management. Despite a high incidence of autoimmunisation, which may lead to AIHA, the heterogeneous nature of thalassaemia complicates risk assessment. Our patient's presentation of mixed-type AIHA and resistance to conventional treatments highlight the need for tailored approaches. The case emphasises the importance of vigilant monitoring, early recognition, and collaborative efforts between clinicians and laboratory personnel. Addressing AIHA in BTM necessitates a comprehensive understanding of its diverse etiological factors, immune mechanisms, and evolving treatment strategies to enhance outcomes in this vulnerable patient population.

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REFERENCES

1. Guirat-Dhouib N, Mezri M, Hmida H, Mellouli F, Kaabi H, Ouderni M, et al. High frequency of autoimmunization among transfusion-dependent Tunisian thalassaemia patients. Transfus Apher Sci. 2011;45:199–202. https://doi.org/10.1016/j.transci.2011.08.003
2. Khaled MB, Ouederni M, Sahli N, Dhouib N, Abdelaziz AB, Rekaya S, et al. Predictors of autoimmune hemolytic anaemia in beta-thalassemia patients with underlying red blood cells autoantibodies. Blood Cells Mol Dis. 2019;79:102342. https://doi.org/10.1016/j.bcmd.2019.102342
3. Voulgaridou A, Kalfa TA. Autoimmune hemolytic anemia in the pediatric setting. J Clin Med. 2021;10:216. https://doi.org/10.3390/jcm10020216
4. Chang C. Neonatal autoimmune diseases: A critical review. J Autoimmun. 2012;38(2–3):J223–J238. . https://doi.org/10.1016/j.jaut.2011.11.018
5. Michalak SS, Olewicz-Gawlik A, Rupa-Matysek J, et al. Autoimmune hemolytic anemia: Current knowledge and perspectives. Immun Ageing. 2020;17:38. https://doi.org/10.1186/s12979-020-00208-7