CASE REPORT

A Rare Case of Anti-tuberculosis Drug-induced Haemolytic Anaemia

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ABSTRACT

Drug-induced immune haemolytic anaemia (DIIHA) is a rare but potentially life-threatening disorder. We herein report a case of DIIHA due to anti-tuberculosis (TB) drugs. A 32-year-old woman was treated with tablet rifampicin/ isoniazid for latent TB. Three weeks later, she developed signs and symptoms of anaemia. Laboratory investigations revealed pancytopenia, hyperbilirubinaemia, elevated lactate dehydrogenase and transaminases, and a positive direct antiglobulin test. HbA1c was notably low. Following discontinuation of anti-TB drugs and initiation of glucocorticoids, both clinical and laboratory parameters improved. Although commonly implicated when using third-generation cephalosporin and penicillin, DIIHA can infrequently occur upon rifampicin and isoniazid administration. This occurs when antibodies target these drugs which are bound to erythrocyte membrane proteins, resulting in intravascular haemolysis. It is essential for clinicians to be aware about this complication caused by commonly prescribed drugs so that timely diagnosis and management can be provided.
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INTRODUCTION

Autoimmune haemolytic anaemia (AIHA) arises from autoantibody-mediated destruction of red blood cells (RBC), with drug-induced immune haemolytic anaemia (DIIHA) accounting for approximately 10% of cases (1). Although DIIHA has been reported in the literature, cases related to anti-tuberculosis (TB) medications remain rare. We describe a case of DIIHA in a young woman following anti-TB therapy, outlining key clinical and laboratory features, and emphasising the need to recognise this potentially life-threatening but underdiagnosed complication in high TB-burden settings.

CASE REPORT

A 32-year-old lady was admitted to the hospital with a one-week history of lethargy, dizziness and poor oral intake. She has a history of hypertension for four years, and was taking tablet amlodipine 5 mg once daily with no recent change in dosage. Three weeks prior, she was also diagnosed with latent TB by the local general practitioner when her tuberculin skin test returned positive. She was since started on tablet rifampicin 750 mg/ isoniazid 375 mg once daily. There was no family history of anaemia or other haematological disorders. In the emergency department, she was noted to be pale and tachycardic. There was no jaundice. Examination of the cardiovascular, respiratory and gastrointestinal systems were unremarkable.

Initial laboratory investigations revealed pancytopenia and reticulocytosis (Table 1). Direct antiglobulin test (DAT) was positive whilst peripheral blood film revealed mild agglutination, rouleaux formation and polychromasia. Other abnormal biochemical investigations include hyponatraemia, hyperbilirubinaemia, raised lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and a notably low HbA1c (Table 1), due to haemolysis. A diagnosis of DIIHA due to anti-TB medications was made based on the temporal relationship between commencement of the drug and development of the illness. Additional investigations were performed to rule out secondary causes of AIHA. Infectious screening for human immunodeficiency virus, viral hepatitis, Mycoplasma pneumoniae and Legionella pneumoniae were negative (Table 1); whereas workup with C3, C4, antinuclear antibody and anti dsDNA antibody were nonconclusive of systemic lupus erythematosus (Table 1).

Table I: Baseline laboratory results on and following hospital admission

Parameter	Admission	Day 5 of admission	Unit	Reference Interval
		Haematology		
Haemoglobin	7.1	6.8	g/dL	12.0 - 15.0
Mean corpuscular volume	90.3	92.0	fL	83.0-101.0
Mean corpuscular haemoglobin	38.2	36.2	pg	27.0 - 32.0
White blood cell	2.23	4.04	10^3/uL	4.00 - 10.00
Platelet	107	208	10^3/uL	150 – 410
Haematocrit	16.8	17.3	%	36.0 - 46.0
Reticulocyte	3.37	-	%	0.5-2.5
G6PD Screening	Normal	-	-	-
Peripheral blood film	Mild red blood cell agglutination with Rouleaux formation. Some polychromatic cells seen. Autoimmune haemolytic anaemia needs to be considered.	-	-	-
Direct antiglobulin test	Positive (3+)	-	-	-
		Renal Profile		
Sodium	125	137	mmol/L	136 - 145
Potassium	3.4	4.3	mmol/L	3.4 - 5.1
Chloride	95	107	mmol/L	98 - 107
Urea	4.2	3.3	mmol/L	2.5 - 6.7
Creatinine	74	49	umol/L	44.2 - 88.4
eGFR	>90	>90	ml/ min/1.73m^3	>90 ml/min/1.73m^3
		Liver Function test		
Total protein	78	71	g/L	64 - 83
Total bilirubin	26	11	umol/L	3.4 - 20.5
Globulin	39	35	g/L	23 - 34
Alanine aminotransferase	44	43	U/L	0 - 33
Aspartate aminotransferase	105	56	U/L	5 - 34
Alkaline phosphatase	45	38	U/L	40 - 150
		Other biochemical investigations		
Lactate dehydrogenase	1133	665	U/L	125 - 220
Fasting blood glucose	5.0	-	mmol/L	3.9-6.0
HbA1c	<3.8	-	%	<5.9
Complement C3	115	-	mg/dL	90-180
Complement C4	36	-	mg/dL	10 - 40
Antinuclear antibody	Positive(speckled) 1:80	-		
Anti-dsDNA antibody	Negative	-		
		Microbiology investigations		
Hepatitis B surface antigen	Non-reactive	-	-	-
Hepatitis C antibody	Non-reactive	-	-	-
HIV Antigen-Antibody	Non-reactive	-	-	-
Mycoplasma pneumoniae IgM	Negative	-	-	-
Legionella pneumoniae IgM	Negative	-	-	-

eGFR, estimated glomerular filtration rate based on Chronic Kidney Disease Epidemiology Collaboration

Following diagnosis, the patient was admitted to the ward. Fluid resuscitation was commenced with strict urine output charting. Rifampicin and isoniazid were withheld. She was started on a trial of tablet prednisolone 95 mg once daily (1mg/kg/day) to suppress autoantibody production and avert further haemolysis. The patient responded well clinically and demonstrated laboratory improvement before being discharged well at day six of admission. She was planned for continuation for steroids and reassessment after six months by the haematology team to determine the need to continue TB treatment, likely with an alternative regimen.

DISCUSSION

In DIIHA, drugs bind to RBC membrane and trigger IgG antibodies that are directed to either the drug, the RBC membrane protein, or both (Figure 1). These antibodies may be drug-dependent (e.g., cephalosporin and rifampicin, as in our case) or drug-independent (e.g. fludarabine) (2). In drug-dependent DIIHA, antibodies react with RBC only in the presence of the drug, whereas in drug-independent DIIHA, antibodies react even without the drug (2). Infrequently, mixed type DIIHA display features of both mechanisms. Several immunopathogenic pathways have been described. In the hapten mechanism, drug binds to the RBC membrane and antibodies against the drug triggers RBC destruction via macrophage phagocytosis or complement activation (3). In the immune complex mechanism, as in our case with anti-TB therapy, the drug forms circulating immune complexes that attach to RBC and activate complement, causing intravascular haemolysis (3). Finally, in non-immunologic protein adsorption, certain drugs alter the RBC membrane, allowing plasma proteins to bind and label the cells for premature clearance (3).

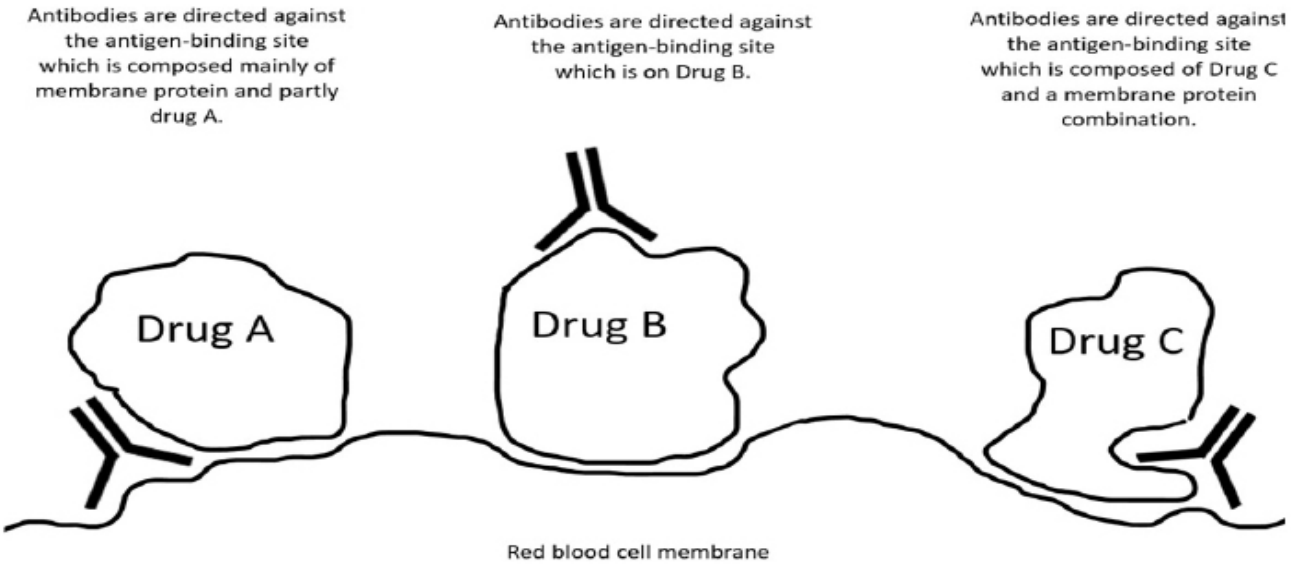

Figure 1: Mechanisms of drug induced autoimmune haemolytic anaemia

Over 130 individual drugs have been associated with DIIHA but the most commonly reported include cephalosporins, beta-lactamase inhibitors and platinum-based chemotherapy (3). DIIHA in our patient may be attributed to a synergistic effect of rifampicin and isoniazid, from isoniazid alone, or more likely from rifampicin, given its higher reported incidence in literature (1). A review of the existing literature on anti-TB drug associated DIIHA revealed only a few reports, some not available in English or without full-text access. Notably, 3 cases of rifampicin-associated DIIHA was described in Germany in 2001, while Garratty (2010) reported a single case over a 10-year period in his United States laboratory (3). In Malaysia, adverse drug reactions (ADR) are monitored by the National Pharmaceutical Regulatory Agency (NPRA). Unpublished NPRA data indicate only five cases of rifampicin-related haemolytic anaemia and none related to isoniazid from 2000 to March 2025 (NPRA, personal communication, August 2025) despite TB being endemic in this region.

Risk factors for DIIHA are not widely researched, probably due to the low reported incidence of approximately 1 per million/year (3). One proposed risk factor involves sensitization and increased production of drug-dependent autoantibodies during high-dose or intermittent drug therapy (2), as illustrated by Sanwal and colleagues, who reported a case of DIIHA following interrupted rifampicin therapy (4). Despite this, DIIHA has also been observed during continuous low-dose therapy, as reported by Sveroni et al. (2), and also in our patient. This variability suggests that development of DIIHA may result from a complex interplay of factors such as genetic predisposition, immune status and concurrent infection.

Clinical manifestation of DIIHA is similar to AIHA and is primarily associated to the underlying anaemia. Patients

with DIIHA can present after weeks of drug therapy from a milder extravascular haemolysis, as observed in our patient; or within hours of drug exposure due to acute intravascular haemolysis, typically seen in those who have a history of exposure to the drug (3). Occasionally, DIIHA may be misdiagnosed as a haemolytic transfusion reaction in patients who receive recent transfusion, or acute sepsis in those who present with infection (1).

Haematological investigations often reveal reflex reticulocytosis as a result of a bone marrow response to premature haemoglobin destruction. A positive DAT confirms an autoimmune mediated aetiology of RBC haemolysis. (1). A positive drug-dependent antibody testing distinguishes drug-dependent DIIHA from drug-independent DIIHA, helping clinicians to discontinue the culprit drug especially if multiple drugs are being used. It is also important to note that negative drug-dependent antibody testing can be attributed to either warm AIHA or drug-independent DIIHA (3) because the autoantibodies produced in warm AIHA cannot be serological differentiated from autoantibodies formed in drug-independent DIIHA. The latter diagnosis can only be confirmed by clinical improvement following cessation of the causative drug, as demonstrated in our case (3). Besides RBC lysis, leukopenia and thrombocytopenia may be observed in patients on rifampicin due to destruction from complement activation. Interestingly, drug-induced immune thrombocytopenia and neutropenia are more common (2-18 cases per million) as compared to DIIHA (1 case per million) (3).

In the biochemical laboratory, many parameters can be influenced by cell lysis. In vivo destruction of RBC results in a significant release of intracellular contents such as LDH, AST and ALT into the extracellular fluid, thus explaining the elevated levels of these analytes in our patient (5). In contrast, the release of sodium-depleted intracellular content from RBC into the plasma during haemolysis results in a dilutional hyponatraemia (5). While hyperbilirubinaemia is expected due to increased haemoglobin catabolism, clinical jaundice of the skin and sclera were not visible in our patient because serum bilirubin concentration was only mildly elevated. HbA1c reflects average blood glucose exposure over the typical three-month lifespan of RBC, assuming normal RBC survival. Any condition that shortens RBC lifespan or decreases their mean age can falsely lower HbA1c levels. In this patient, a markedly low HbA1c ordered as part of routine testing was inconsistent with her clinical findings and plasma glucose level, indicating increased RBC destruction from DIIHA. During such acute haemolytic episodes, clinicians should instead assess glycaemic control using plasma glucose or fructosamine levels.

Confirmatory drug-specific antibody testing provides a definitive evidence of a drug-dependent antibody. Nevertheless, this technically complex testing is performed only in specialised reference laboratories, often with long turnaround times. Hence, in resource-limited settings such as our centre, good clinical judgement, followed by immediate withdrawal of the suspected drug, initiation of glucocorticoids, and close collaboration with haematologists are vital. In severe cases, dialysis and blood transfusion might be required (1), with intravenous immunoglobulins and immunosuppressants considered if no response occurs after drug cessation (2). Haematological remission is expected between 1-2 weeks upon drug discontinuation, as demonstrated in our patient. Re-administration of the accountable drug is contraindicated in DIIHA whereas future use of medications within the same class needs to be judiciously considered due to the possibility of cross-reactivity. While a single case does not justify new clinical practice guidelines, strengthening clinical vigilance in patients receiving anti-TB therapy and enhancing pharmacovigilance reporting through the NPRA is crucial for improving detection of adverse events and supporting safer prescribing practices.

CONCLUSION

DIIHA risk factors are poorly understood and may relate to both patient and drug. Further research is imminent to explain why DIIHA is not as frequently encountered in patients taking anti-TB medication despite it being a commonly prescribed drug. Diagnosis relies on careful drug history and laboratory workup, and stopping the offending drug typically leads to rapid resolution.

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