Coombs-negative haemolytic anaemia due to diffuse large B-cell lymphoma

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Introduction

Autoimmune Haemolytic Anaemia (AIHA) is characterised by shortened red cell survival and the presence of autoantibodies directed against autologous RBCs. Demonstration of antibodies or complements on RBC membranes, usually by a positive direct antiglobulin test (DAT/ Coombs test) result, is essential for diagnosis (1). They can occur in patients who have no antibodies detectable by routine procedures representing 5% to 10% of all AIHAs (2). While AIHA associated with lymphoproliferative neoplasms is well recognised, it remains a rare clinical entity. Particularly noteworthy is the presentation of diffuse large B-cell lymphoma (DLBCL) accompanied by Coombs-negative AIHA, an exceedingly uncommon event.

Case presentation

55-year-old male, a patient diagnosed with type 2 diabetes and hypothyroidism admitted with progressively worsening shortness of breath, loss of appetite and loss of weight over 3 months. He further noticed intermittent passage of tea colour urine. There was no childhood history of haemolytic disorders, and there was no family history of malignancy.

On examination, the patient was pale and icteric. There was right side level 2 cervical lymph adenopathy. Vital parameters were normal. There was 5 cm splenomegaly, and the rest of the examination was normal. At the presentation, a full blood count revealed: haemoglobin 6.1 g/dL, RBC count 2.0×10^{12}/L, mean corpuscular volume 98.8 fL, haematocrit 23.2%, Total white blood cells count 4.56×10^{9}/L and platelet count 197×10^{9}/L. Reticulocyte count was 3.8% (Retic index 3.1). Peripheral blood smear examination showed normocytic normochromic red cells with mild agglutination. No white blood cell or platelet abnormalities were detected. Serum total bilirubin level was 30 µmol/L (5-21 µmol/L), and the serum indirect bilirubin level was 24 µmol/L (0-3.4 µmol/L). Serum lactate dehydrogenase (LDH) was 1430 IU/L (140-280 IU/L), and serum ferritin level was 1680 ng/dL (12-300 ng/dL). Urine for urobilinogen, haemoglobin and haemosiderin were positive. Serum Haptoglobin level testing was not done. The Direct Antiglobulin Test (DAT) with poly-specific anti-sera IgG+ C was negative. Monospecific antibody testing with microcolumn agglutination method was also negative. Brewer's test, Donath-Landsteiner test, heat test for unstable haemoglobin and flow cytometry for paroxysmal nocturnal haemoglobinuria were negative. Contrast-enhanced computed tomography of the neck, chest, abdomen, and pelvis revealed multiple para-aortic, para-oesophageal lymphadenopathy and bilateral cervical lymphadenopathy with multiple splenic lesions suggestive of lymphoma (Figure 1 and 2). In histological and subsequent immunohistochemical examination of the cervical lymph nodes the diagnosis turned out to be a diffuse large B cell lymphoma with CD 20 positivity.

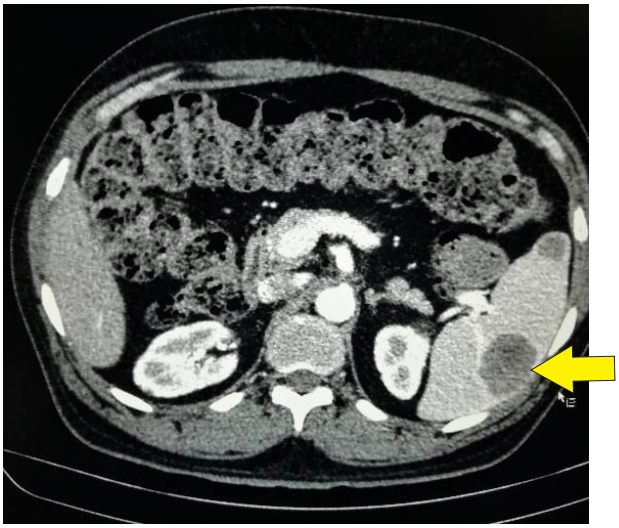

Figure 1: Splenic lesions (yellow arrow)

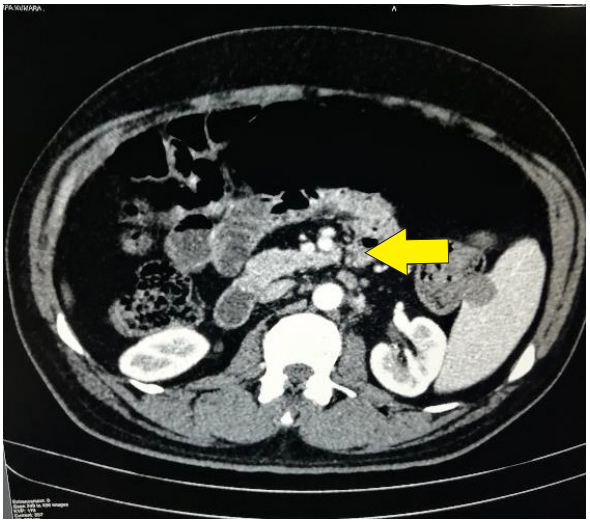

Figure 2: Para-aortic lymphadenopathy (yellow arrow)

Upon confirmation of the diagnosis, the patient was promptly referred to the oncology team for further management. Subsequently, he was initiated on a regimen of R-CHOP chemotherapy, which includes rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone. Encouragingly, the patient has exhibited significant clinical improvement in terms of anaemia as well as general wellbeing in response to the treatment regimen.

Discussion

As the most common subtype of non-Hodgkin lymphoma (NHL), the incidence patterns of diffuse large B-cell lymphoma (DLBCL) generally mirror those of NHL. Globally, DLBCL accounts for one third of all NHLs, ranging between 20% and 50% by country. Based on United States cancer registry data, age-standardized incidence rate for DLBCL was 7.2 per 100,000 (3).

The association between NHLs and the development of secondary AIHA has been extensively studied, highlighting a clinicopathological link between these two conditions. A retrospective analysis conducted on clinical and laboratory data of AIHA/NHL patients revealed significant insights: approximately one-fifth of AIHA patients develop lymphoma, while 7% to 10% of lymphoma patients have co-existing AIHA (4).

Coombs-negative AIHA presents a diagnostic challenge due to its rarity and the absence of definitive criteria. Negative DAT results can stem from various mechanisms, including low-affinity IgG antibodies, sensitization with IgA or IgM antibodies, or antibody levels below detection (2). Additionally, antibody-independent cytotoxic events mediated by natural killer (NK) cells have been implicated. In such cases, a high index of suspicion is crucial, relying on clinical findings, imaging studies, and histopathological examination for diagnosis. In our patient, despite haemolysis, negative DAT results prompted the exclusion of other possible causes of haemolytic anaemia. With a heightened suspicion of a lymphoproliferative neoplasm, investigations were directed accordingly. Ultimately, detection of diffuse large B-cell lymphoma (DLBCL), alongside excluding alternative aetiologies, facilitated the diagnosis of Coombs-negative cold autoimmune haemolytic anaemia by the multidisciplinary team.

Conclusion

The intricate interplay between AIHA and NHL, particularly diffuse large B-cell lymphoma, underscores the complexity of haematological disorders. This highlights the diagnostic challenges posed by Coombs-negative AIHA and the importance of a comprehensive diagnostic approach.

Despite the rarity of Coombs-negative AIHA, clinicians must maintain a high index of suspicion, especially in the context of lymphoproliferative neoplasms.

Informed written consent was obtained from the patient to publish this case report.

Acknowledgements

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