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CASE REPORT

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Autoimmune hemolytic anemia associated with vitamin B12 deficiency and viral illness in DiGeorge syndrome. Case report and literature review

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Abstract

Vitamin B12 plays a crucial role in cell maturation and differentiation. Its deficiency can lead to cytopenias and even hemolysis. We suggest regular monitoring and maintenance of Vit B12 levels in DiGeorge syndrome patients to prevent such triggers.

KEYWORDS

AIHA, autoimmune hemolysis, B12 deficiency, DiGeorge syndrome, viral illness

1 | INTRODUCTION

DiGeorge syndrome is a primary immunodeficiency resulting from a microdeletion 22q11.2 and leads to a multifaceted disorder. This microdeletion results in abnormal development of third and fourth pharyngeal pouches. The presentation and clinical features vary from person to person and commonly include facial abnormalities, hypoparathyroidism, heart defects, thymic hypoplasia, immunodeficiency, and other clinical problems.[1] It is occasionally associated with cytopenias, including idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA.) Usually, more than one cell line is affected by the patient experiencing cytopenias. We report a case of AIHA secondary to DiGeorge syndrome in an adult female, likely precipitated by a viral illness and vitamin B12 deficiency.

2 | CASE REPORT

18-year-old Qatari lady, known case of DiGeorge syndrome, presented with a history of intermittent high-grade fever, runny nose, and cough productive of whitish sputum. On the day of presentation, the patient developed nausea and three episodes of yellowish, nonblood-stained vomiting. There were no sick contacts or recent travel. The review of the system was remarkable for dark urine and 5 Kg of weight loss over the preceding 10 days. The patient had no history of alcohol use and did not follow a specific diet; however, meat was limited in her diet due to dietary preferences.

Her history was significant for recurrent childhood infections, attributed to immunosuppression secondary to DiGeorge syndrome. She was also diagnosed with patent ductus arteriosus and a small ventricular septal defect. Both were hemodynamically insignificant and managed conservatively.

The patient also suffered from a learning disability and attention deficit hyperactivity disorder (ADHD), which were also attributed to the DiGeorge syndrome.

Upon presentation, the patient was febrile (38.7°C) and tachycardiac (118 beats per minute) but had no desaturation, tachypnea, or hypotension. Physical examination revealed a young lady sitting comfortably in bed, not in any distress. The conjunctivae were pale, and scleral icterus was noted. The rest of the physical examination was within normal limits. A complete sepsis screen, including a chest X-ray, urine culture, blood cultures, malaria screen, and a nasopharyngeal swab for the respiratory viral screen, including RT-PCR for COVID-19, was sent looking for an underlying infection. The results were negative except for the presence of rhinovirus and adenovirus in the nasopharyngeal swab. A complete blood count showed neutrophilic leukocytosis and severe macrocytic, hypochromic anemia (hemoglobin 3.5 gm/dL) with high red cell distribution width. [Table 1].

An anemia workup showed reticulocytosis, a high LDH, and low haptoglobin with indirect hyperbilirubinemia keeping in line with intravascular hemolysis. Peripheral blood smear showed marked macrocytic anemia with anisocytosis, basophilic stripling, nucleated red blood cells, increased rouleaux formation, and red cell agglutination. Hypersegmented neutrophils (>6 lobes) were also noted. Other laboratory workup was unrevealing. [Table 1].

With a working diagnosis of hemolytic anemia likely precipitated by an underlying infection, the direct Coomb's test for polyspecific antihuman globulin (AHG) was sent and was positive. The monospecific AHG was positive for anti-IgG and negative for anti-C3d. An eluate was prepared and tested for confirmation of antibodies, and the positive elution test confirmed the presence of warm IgG antibody-induced autoimmune hemolytic anemia (AIHA). A complete autoimmune screen was negative. Serum IgG, IgM, C3, and C4 levels were within normal limits. A computerized tomography scan of the chest, abdomen, and pelvis was performed to rule out any underlying malignancy as the cause of hemolysis and was unrevealing. Bone-marrow examination showed features consistent with active hematopoiesis and a normal B- and T-cell population.

The patient received two units of packed red cells and 100 mg intravenous of methylprednisolone. A hematology opinion was sought, and the patient was planned to receive 7 days of intravenous (IV) methylprednisolone, followed by a tapering course of oral steroids. Also, she received intravenous immunoglobulin (IVIG) for 3 days. She also received IV cyanocobalamin 1000 mcg daily for the duration of her hospital stay and will continue oral vitamin B12 therapy. The patient's hemoglobin was stable throughout her hospital stay, and she will be followed up in the hematology clinic for further management. [Figure 1].

TABLE 1 Laboratory parameters

Variable	Day 1 (admission)
White cells (per mm^3)	15.3
Differential (per mm^3)	
Neutrophils (per mm^3)	11
Lymphocytes (per mm^3)	1.3
Eosinophils (per mm^3)	0.5
Monocytes (per mm^3)	3
Platelet count (per mm^3)	210
Hemoglobin (gm/L)	3.5
Hematocrit	5.8
Mean corpuscular volume	126.1
Mean corpuscular hemoglobin	
Mean corpuscular hemoglobin concentration	76.1
Red cell distribution width	28
Retics count	102.4
Retics percentage (%)	22.3
LDH	640
Haptoglobin	<10
Direct bilirubin	13
Total bilirubin	35
Iron	19
TIBC	50
Transferrin	2
Fe%	38
Ferritin	228
Folate	14
B12	202
CRP (mg/L)	53
Procalcitonin	0.06
Total protein (g/L)	79
Albumin (g/L)	40
Alkaline phosphatase (Unit/L)	47
Alanine aminotransferase (Unit/L)	10
Aspartate aminotransferase (Unit/L)	30
Glucose (mmol/L)	5.6
Urea (mmol/L)	4.2
Creatinine (μmol/L)	65
Sodium	135
Potassium (mmol/L)	4.1
Chloride (mmol/L)	100
Bicarbonate (mmol/L)	21
Corrected calcium (mmol/L)	2.23

3 | DISCUSSION

Hemolytic anemia is a diverse group of hematologic disorders that can be either congenital or acquired. An extensive workup for identifying an underlying etiology of hemolysis is needed due to the wide range of causes ranging from drugs

FIGURE 1 Hemoglobin through the hospital stay

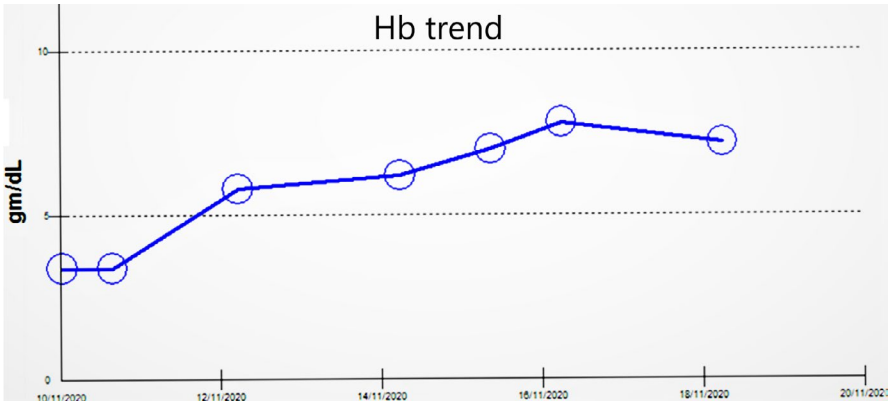

TABLE 2 A literature review for the association of AIHA with DiGeorge syndrome

Author (y)	N/Age/ gender	Cell lines involved	Nadir Hb/ Plt	Steroids IVIG plasma exchange	Cardiac defect	Neuro-psychiatric involvement	Recurrent infections	Family Hx	Spleen
Hamiel et al (1994)[7]	NA	AIHA/ITP	NA	NA	NA	NA	NA	NA	NA
Kratz et al (2003)[8]	1/1Y/F	AIHA/ITP	4.30/ 7000	Steroids	DORV	cerebral atrophy	yes	No	N/A
DePiero et al (1997) Case 1[9]	1/4Y/M	AIHA/ITP/ Leukopenia	NA	NA	NA	Learning disabilities	Yes	NA	Yes
DePiero et al (1997) Case 2[9]	1/10Y/F	ITP/AIHA	NA	NA	TOF	NA	NA	NA	NA
J K Davies et al (2003)[10]	1/1.25Y/F	AIHA/ITP/ Leukopenia	6/40/1.5	NA	Normal	No	No	NA	Yes
Bruno et al (2002)[11]	1/10Y/F	AIHA/ITP/ Leukopenia	4/25	Steroids	PAVSD	NA	No	No	Yes
Soldatou et al (2013)[12]	1/3Mo/M	AIHA/ITP/ Leukocytes	3.9/66	Steroids IVIG rituximabbmt	NA	NA	Yes	NA	NA
Sakamoto et al (2004)[13]	1/9Mo/M	AIHA	4.9	Steroids	TOF	NA	Yes	No	NA
Damlaj et al (2014)[14]	1/20Y/F	ITP/AIHA	5.5/50	Steroids IVIG rituximab romiplostim plasma exchange Splenectomy	NA	NA	NA	NA	NA

Abbreviations: Age, at the time of diagnosis of cytopenias; AIHA, autoimmune hemolytic anemia; BMT, bone marrow transplant; DORV, double outlet right ventricle; F, female; ITP, immune thrombocytopenia purpura; IVIG, intravenous immunoglobulins; M, male; MMF, mycophenolate mofetil; Mo, month; NA, not available; PAVSD, pulmonary atresia with ventricular septal defect; TOF, tetralogy of fallot; Y, year.

to autoimmune and infectious to deficiency of B12 or folate. A deficiency of vitamin B12 can lead to megaloblastic anemia. Vitamin B12 is involved in DNA synthesis and red cell maturation.[2] The deficiency of vitamin B12 can lead to hemolysis in up to 10% of the affected.[3] Several mechanisms are attributed to this deficiency. Ineffective erythropoiesis due to intramedullary destruction of red blood cells (RBC) is one of the mechanisms. Deficiency of vitamin B12 inhibits purine and thymidylate syntheses, which impairs DNA synthesis. This impairment of DNA synthesis causes

erythroblast apoptosis, resulting in anemia from ineffective erythropoiesis.[4] A deficiency of vitamin B12 can increase the precursors, including methylmalonic acid and homocysteine. The accumulation of homocysteine can increase hemolysis by oxidative damage and interaction with RBC structural and enzymatic proteins.[5] Homocysteine's hemolytic action depends on a high ratio of PMNL to RBC, which was high in our patient.[6]

A literature review of reporting of autoimmune hemolysis associated with DiGeorge syndrome (DS) using the search strategy of "([hemolysis] OR [hemolytic anemia]) AND (DiGeorge)" on PubMed yielded fifteen results. The literature consists of 8 case reports and a retrospective multicenter case-control study with 23 patients of 22q11.2 deletion syndrome (22q11.2DS) with hemolysis discussed the predictors for hematologic development autoimmunity (HA) [7-15] [Table 2].

Most of the cases describe AIHA associated with ITP or triple line cytopenia. To the best of our knowledge, three cases with AIHA as the sole autoimmune cell line involvement associated with DiGeorge syndrome are reported. This makes it the 4th reported case in the literature to the best of our knowledge. What makes this case unique is the single-cell line involvement and the late presentation. The other unique attribute of this case is vitamin B12 deficiency. The patient had a low normal vitamin B12 level, a normal thyroid function, a normal folate level, and was a nonalcohol user, with multi-lobulated neutrophils on the peripheral smear suggestive of vitamin B12 induced macrocytic anemia.

4 | CONCLUSION

Even though AIHA is associated with DiGeorge syndrome, our patient did not develop any AIHA episodes since birth. The authors believe that the combination of viral respiratory infection and vitamin B12 deficiency was the triggers associated with the late onset of hemolysis. Therefore, we suggest that regular monitoring and maintenance of serum B12 levels in patients with DiGeorge syndrome can prevent severe hemolytic episodes in this respective cohort of patients.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

ZY: involved in case identification, manuscript writing, and literature review. FA: involved in literature review and manuscript writing. PI: involved in manuscript writing, editing, and review before submission. BM and AAK: involved in manuscript writing and review. JA: served as corresponding author, and involved in manuscript writing, editing, and submission. AK: involved in manuscript review and supervision.

ETHICAL APPROVAL

The patient and her family has given verbal consent to publish this case. The study is conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

APPROVAL FROM THE INSTITUTIONAL RESEARCH BODY

The manuscript will complete the review process by the medical research council of Hamad Medical Corporation, using their online platform "www.abhath.hamad.qa". It will only be published once all relevant institutional approvals are obtained.

PATIENT CONSENT

Subject has given his verbal informed consent to publish the case.

DATA AVAILABILITY STATEMENT

Authors confirm that all relevant data or information are included in the article and are available via open access platform of this journal.

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