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

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Abstract

DiGeorge syndrome, an immunodeficiency disorder due to long arm microdeletion of chromosome 22. Isolated hemolysis is rarely seen in DiGeorge syndrome and is usually reported in conjunction with idiopathic thrombocytopenic purpura. We report a case of DiGeorge syndrome with AIHA, which was successfully managed by intravenous steroids and intravenous immunoglobulins.

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Running Title: Autoimmune hemolysis in DiGeorge syndrome

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.

Keywords: DiGeorge Syndrome, Autoimmune hemolysis, AIHA, B12 deficiency, Viral illness.

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, non-blood-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 10days. 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 exam 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 3.5gm/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. Hyper-segmented 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 100mg intravenous of methylprednisolone. A hematology opinion was sought, and the patient was planned to receive seven days of intravenous (IV) methylprednisolone, followed by a tapering course of oral steroids. Also, she received intravenous immunoglobulin (IVIG) for three days. She also received IV cyanocobalamin 1000mcg 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]

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 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, 3 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 non-alcohol user, with multi-lobulated neutrophils on the peripheral smear suggestive of vitamin B12 induced macrocytic anemia.

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 were the triggers associated with the onset of hemolysis. Combining these triggers is possibly the underlying reason for the late-onset AIHA in our patient with a history of DiGeorge syndrome. Authors suggest checking serum B12 levels regularly in patients with DiGeorge syndrome and a diet deficient in vitamin B12, which may prevent severe hemolytic episodes in this cohort of patients.

Tables and figures with legends:

Table 1: Laboratory Parameters.

Table 2: A literature review for the association of AIHA with DiGeorge Syndrome

(NA: not available, TOF: Tetralogy of Fallot, IVIG, intravenous immunoglobulins, ITP: immune thrombocytopenia purpura, AIHA: autoimmune hemolytic anemia, MMF: mycophenolate mofetil, PAVSD: Pulmonary atresia with ventricular septal defect, DORV: Double outlet right ventricle, BMT: bone marrow transplant, Y: year, Mo: month, M: male, F: female, Age: at the time of diagnosis of cytopenias)

Figure 1: Hemoglobin through the hospital stay.

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Statement of Ethics

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.

Conflict of interest/Disclosure statement

The authors certify that they have no conflict of interest and no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

Patient consent:

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