INSTRUCTIVE CASE

Autoimmune haemolytic anaemia secondary to influenza A in an allogeneic haematopoietic stem cell transplant recipient

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Case Report

A three-year old girl with a moderate grade, pulmonary stenosis and 10 months post a haematopoietic stem cell transplant (HSCT) for juvenile myelomonocytic leukaemia (JMML), which had been complicated by chronic graft versus host disease (GvHD) including bronchiolitis obliterans syndrome (BOS) (Figure 1) presented with increasing respiratory distress. Although she had been off all systemic immune suppression for two months, her immune function was known to be sub-optimal, with reduced serum immunoglobulins and ineffective T cell function. She was therefore receiving regular immunoglobulin replacement in addition to inhaled fluticasone, oral montelukast and oral azithromycin as treatment for BOS. She had also received one seasonal quadrivalent influenza vaccination (Fluarix Tetra) four weeks previously but had not been otherwise re-immunized.

The patient had developed coryza, a non-productive cough, and increased work of breathing. On examination, the child was irritable, afebrile (temperature 37.4⁰ C), heart rate 120 /min, respiratory rate 30 /min with O₂ saturations of 92% in air. She exhibited subcostal retraction and accessory chest wall muscle use. On auscultation a loud ejection systolic murmur over the pulmonary area could be heard. There was poor air entry bilaterally but no added crackles or wheeze. Initial investigations included a full blood count (haemoglobin 130g/L, white blood cell count 5.2/nL, absolute neutrophil count 1.3/nL, platelets 304/nL), CRP (1.6 mg/L), mycoplasma serology (negative) and a blood culture (negative). A subsequent naso-pharyngeal aspirate screening for common respiratory pathogens, including influenza A, was negative. A chest X-ray demonstrated increased peri-hilar bronchial markings bilaterally, with no collapse or

consolidation. An echocardiogram showed moderate pulmonary stenosis with mild pulmonary insufficiency.

The patient was admitted to hospital with a presumed viral illness. Because of intermittent fevers, increased work of breathing and decreasing oxygen saturations, a second naso-pharyngeal aspirate and blood culture were sent on day three. The viral screen was again negative, and the blood culture exhibited no bacterial growth. She remained on low flow (0.5L / min) oxygen and intravenous antibiotics (ceftriaxone, azithromycin and co-trimoxazole) to cover bacterial pneumonia, including atypical pneumonias and pneumocystis jiroveci pneumonia.

Despite these measures, there was a rapid decline in the patient's clinical status on day six of admission (increased work of breathing and increasing oxygen requirement). A repeat chest X-ray was unchanged. The child was initially transferred to the hospital's intensive care unit and subsequently to the transplant centre. In the 24 hours prior to the latter transfer, the patient's haemoglobin dropped from 87 g/L to <20g/L. The blood film showed evidence of haemolysis (increased polychromasia, spherocytes and many nucleated red cells with mild red cell agglutination (Figure 2). She had an unconjugated hyperbilirubinaemia of 15mM/L (0 – 15), a haptoglobin < 0.10 g/L (0.22 – 1.64) and an LDH of 950 U/L (310 – 620). Her Direct Antiglobulin Test (DAT) was positive for Immunoglobulin G (IgG) 10/12 and complement (C3d) 10/12. Her red cell serological investigations (forward and reverse blood grouping, DAT and antibody screens) were unable to be performed at room temperature due to interference from cold reacting autoantibodies and were performed warmed at 37^o C. She was initially transfused emergency uncross-matched O negative red blood cells (RBC) through a blood warmer.

The patient required intubation and ventilation on day nine of admission. A subsequent bronchoalveolar lavage demonstrated the presence of Influenza A. An echocardiogram also demonstrated a significant pericardial effusion, which required drainage. She was immediately started on intravenous oseltamivir (Tamiflu) in addition to re-introducing her immune suppression agents (methylprednisolone, sirolimus) and regular immunoglobulin infusions. Within a week, the patient showed significant

improvement and was extubated and moved out of intensive care. Her blood film and laboratory parameters showed evidence of persistent AIHA however, requiring regular RBC transfusions (Figure 3). On day 30 of admission she was commenced on weekly intravenous rituximab ($375\text{mg}/\text{m}^2$), an anti-CD-20 monoclonal antibody directed primarily against B lymphocytes. Following the second dose of rituximab, the patient became RBC transfusion independent. She subsequently commenced a slow wean of her T cell immune suppression lasting three months.

Discussion

JMML is a rare, aggressive haematopoietic malignancy of early childhood resulting in excessive proliferation of cells derived from the monocytic and granulocytic lineages. It is strongly associated with underlying genetic conditions affecting the RAS pathway, including neurofibromatosis type 1 and Noonan syndrome. Allogeneic HSCT remains the therapy of choice for most patients with JMML, leading to a cure in more than 50% of cases.¹ The incidence of both acute and chronic GvHD after HSCT tends to be lower than for other leukaemic diseases, likely reflecting the young age of most JMML patients. While the presence of GvHD is associated with a lower incidence of relapse, it requires ongoing immune suppression to mitigate the adverse effects / damage to vital organs, including skin, liver, gastro-intestinal tract and lungs.

BOS, a type of small airways obstructive lung disease characterized by inflammation and subsequent fibrosis of terminal bronchioles, is the most common non-infectious pulmonary complication occurring after HSCT. It is considered a component of graft versus host disease and can present months to years after transplantation.² Other

triggers include undergoing a solid organ transplant as well as exposure to inhaled toxins and respiratory pathogens. The combination of inhaled fluticasone, oral montelukast and oral azithromycin has been shown to decrease decline in lung function in BOS after HSCT.³ A wide spectrum of respiratory co-infections can cause further morbidity and mortality in these patients.

Influenza is a highly contagious illness caused by influenza viruses, most often affecting the nose, throat and lungs. Although generally an acute and self-limiting illness, it can be the cause of major morbidity and mortality, particularly in those who are immunosuppressed. In addition to respiratory disease, influenza A can cause haematological (autoimmune haemolytic anaemia (AIHA), haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura), cardiac (myocarditis, pericardial effusions and congestive heart failure) and neurological (encephalitis and Guillain-Barre syndrome) complications.⁴ Influenza vaccinations are available each year, based on identification of recent prevalent strains. The influenza vaccine is generally effective, with most people developing immunity within two to three weeks of vaccination.⁵ In this case, ongoing immune suppression and insufficient immune stimulation after just one vaccination may have contributed to the lack of protection.

AIHA is characterised by increased red blood destruction, due to autoantibodies coating a patient's red cells, causing haemolysis and if uncompensated, symptomatic anaemia. The diagnosis of AIHA may be suspected when a child presents with pallor, tachycardia and jaundice, and laboratory investigations reveal anaemia, red cell spherocytosis or agglutination on the blood film, hyperbilirubinaemia and reticulocytosis. Other supportive laboratory findings include an elevated LDH, low serum haptoglobin and increased free plasma haemoglobin. A positive DAT is the hallmark feature of AIHA and characterises the nature of the RBC antibodies as either IgG or complement (C3d).

AIHA can be divided into warm- or cold- mediated disease based on the autoantibody class (the thermal amplitude of the antibodies). Cold agglutinin disease (CAD) occurs rarely in infants and children, accounting for approximately 20% of paediatric AIHA cases.⁶ The diagnosis of CAD is made with a DAT that is positive for C3d, rather than

IgG. It usually occurs secondary to bacterial or viral infections, most commonly attributed to Epstein-Barr virus infection or *Mycoplasma pneumonia*. In our patient, infection with the influenza A virus appeared to be the precipitant of AIHA.

Initial supportive measures are key to management and include; keeping the patient warm, avoiding exposure to cold intravenous fluids and pre-warming blood products to minimize exacerbation of the haemolysis. Most CAD cases are self-limiting and resolve within a few weeks, and treatment largely focuses on treating the underlying infection. RBC transfusions may be required to support severe, symptomatic anaemia. In contrast to warm AIHA, corticosteroids are rarely effective in CAD. Steroids and intravenous immunoglobulin (IVIg) are generally limited to cases with ongoing severe haemolysis and transfusion dependence. Rituximab is a monoclonal antibody targeting the CD20 cell surface marker removes B cell lymphocytes from the circulation. Rituximab has been demonstrated to well tolerated and effective in treating AIHA. A recent retrospective study reported a 100% response rate in eight children treated with rituximab for AIHA after HSCT.⁷

Key Points

1] Bronchiolitis Obliterans Syndrome (BOS) is an obstructive lung disease which affects the small airways. It is characterized by inflammation and subsequent fibrosis of terminal bronchioles and is the most common non-infectious pulmonary complication occurring post allogeneic haematopoietic stem cell transplant (HSCT). Patients require ongoing immunosuppressive therapy and are at risk of further clinical deterioration from respiratory pathogens.

2] Children older than six months who have undergone a HSCT or solid organ transplant and are receiving the influenza vaccine for the first time after transplant are recommended to receive two doses at least four weeks apart in the first instance and one dose each year after that. Vaccination is not entirely protective however and a high index of suspicion in this at-risk group is warranted.

3] In addition to respiratory disease, influenza A can cause haematological (autoimmune haemolytic anaemia (AIHA), haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura), cardiac (myocarditis, pericardial effusions and congestive heart failure) and neurological (encephalitis and Guillan-Barre syndrome) complications

4] AIHA is an uncommon condition in children, but should be suspected when pallor and jaundice are present. Laboratory investigations reveal anaemia with reticulocytosis in association with hyperbilirubinaemia. Red cell spherocytes and / or agglutination on the blood film are characteristic of increased red blood destruction, due to autoantibodies coating a patient's red cells, causing haemolysis and if uncompensated, symptomatic anaemia. A positive Direct Antiglobulin Test is the hallmark feature of AIHA.

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Figure 1 (a) Axial and (b) coronal computerized tomography scan of patient's lungs prior to acute presentation, demonstrating bronchial wall thickening / bronchiectasis and air trapping, both features of bronchiolitis obliterans syndrome

Figure 2 A blood film taken from patient on day eight of presentation, showing red cell spherocytes, polychromasia and nucleated red blood cells, all features of a haemolytic anaemia

Figure 3 Patient's haemoglobin over time (days), also showing red blood cell (RBC) transfusions and time of therapeutic interventions

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