CASE REPORT

Achromobacter xylosoxidans Sepsis Unveiling X-linked Agammaglobulinemia Masquerading as Systemic-onset Juvenile Idiopathic Arthritis

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Received: July 28, 2018;
Initial review: January 03, 2019:
Accepted: March 16, 2019.

Background: X-linked agammaglobulinemia, a primary immunodeficiency, can present with musculoskeletal manifestations. **Case characteristics:** A 4-year-old boy, diagnosed as systemic juvenile idiopathic arthritis at the age of 3 years and treated with biological agents, presented with fever, dyspnea and chest pain. Blood culture and pericardial fluid culture revealed *Achromobacter xylosoxidans*. **Outcome**: Investigation revealed normal serum ferritin but low levels of serum immunoglobulins. Further immunological work-up revealed diagnosis of X-linked agammaglobulinemia. Child improved on antibiotic therapy; treatment with steroids and biological was discontinued. **Message:** Underlying immunodeficiency disease must be looked for in children suspected to have juvenile arthritis, more so if they develop unusual serious infection in response to immunomodulatory therapy.

Key messages: *Pericarditis, Macrophage activation syndrome, Primary immune deficiency.*

X-Linked agammaglobulinemia (XLA) or Bruton's agammaglobulinemia is characterized by a severe congenital defect in the development of B lymphocytes. This results in absence of circulating B cells, severe pan-hypogammaglobulinemia and absent lymphoid tissue such as tonsils or lymph nodes. Children with XLA tend to present with recurrent infections of the respiratory tract with extracellular pyogenic organisms like *Streptococcus pneumoniae* and *Hemophilus influenzae*, diarrhea, and skin infections. They can also have severe infections like septicemia or meningitis [1] or uncommonly musculoskeletal manifestations [2,3]. Systemic juvenile idiopathic arthritis (SJIA), an autoinflammatory disease characterized by the presence of fever, rashes, arthritis, serositis, lymphadenopathy and hepatosplenomegaly, can present similarly [4].

CASE REPORT

A 4-year-old boy, who was born by assisted conception, presented with a history of shortness of breath, chest pain and low grade fever for 6 days. He had nocturnal chest pain and was unable to lie down supine. About 2 weeks prior to this presentation, he had bilateral ear infection for which he received treatment with oral amoxicillin/ clavulanic acid and azithromycin. There was no significant medical history in the family and the child had a healthy 10-year-old female sibling.

The boy had been well until three years of age, except for occasional episodes of ear infections. He had also been immunized as per schedule, and had received live vaccines including oral polio and Measles Mumps Rubella (MMR) vaccines without any adverse events. At three years of age, he presented with fever, and arthritis involving multiple joints for more than a month duration, and was diagnosed as having SJIA at a peripheral hospital. Investigations revealed total blood count 29×10^9/L, differential blood count with neutrophils 84% and lymphocytes 9%, platelet count 693×10^9/L and CRP 82 mg/dL. It is likely that he received empirical antibiotics during this episode; although, no discharge summary was available. He had been treated with oral methotrexate 15 mg/m^2 and folic acid 5 mg once a week. After being on this treatment for a year, as there was no improvement of arthritis, he was treated with Tocilizumab (anti-interleukin 6 receptor antibody) infusions every 2 weeks. He developed bilateral ear infection at the time of third dose of the biologic agent.

When he presented to us, he had tachypnea (respiratory rate of 36/min) and tachycardia (heart rate of 120/min), but was maintaining 100% oxygen saturation

in room air. Liver was palpable 2 cm below right costal margin and the spleen was palpable 6 cm below left costal margin. He also had bilateral knee effusion. There was no lymphadenopathy. Bedside echocardiogram revealed moderate to large pericardial effusion. Baseline blood tests showed Hemoglobin 9.3 g/dL, total leukocyte count 4.5×10^9/L, platelet count 85×10^9/L, ESR 42 mm/hr and CRP 2.4 mg/dL. Considering initial diagnosis of systemic juvenile arthritis and investigations showing pericardial effusion, low white cell and platelet count, macrophage activation syndrome was suspected. He was started on high dose methylprednisolone and empirical broad spectrum antibiotics (piperacillin/tazobactum and cloxacillin).

However, laboratory investigations revealed serum ferritin 105.2 ng/mL, fasting triglycerides 105 mg/dL, serum fibrinogen 308 mg/dL (normal 250-530 mg/dL), d-dimers 190 mg/dL (normal 170-405 mg/dL); all within normal range. C3 was low (61 mg/dL) and C4 (17.9 mg/dL) slightly towards lower range of normal (17.4-52.2 mg/dL). Anti-nuclear antibody (ANA) and double stranded DNA were negative. Mantoux test was negative and gastric aspirates were negative for acid-fast bacilli. Serology for CMV, EBV, HIV and Parvovirus were negative. A bone marrow aspirate revealed normocellular reactive marrow and the bone biopsy showed hypocellular reactive marrow with trilineage hematopoesis. The clinical and laboratory parameters did not fit with SJIA, or its complication macrophage activation syndrome [5].

At this stage, pericardiocentesis was done in view of respiratory distress and increasing effusion. Pericardial fluid analysis revealed a hemorrhagic exudate with protein of 3.6 g/dL, glucose 35 mg/dL, white cell count 7300 cells/mm^3; polymorphs 75%, lymphocytes 25%, red blood cells 86000 cells/mm^3. Gram's and acid-fast staining of the fluid were negative. GeneXpert for *Mycobacterium tuberculosis* was negative. Cell cytology was negative for malignant cells and showed predominantly neutrophils and few lymphocytes.

Blood culture at admission and pericardial fluid cultures done on day 3, 8 and 11 revealed *Achromobacter xylosoxidans* sensitive to amoxicillin/clavulanic acid, cefoperazone with sulbactum, cefepime, co-trimoxazole, piperacillin/tazobactum and resistant to amikacin, ceftriaxone, cefuroxime, ciprofloxacin and gentamicin. Piperacillin/tazobactum was continued and oral co-trimoxazole was added.

As a primary immunodeficiency was considered at this stage, serum immunoglobulins were tested, and this revealed panhypogammaglobulinemia with IgG <137 (normal 504-1411 mg/dL), IgA <26 (27-195 mg/dL), IgM <17.8 (normal 24-210 mg/dL). Flowcytometry analysis showed complete absence of CD19 B lymphocytes, CD3 T lymphocytes 1479 (normal 1600-2700 cells/mm^3), CD3/CD4 Th lymphocytes 736 (normal 700-2200 cells/mm^3), CD3/CD4 Tc lymphocytes 674 (normal 490-1200 cells/mm^3), CD3/CD16 NK cells 164 (normal 130-720 cells/mm^3). Gene sequencing revealed a hemizygous mutation (p.Asn72fs) in *BTK* gene. The mother of the patient was a heterozygous carrier for this mutation.

The patient improved with intravenous immunoglobulin (IVIG) therapy and antibiotics were prescribed for six weeks. Steroids were weaned rapidly. Splenomegaly regressed and arthritis resolved with treatment. The patient continues on regular IVIG replacement therapy and is well on follow-up.

DISCUSSION

Achromobacter xylosoxidans also known as *Alcaligenes xylosoxidans* is a gram negative bacilli found in water and soil. It is an uncommon cause for infection but may cause bacteremia, pneumonia, osteomyelitis, abscess, meningitis or ear infections in immunocompetent and immunocompromised patients. It has also been isolated from the gut and ear canal. Infection with this organism can result in significant mortality in children [6]. In our child, the likely source of *Achromobacter xylosoxidans* could have been from his recent ear infection. In addition to the underlying immune-deficient state, biologic therapy might have facilitated the spread of the infection into the blood stream and pericardial fluid.

The association between immune deficiency and autoimmune inflammatory manifestations is known. Joint manifestations in primary immune deficiency may occur due to inflammation or infection [3,4]. An Indian series of 28 patients reported arthritic manifestations in 42% of patients, and this was attributed to low IgG levels in these patients [7]. Defective B-cell tolerance has been postulated to contribute to infection susceptibility in inflammatory conditions [3]. There have been previous published reports of XLA presenting with features of juvenile arthritis and of *Achromobacter xylosoxidans* infection in primary immunodeficiencies [8,9]. The disease course in this patient was complicated due to misdiagnosis, the immune-modulation therapy he was subjected to, and the unusual infection he developed as a result.

Children on therapy with biological agents are at an increased risk of infections. Published literature on this subject reveals higher incidence of pneumonia, gastroenteritis, chickenpox, and ear infections but

opportunistic infections were less likely [10]. The patient presented to us with clinical features of fever, arthritis, hepatosplenomegaly and pericardial effusion. These features fit very well with a flare of SJIA, and this led to the patient being started on intravenous pulse therapy of steroids in addition to empirical antibiotics. The low white cell count, thrombocytopenia and the low CRP in this patient inspite of severe infection may be attributed to recent therapy with biological agents. It was the isolation of *Achromobacter xylosoxidans* in the blood culture and pericardial fluid that prompted us to look for an alternative diagnosis.

In young children presenting with arthritis, particularly in those with history of recurrent ear infections or other serious infections, a primary immune deficiency should be considered. The case highlights the importance of complete evaluation of children with joint disease before making a diagnosis of juvenile idiopathic arthritis and the serious risks associated with immunosuppression in patients with immune deficiencies.

Acknowledgement: Dr Amit Rawat, Pediatric Allergy Immunology Unit, PGIMER, Chandigarh for carrying out genetic studies in the family.
Contributors: MJ, SS: contributed to diagnostic work-up of patient and supervised patient management; SG: drafted the manuscript, which was revised by MJ and SS. All authors approved the final version of manuscript.
Funding: None; *Competing interest*: None stated.

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