Pediatric Oncall Journal

DOI: https://doi.org/10.7199/ped.oncall.2026.67

CASE REPORTS

T-CELL LYMPHOMA COMPLICATING BRUCELLOSIS: A UNIQUE CLINICAL SCENARIO

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ABSTRACT

Brucellosis is an important but neglected cause of febrile illness in children in areas with high exposure to animals or unpasteurized milk and dairy products. Pyrexia of unknown origin has multiple causes and underlying conditions in paediatric population including multiple infectious, autoimmune, and malignant conditions. Although closely mimicking but some of these conditions can co-exist in a single patient as in our case and a second diagnosis should always be kept in mind in initially improved but then deteriorating patients. Our patient was an eight years old male child who presented with a systemic illness involving lymphadenopathy, hepatospleenomegaly and signs of CNS involvement. He came out to be positive for B.Melitensis and APLA antibodies. He was treated with combination therapy of rifampicin, doxycycline and oral steroids. Even though his initial workup was negative for any malignancy and he responded to the initial treatment but the recurrence of symptoms and deterioration in his general condition led us to repeat some of his investigation which later on came out to be positive for non-Hodgkin's T cell Lymphoma (peripheral T cell Lymphoma).

ARTICLE HISTORY

Received : 14 June 2024

Accepted : 01 August 2024

KEYWORDS

Brucellosis, brucella, T-cell Lymphoma

Introduction

The genus Brucella is responsible for human brucellosis, which continues to be a global public health concern. As unintentional hosts, humans get this disease from consuming animal products or coming in close contact with diseased animals like cattle, goats, pigs, camels and sheep. Consuming unpasteurised dairy products or cheese from sick sheep or goats is the primary cause of most infections. The four main Brucella species that may infect humans and cause disease are B. abortus, B. melitensis, B. canis, and B. suis.[1] Brucella The most common species that causes brucellosis in humans is Melitensis. Brucella is considered endemic in South Asian countries in livestock animals[1] but number of cases of distinguish brucellosis in Pakistan is very limited which could be due to lack of awareness, failure to obtain thorough history and detailed examination.

Risk of anti thrombotic syndrome has been associated with an autoimmune disorder called antiphospholipid syndrome (APS). The paediatric APS refers to diagnosis of APLA in population less than 18 years old. Sapporo classification is used for diagnosis of APLA in adults but due to limited number of cases in paediatric population no proper scale or criteria has been allotted to paediatric population.[2]

The rare and severe form of non-Hodgkin lymphoma (NHL) types is peripheral T-cell lymphomas (PTCLs) which form in adult white blood cells known as "T cells" and "natural killer (NK) cells.'' The WHO classification of Lymphoma has been widely used for classifying the Peripheral T cell lymphoma, which has divided the broader term into multiple categories. [3] PTCLs are among the rare disorder which are associated with poorer prognosis as compared to their B cell origin counterparts and show poor response to conventional therapies along with frequent relapses. The prevalence rate of PTCL is low in children and its heterogeneity pose significant obstacles to properly identify and manage PTCL. Their response to treatment, remissions and relapses are understudied phenomena in paediatric population which has led to difficulty in the management. Regardless of the recent advancements, the treatment for PTCL still comprise of vincristine ,doxorubicin, cyclophosphamide and prednisone (CHOP) or CHOP-like combination chemotherapy[4], whereas studies related to High dose combination chemotherapy and stem cell transplant has shown promising results.[5,6,7]

Case Report

An 8-year-old male boy weighing 20 kg, resident of urban area, presented through emergency department with complains of fever for 3 months, lower limb pain for 1 month and inability to walk for 15 days. The fever was reported as high grade in intensity (axillary temperature 102°F), not associated with rigors and chills, intermittent more at night. Patient developed complain of lower limb pain starting from his ankle joints and progressed to his thighs, pain's intensity increased with progression of time and patient became unable to walk 15 days back. He was prescribed oral antibiotics, paracetamol, and multivitamins by local GP but to no avail.

Medical examination at the time of presentation

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showed fever of 102°F with heart rate of 115 beats/min, sub vitally patient was found to be moderately anaemic with grade 2 clubbing and posterior cervical lymphadenopathy was also observed. His abdominal examination revealed hepatosplenomegaly and his CNS examination showed increased tone in lower limbs with power of 3/5, his plantar reflex was mute bilaterally. No joint swelling, erythema, skin rash ulcers were noticed during examination. Rest of the systemic examination was found to be unremarkable.

Laboratory results showed normocytic normochromic anaemia with Hb levels of 8 g/dl, leukopenia ($4*10^9$/L) with predominant neutropenia 15% and lymphocytes 80% and thrombocytopenia (98,000). His biochemistry (UCEs and LFTs) was normal. Blood and urine culture showed no growth and workup for tuberculosis, Malaria parasite and ICT malaria also came out to be negative. Patient was admitted for further workup and fever documentation and he was started on 3rd generation cephalosporins and paracetamol.Bone marrow biopsy was done with impression of myeloproliferative disorder which showed reactive lymphocytosis. His workup for HLH was negative and lymph node biopsy showed reactive hyperplasia. CT scan chest and abdomen revealed involvement of multiple levels of lymph nodes and hepatosplenomegaly.

Patients MRI brain showed cortical thickening with abnormal signal intensity involving bilateral mesial temporal lobes along with cingulate and hippocampal gyri.

MRI spine was normal. On the basis of his MRI findings autoimmune workup was sent including ANA, Anti DsDNA, ENA profile, Anti CCP and poly specific coombs test came out to be negative. As patient's initial autoimmune and malignancy associated workup was negative and he was not responding to conventional treatment his serology for brucellosis was sent which showed 2 folds increase in antibodies against Brucella Melitensis. He was started on combination therapy of rifampicin 15 mg/kg/day and doxycycline 4 mg/kg/day. As patient's condition improved so he was discharged.

On follow up visit after 1 week patient was found to have high grade fever, livedo reticularis and ulcer on his left foot. Patient was readmitted, baseline investigations were repeated which showed normocytic normochromic anaemia and thrombocytopenia, ultrasound doppler of both legs was done which was normal, his d-Dimer levels were 1.4 mg/L. APLA profile showed positive anticadiolipin IgM and IgG (10.6 and 10.98 respectively). His Lupus Anticoagulant was also positive. Patient was started on oral steroids which showed visible improvement in patient's condition and patient was discharged on 3rd day of starting steroids.

On follow up visit after 3 weeks patient was found to have high grade fever, livedo reticularis ulcer on his left foot with decreased appetite and appeared to be mildly jaundiced. Patient was readmitted, baseline investigations were repeated which showed normocytic normochromic anaemia, severe neutropenia with ANC of 300 and thrombocytopenia, LFTs showed 2 folds increase in SGPT. Ultrasound Abdomen showed increase in the size of liver and spleen. Ultrasound doppler of both legs was done which was normal, his d-Dimer levels were slightly raised 1.4 mg/L. APLA profile showed positive anticardiolipin IgM and IgG (10.6 and 10.98 respectively). His Lupus Anticoagulant was also positive. As patient was deteriorating and his blood workup showed persistent pancytopenia despite treatment and intervention, so his bone marrow trephine biopsy was repeated which this time around showed an extensive interstitial infiltration with small mature T lymphocytes. The abnormal lymphoid cells were positive for CD 3, CD 8, and CD 45 on flow cytometry. Patient was diagnosed as a case of Peripheral T Cell Lymphoma NOS variety. Patient was than referred to oncology department for further treatment and management.

Discussion

There are many causes of pyrexia of unknown origin in paediatric population which include common and rare disorders. Brucellosis is a zoonotic disease, fairly common in areas with exposure of animals and unpasteurized milk, but its diagnosis can easily be missed out in patient with no history of direst exposure to animals. Childhood Brucellosis accounts for 20-30% cases worldwide[1] and could present as multisystem involvement which makes it difficult to differentiate from multiple other illnesses common in this age group. Symptoms can be cute or insidious in nature and usually non-specific. Fever is the most common symptom.[8] Physical examination may reveal hepatospleenomegaly, arthritis or arthralgia, lymphadenopathy and weight loss. Multisystem involvement including musculoskeletal, gastrointestinal, respiratory and Central nervous system has also been reported in literature.[1] Neurobrucellosis has been reported in adolescent and adult population in literature over the course of past few years, but data related to children is very limited and less studied. The diagnosis of brucellosis is generally based on positive serology, blood cultures, bone marrow cultures and antibody titers.[1] There are 2 effective treatment regimens for different age groups. For children over 8 years old, oral doxycycline (4 mg/kg/day) and rifampicin (20 mg/kg/day) are typically prescribed, and for children under 8 years old, oral trimethoprim TMP (6-8 mg/kg/day), sulphamethoxazole SMX (30-40 mg/kg/day), and rifampicin (20 mg/kg/day) are typically prescribed. Both are prescribed for 6-8 weeks.[1] Complications and relapses are usually treated with 3 drug regime adding an aminoglycoside in the treatment.

Brucella has been linked to autoimmune haemolytic anaemia, neutropenia and thrombocytopenia in literature as found in our case. Pargini V. et al reported a case of a boy presenting as SLE but ultimately was diagnosed as Brucellosis[9], another case associated it with haemolytic anaemia[10] but it has never been associated with APLA in past which makes our case a unique presentation.

APLA itself is a less understood and studied entity in paediatric population due to lesser number of cases, vague presentation, its association with pregnancy related complications and lack of any formal criteria for its diagnosis in paediatric population. The updated Sapporo criteria has been used for diagnosis of APS.[11] Clinically, the occurrences that meet the criteria include specific forms of pregnancy morbidity and confirmed vascular thrombosis in arteries, veins, or small

vessels. A positive lupus anticoagulant (a functional test that screens for APLA), anticardiolipin IgG or IgM in medium or high titer, or anti-beta-2 glycoprotein I (β2GPI) IgG or IgM in high titer might satisfy the laboratory requirements. However, since the modified Sapporo criteria is designed for adult population and go beyond thrombosis and the parameters, they are not very useful for the paediatric population. While some children with APS may have positive antibody tests but no clinical symptoms, other children with the condition may exhibit other "non-criteria" indications such as haematologic and neurologic problems.[11] Peripheral T cell lymphomas (PTCL) have a poorer prognosis after conventional treatment than do high-grade B cell lymphomas, so the treatment of PTCL remains clinically difficult. The response rate to first-line treatment for PTCL is low, and the current 5-year overall survival is only 10–30%.[12] Their response to treatment, remissions and relapses are understudied phenomena in paediatric population which has led to difficulty in the management. To date, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like combination chemotherapy still represents the standard approach to the treatment of most PTCLs[4], whereas studies related to High dose combination chemotherapy and stem cell transplant has shown promising results.[5,6,7]

Combination chemotherapy with anthracycline-based regimens both in the United States and in the UK have been established as the standard therapy for these neoplasms. One study conducted in Japan has shown the 5-year overall survival rate after stem cell transplantation to be 62.96%. Although the 5-year event-free survival was 55.56%.[7]

Multiple studies conducted on adult population has shown Positive APLA antibodies result in patients with Non Hodgkin's Lymphoma and its association with adverse outcomes[13,14] but no such studies has been done for paediatric population.

Compliance with Ethical Standards

Funding None

Conflict of Interest None

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