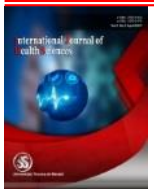

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Brucellosis Revealed Via Persistent Urinary Tract Infection

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Abstract

Urinary tract infection is common in children. Bacterial infections are the most common cause of it. Pyuria is sensitive but nonspecific in making a diagnosis; urine culture is the criterion standard. Persistent urinary tract infection associated with fever is a very concerning finding in pediatric patients. Here is reported the case of an adolescent, in whom the persistence of fever with pyuria aroused suspicion towards Brucellosis. Brucellosis in children is associated with non-specific symptoms. It is a systemic disease that may be presented with focal symptoms of any organ system, including the urinary tract.

Keywords

adolescent;
brucellosis;
non-specific;
persistent;
urinary tract infection;

Contents

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1 Introduction

A urinary tract infection is defined as the inflammation of any part of the urinary tract (bladder, urethra, or kidney), caused by the presence of pathogens in it. In normal conditions, the urinary tract is sterile. Despite the fact that urine is a good culture medium, it possesses antibacterial features that suppress bacterial growth. The acid nature of the urine (a low pH 5.5), a high concentration of urea, and the presence of organic acids, which derive from fruits and proteins in the diet, are unfavorable factors to bacterial growth. The main way by which pathogens invade the urinary tract is from the colonized perineal area, ascending the urethra to the bladder or kidney. Turbulent flow during normal voiding, dysfunctions in voiding, or catheterization serve as assistance for pathogens to enter the urinary tract (Hooton, 2012). In infants, the urinary tract may be colonized during systemic bacteremia. Even after complete voiding, a small quantity of urine remains in the bladder; in case bacteria are present, they are removed by the mucosal production of organic acids. When the pathogens surpass the defense mechanisms of the lower urinary tract, they invade the kidney, causing pyelonephritis. Host defenses in the upper urinary tract include local leukocyte phagocytosis and renal production of antibodies that kill bacteria by complement mediation (Flores-Mireles et al.,2015).

Bacterial infections are the most common cause of urinary tract infection, with *E coli* being the most frequent pathogen, causing 75-90% of urinary tract infections. Other bacterial sources of UTI include: *Klebsiella* species, *Proteus* species, *Enterococcus* species, *Staphylococcus saprophyticus*, especially among female adolescents and sexually active females, *Streptococcus* group B, especially among neonates, and *Pseudomonas aeruginosa*. Fungi (*Candida species*) may also cause urinary tract infections, especially after instrumentation of the urinary tract. Viruses are a rare cause of urinary tract infection; adenovirus may cause hemorrhagic cystitis (Foxman, 2014). Prevalence of first-time, symptomatic urinary tract infections is highest in boys and girls during the first year of life and markedly decreases in the following years. The incidence of urinary tract infection in children aged 1-2 years is 8.1% in girls and 1.9% in boys (Marild, 1998).

The clinical presentation of urinary tract infection in children depends on the age of the child. In the first 2 months of age, urinary tract infection manifests with jaundice, fever, failure to thrive, poor feeding, vomiting, and irritability. In infants and toddlers, urinary tract infection presents with poor feeding, fever, vomiting, strong-smelling urine, abdominal pain, and irritability. In older children and adolescents, urinary symptoms (dysuria, urgency, frequency, strong-smelling urine, enuresis, incontinence) dominate and are associated with fever, vomiting, abdominal pain, and flank/back pain (Zorc et al., 2005; Shaikh, 2007). Urinary tract infection is associated with bacteriuria (presence of bacteria in urine) and pyuria (presence of white blood cells in urine). Pyuria is a sensitive (80-95%) but nonspecific (50-76%) sign of urinary tract infection. Urine culture is the standard criterion for the diagnosis of urinary tract infection (Finnell et al., 2011).

Persistent urinary tract infection is a stressful and very concerning situation for children, families, and physicians, too. This case report highlights how a persistent urinary tract infection revealed Brucella infection in an adolescent (Chu & Lowder, 2018).

2 Case Report

An adolescent was admitted to the Hospital with a history of 10 days of continuous fever, fatigue, and abdominal pain. Previously was treated with oral antibiotics by a local clinic for urinary tract infection, but fever, fatigue, and abdominal pain persisted. The patient lived in a rural area with the family, the parents, and two older siblings. All the family members were healthy, and the patient had been healthy till then and was fully vaccinated. The family did not keep domestic animals at home and consumed safe foods.

On physical examination, the patient did not appear ill, was active and vivid despite a persistent fever at a moderate degree 38,5°C. The patient complained about fatigue and discomfort when having a fever. Abdominal pain was of concern but was not associated with increased frequency in voiding or a sense of burning.

No weight loss was reported. Sclera and mucous membranes were normal; no pharyngeal injection or cervical lymphadenopathy was observed. Respiratory and cardio-vascular systems displayed no abnormalities, no tachycardia, nor tachypnea were present. The abdomen was soft, not distended, bowel

sounds were present, the liver was not palpable, whereas the spleen was slightly palpable under the left costal margin. No edema on the extremities or rash on the skin was found.

Laboratory investigations on admission revealed normal blood count with low levels of hemoglobin and hematocrit, normal function of the kidney and liver, normal C-reactive protein, and increased leukocyte count on urine smear (Table 1)

Table 1
Laboratory results on admission

WBC	10,800 cells/mm^3 (4,000 -10,000 cells/mm^3)
Neutrophils	83,8% (13 - 40%)
Lymphocytes	9,3% (46 - 76%)
RBC	4,160,000 cells/mm^3 (3,800,000 - 5,000,000 cells/mm^3)
Hemoglobin	8.2 g/dl (9,7 - 12g/dl)
Hematocrit	23.4% (32 - 42%)
Platelet	292,000 cells/mm^3 (150,000 - 400,000 cells/mm^3)
Erythrocyte sedimentation rate	15 mm/h (<15 mm/h)
Aspartate aminotransferase (AST)	21 U/L (0 - 35 U/L)
Alanine aminotransferase (ALT)	20 U/L (0 - 45 U/L)
Blood Urea Nitrogen (BUN)	23.5 mg/dL (10 - 43 mg/dL)
Creatinine	0.52 mg/dL (0.6 - 1.4 mg/dL)
Serum Total Protein	6.8 g/dL (6 - 8 g/dL)
Albumin	4.5 mg/dL (3.2 - 4.5 mg/dL)
C reactive protein	0.15 mg/dL (<0.5 mg/dL)
Urine count	45 WBC/mL (< 10 WBC/mL)

Thorax X-ray revealed no abnormalities in the respiratory tract. Abdominal ultrasonography revealed a slightly increased spleen (134 mm in diameter) without any abnormality of the genitourinary tract. Blood and urine cultures were taken on admission, too.

Based on medical history, physical examination, and laboratory results on admission, therapy for urinary tract infection was initiated, with intravenous cephalosporin and aminoglycoside. After 48 hours of treatment, the fever continued, and the urine culture resulted in no bacterial growth.

The existence of pyuria without bacteriuria indicated that the urinary tract inflammation was not caused by a common urinary pathogen. Facing these facts, suspicion was raised of Brucella infection. Urinary tract inflammation, anemia, and continuous fever despite antibiotic treatment were clues that directed suspicions towards Brucellosis. Serologic tests using enzyme-linked immunosorbent assay (ELISA) resulted in increased levels of IgM antibodies for Brucella, IgM 11.8 IU/mL (> 11 Positive).

Ciprofloxacin intravenous was initiated, and the fever abated after 24 hours.

The patient was discharged on day 5 of treatment.

Doxycycline and Rifampin were prescribed for 6 weeks, accompanied by an iron supplement.

Upon reevaluation, after the treatment completion, the patient had completely recovered. Anemia was corrected. The patient was energetic. Blood count and urine analysis resulted in normal. The spleen was no longer palpable and resulted within normal range in abdominal ultrasonography.

3 Results and Discussions

Discussion

Urinary tract infection is one of the most common infections in children. Only in the first year of life are boys more affected by urinary tract infection; after this age, girls suffer more from urinary tract infection than boys. It is estimated that 8% of girls have a symptomatic urinary tract infection during childhood. The reason for the

greater prevalence of urinary tract infection in girls is the shorter length of the female urethra, which allows urinary pathogens easier access to the bladder (Prentiss et al., 2011). Urinary tract infection, especially when it is persistent and accompanied by continuous fever, is a source of distress for the child and the parents, and may inflict permanent kidney damage. Children with pyelonephritis may develop focal inflammation of the kidney or renal abscess. However, any inflammation of the renal parenchyma may lead to scar formation, and circa 10-30% of children with urinary tract infection develop some renal scarring. In such conditions, accurate diagnosis and effective treatment of a febrile urinary tract infection, despite preventing discomfort, prevents kidney damage (Schroeder et al., 2015).

In the presenting case, continuous fever and the presence of white blood cells in urine were indicators of an inflammatory process of the urinary tract. So, at first sight, the diagnosis of urinary tract infections seemed the most probable. However, the result of the culture of urine, which showed no bacterial growth, opposed the diagnosis of urinary tract infection. Persistence of fever after antibiotic use and the absence of other inflammatory markers (normal white blood cells, normal C-reactive protein) were not in favor of urinary tract infection caused by a bacterial urinary pathogen. All these findings, including the presence of spleen enlargement and anemia, raised suspicion of Brucella infection.

Brucella species infection in children presents with nonspecific symptoms, with fever being the most consistent symptom, making so Fever of unknown origin the most common presenting diagnosis in the pediatric population. However, even in children, as in adults, Brucellosis may present with focal symptoms of the system or organ where the pathogen is settled. After entering the child organism through infected food products, mainly unpasteurized dairy, or direct contact with infected animals, they diminish the function of the mucosal epithelial barriers (Qureshi et al., 2023). Brucella species trigger only a minor innate immune response and show modest pro-inflammatory activity; this is the reason the laboratory examination did not show elevated inflammatory markers (normal C-reactive protein and normal neutrophil count). Soon after entering the bloodstream, they invade circulating polymorphonuclear cells (PMNs) and macrophages. Brucella reduces or hides its pathogen-associated molecular pattern to evade the immune system, they live in vacuoles inside mononuclear phagocytic cells (Martirosyan et al. 2013; Lecaroz et al. 2006; Ghssein et al. 2025). Approximately 10-30% of ingested Brucella survive and multiply inside macrophages indefinitely, through the ability to manipulate hot cell processes, hinder phagocytosis, and prevent host cell apoptosis. Brucella that survive are transported into the lymphatic system and may replicate there locally, or in the kidney, liver, spleen, breast tissue, or joints, causing both localized and systemic infection (Oliveira et al. 2008; Köhler et al. 2002; Barquero-Calvo et al. 2007).

Brucella strains require iron, manganese and magnesium for optimal growth. Heme is an iron source for Brucella, and macrophages provide an environment of relevant heme and Fe supply (Danese et al. 2004; Paulley et al. 2007; Bellaire et al. 2003). In adolescents during puberty growth spurt, a great supply of iron is required, and combined with Brucella infections, which use host heme-iron for their growth, the probability of developing iron-deficient anemia is increased. This scenario, represented in this case report, the patient developed iron deficiency anemia during the acute infection from Brucella. Enlargement of the spleen was result of cell recruitment, mainly neutrophils, monocytes, and B cells, mediated by pro-inflammatory cytokines (Roset et al., 2014).

Although Brucellosis is the most common zoonotic infection, it is a neglected zoonotic disease. Albania due to its geographic location in the Mediterranean basin, is considered an endemic county for brucellosis. However, in the last two decades with the implementation of veterinary programs of mas vaccination of herds, human Brucellosis significantly declined, with only sporadic cases recorded in children (Nielsen, 2002). In clinical practice, children with Brucellosis are rarely seen, so the index of vigilance is low. Brucellosis is an easily curable disease when it is treated appropriately and within few months of onset. Cases in which diagnosis and treatment are delayed are associated with a high risk of complications, relapses or chronic disease. Internationally, the incidence of Brucellosis is increased, are estimated between 1.6 to 2.1 million new cases annually (Laine et al., 2023). Nowadays Brucellosis is present not only in endemic countries, but in non-endemic countries too, due to increased phenomena of international tourism and migration. It is a systemic disease, and it may present with non-specific symptoms and signs, or with focal symptoms of a wide range, as it invades every organ system. Urinary tract is involved too and may present as a persistent urinary tract infection. A major index of suspicion should be maintained while valuating a child with fever and persistent

focal symptoms. It should be highlighted that the mayor risk for the development of focal complications is the duration greater than 30 days before diagnosis.

4 Conclusion

Urinary tract infection is one of the most common infections in children, with females being more affected. Persistent fever associated with sterile pyuria, arouse many concerns about the cause of urinary tract inflammation. Brucellosis although a neglected disease is a significant global burden. As it presents with non-specific symptoms and signs in children, a great index of suspicion should be maintained while valuating a child with persistent fever and focal signs such as urinary tract inflammation, but it may involve every organ system as well.

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Informed Consent was taken by the parents of the child, providing anonymity.

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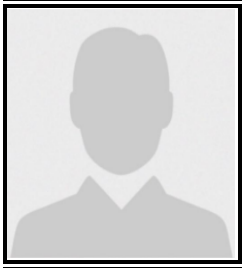

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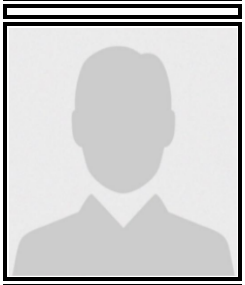

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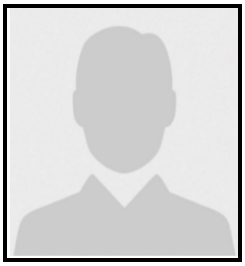

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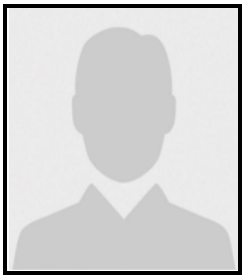

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