

A 13-Year Girl with Reversible Acute Kidney Failure and Weakly Positive Wright and 2me Tests

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Introduction

Renal involvement in brucellosis in the form of acute kidney injury is rare, but interstitial nephritis, pyelonephritis, exudative glomerulonephritis, mixed cryoglobulinemia, and IgA nephropathy have been reported.

Case Presentation: A teenager girl with acute kidney failure, oliguria, gross hematuria, hypertension, arthralgia and urinary abnormal sediment (proteinuria and hematuria) was admitted in pediatric nephrology department. Clinical manifestations mimicking rapidly progressive glomerulonephritis. She needed temporary hemodialysis because of symptomatic uremia. Despite clinical presentations, kidney biopsy findings were near normal with no crescent formation, no evidence of interstitial inflammation or glomerular involvement. Results of wright agglutination (a positive titer of 1/80) and 2 ME tests (positive titer at 1/40) in association with clinical presentation and prodromal symptoms (fever, vomiting and arthralgia) suggested acute brucella infection that should be confirmed by repeating the titer in follow up.

Conclusion: Acute brucella infection should be considered in cases with acute kidney injury when symptoms such as arthralgia or arthritis are present especially in areas where brucellosis is endemic.

Keywords: Brucellosis; Renal Involvement; Acute Kidney Injury

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Introduction

Acute Kidney Injury (AKI) defined as a sudden decrease in renal function over a variable period of time (hours to days). The Acute Dialysis Quality Initiative (ADQI) established in 2004 the RIFLE criteria, definition and staging system used for AKI [1]. In a study by Prakash et al. [2]. 1122 cases with AKI with different etiologies were studied over a period of 16 years. Intrinsic renal diseases were responsible for AKI in about 80% of cases. The most common intrinsic renal diseases causing AKI were ischemic/toxic acute tubular necrosis (79.4%), acute glomerulonephritis (9.3%), acute interstitial nephritis (7%), and renal cortical necrosis (4.6%). Brucellosis is a multisystem disease that rarely involves the kidney. The most common urogenital presentation of brucellosis is epididymo-orchitis. Renal involvement in the form of AKI is rare, but interstitial nephritis (the most common forms), pyelonephritis, exudative glomerulonephritis, mixed cryoglobulinemia, and IgA nephropathy have been reported [3].

We describe a patients presented by AKI and clinical picture resembling Rapidly Progressive Glomerulo Nephritis (RPGN), joints involvement and slightly positive standard agglutination (wright) and 2 Merkaptoethanol (2-ME) tests. We ruled out conditions that can mimic similar clinical presentations by specific serologic tests and kidney biopsy .The kidney biopsy was near normal and renal function returned to normal by administrating pulse of steroid and antibiotic.

Case Presentation

A 13-year girl was admitted in pediatric nephrology section of an academic health center by fever, vomiting, abdominal pain, restlessness and seizure .Also she complained of decreased urine output, dysuria and arthralgia with involvement of both knees from two days ago. There was no history of diarrhea, symptoms of upper respiratory tract infection and pharyngitis in

past few days. At presentation there was oliguria (urine output < 500cc/1.73m² / day) and mild hypertension (Blood pressure = 140/90) with no edema and normal neurologic examination. During first days of admission oliguria changed to anuria. Kidney-bladder ultrasonography revealed normal kidneys sizes with mild increased parenchymal echogenicity. Preliminary laboratory tests were requested to define the renal function, detected evidence of glomerular involvement and determine the etiology of joint involvement. Table I presents the details of laboratory findings at presentation. And during admission. Blood culture was negative and wright agglutination and 2 ME tests showed weakly positive reactions (positive at a titer of 1/80 and 1/40 respectively).Bone marrow analysis and culture were not done.

Table I: laboratory details of patient at admission and before discharge

Laboratory findings	At time of admission	At discharge(day 23)
Serum urea (mg/dl)	226	88
Serum creatinine (mg/dl)	9.4	1
Blood sugar (mg/dl)	201	75
Hb1/HCT2/Reticulocyte count	7.8 3/24.6/6.6	9.2/29.4/2.2
Platelet count(× 109/L)	279	206
Serum Calcium (mg/dl)	8.6	8.6
Serum Phosphorous (mg/dl)	6.6	4.4
Serum sodium (meq/L)	137	138
Serum potassium (meq/L)	6	3.8
Lactate dehydrogenase(U/L)	2694	715(at day 16)
Serum albumin(mg/dl)	3.9	-----
ESR 4 (mm/h)	111	56(at day 19)
Wright agglutination titer	1/80 positive	-----
2ME test 5	1/40 positive	-----
ASO titer ,widal test	100,negative	-----
Anti-nuclear antibodies (ANA) test	Negative	-----
Serum C3/C4	198(within normal range)/32(within normal range)	-----

HBS Ag, HCV antibody and Anti HIV antibodies	All negative	-----
Indirect Combs' test	Negative	
Urine analysis and	Color =brown ; SG=1005 ; protein =+ ; Sugar=+ blood = +++; WBC=10-15 HPF; RBC= HPF ;epithelial cell= 10-15HPF; U/C=negative (at day 3 of admission)	Color =yellow; SG=100 3; protein =++ ; Sugar=negative blood = ++; WBC=20-25HPF; RBC=18-20 HPF; epithelial cell=12-15 HPF
Urine culture	Negative	

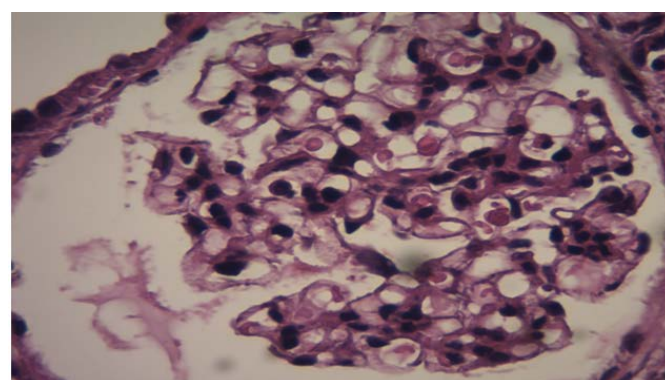
1) Hemoglobin; 2) Hematocrit; 3) Patient received packed cell; 4) Erythrocyte sedimentation rate; 5) Two-mercaptoethanol test

Clinical presentations (hypertension and anuria) and laboratory findings(proteinuria ,gross hematuria and severe increase in serum urea and creatinine levels) were suggestive of Rapidly Progressive Glomerulo Nephritis (RPGN), so high dose of methylprednisolone pulse (1gr/m2) was administrated for 6 consecutive days that then changed to high dose oral steroid(oral prednisolone 2mg/kg /day), and ceftriaxone 2 gr daily for 10 days .At the same time she underwent hemodialysis in alternate days for 9 sessions because of severe symptomatic uremia and anuria . About 2 weeks after admission, when symptoms of uremia were controlled, needle kidney biopsy was performed under local anesthesia. Figure 1(A, B) shows findings in light microscopy examination. Immuno Fluorescence (IF) examination of biopsy specimen revealed C3 positivity in arteriolar walls (1+), and focal depositions of IgM in glomerular mesangium which indicated negative immune reaction in IF study.

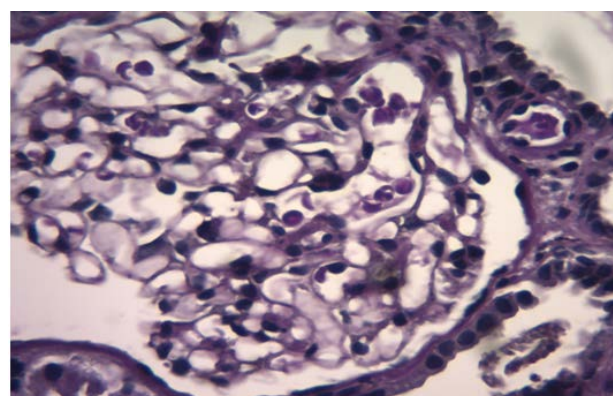
Few days later renal function tests dramatically improved and abruptly urine output returned to normal levels and serum urea and creatinine levels decreased and at day 23 of admission the levels were 88mg/dl and 1 mg/dl respectively. At this time blood pressure reached normal levels by low dose furosemide (1-2mg/kg) and nifedipine .Patients was discharged in day 23 of admission .She was recommended to decrease oral steroid abruptly and discontinued during a 2-3 weeks period and

comeback for follow-up after one week. Unfortunately she didn't refer for follow up.

Figure 1: Mild mesangial hyper cellularity and delicate glomerular basement membranes:



A) Hematoxylin&eosin X 400



B) Periodic acid –Schiff X 400

Discussion

Our case presents a teenager girl with AKI (stage of acute kidney failure based on RIFLE criteria) and symptoms and signs (oliguria, gross hematuria and hypertension) and urinary abnormal sediments (proteinuria and hematuria) mimicking RPGN who needed to temporary hemodialysis because of symptomatic uremia. Despite clinical presentations resembling RPGN, kidney biopsy findings were near normal with no crescent formation, no evidence of interstitial inflammation or glomerular involvement. Results of wright agglutination (a positive titer of 1/80) and 2 ME tests (positive titer at 1/40) in association with clinical presentations and prodromal symptoms (fever, vomiting and arthralgia) strongly suggested acute brucella infection. For confirmation of diagnosis repeated the tests after a 2 -week period was helpful, but it was missed. We considered to check the tests at first follow-up after hospital discharge, but unfortunately she didn't comeback for follow-up.

Brucellosis is primarily an infectious disease of domestic animals that is transmissible to humans. It remains an important health problem in developing countries, particularly in the Mediterranean region, Middle East and West Asian countries [4]. Clinical features of acute illness are fever, chills, headache, muscle and joint pain, malaise, nausea, night sweat and loss of appetite persisting 3 to 6 weeks [5]. Hepatomegaly, splenomegaly, and arthritis may be found in some cases [6]. However the exact diagnosis is made by isolation of the brucella species in various samples (mainly blood and bone marrow), the diagnosis can be established by a positivity of wright test in a titer of $\geq 1/160$ or rising antibody titers in association with appropriate clinical setting [5, 6].

Sensitivity of cultures for diagnosis of brucellosis is 30-90 % which correlate with the stages of the disease [7]. Antibodies begin to form 2 weeks after the beginning of disease, IgM antibodies appear after one week and reach a peak in 3 months, whereas Ig G antibodies appear in 3 weeks and reach a peak in 6-8 weeks. Negative results in agglutination tests is a common problem which may be due to presence of blocking antibodies. Blocking antibodies are detectable by Coombs test

[8]. The Sensitivity of standard wright agglutination and 2-ME tests in diagnosis of brucellosis are 92.6% and 57.4% respectively [9]. In our subject blood culture was negative for brucella, but we didn't check the bone marrow culture for growth of the brucella species. A problem related agglutination tests used for diagnosis of brucellosis is that false positive results may reported in diseases mimicking brucella infection.

Mert et al. [6] assessed the results of brucella agglutination tests in 280 patients with diseases mimicking brucellosis including military tuberculosis, malaria, typhoid fever, steel disease, rheumatoid arthritis and systemic lupus erythematosus, and compared them with results of tests in 30 patients with hemoculture-positive brucellosis. Rose-Bengal and Wright tests in a titer of 1/160 or higher were positive in all of the patients with brucellosis. Although the test was slightly (1/40) to weakly (1/20) positive in 3 cases with malaria, non-Hodgkin's lymphoma, and typhoid fever. It showed negative results in the remaining.

Although the clinical presentations including fever, joint and kidney involvements were strongly suggestive of brucella infection, based on the laboratory findings the diagnosis was not consistent with Brucella infection since neither there was a positive culture for brucella nor positive wright or 2 ME tests. We had two main limitations for definite diagnosis. First bone marrow culture which is a sensitive test for detection of brucella infection was not obtained, second we missed repeating the serologic tests because of no follow up after discharge. A positive point about our case is that we ruled out conditions that can mimic similar clinical presentations by specific serologic tests and kidney biopsy. In final evaluation brucella infection was the main diagnosis that needed to be confirmed.

However in our case the indirect Combs' test was negative, wright agglutination and 2Me tests were slightly-weakly positive respectively. We didn't find any clinical or laboratory findings that suggested other diseases which may mimic brucella infection and result to weakly positive wright and 2Me tests (malaria, non-Hodgkin's lymphoma, and typhoid fever).

Gad El-Rab et al. [10] evaluated the sensitivity of Enzyme Linked Immuno Sorbant Assay (ELISA) test for anti-brucella antibodies (IgG and IgM). Their cases consisted of 30 patients of culture positive brucellosis; with negative standard agglutination tests in 10% of cases. Negative results for agglutination tests have been reported more commonly in infections with brucella canis [11]. It has been observed that the 2ME test is a better indicator of recent infection than the standard tube tests and a positive 2ME test (a titer $\geq$ /160) indicates an active infection and the need for antibiotic therapy [12]. Another disadvantage of agglutination tests is that they remain positive for months after infection, even when patients receive adequate antibiotic treatment. The standard tube test remains positive for 1.5 years in 48% of cases, whereas 2ME titers remain positive in 9% and 4% of case after 1 and 1.5 years respectively [12].

Reversible AKI and recurrent rhabdomyolysis have been reported in acute brucella infection [13-15]. Faris et al. [13] reported a case of brucella infection with renal biopsy findings that showed diffuse proliferative glomerulonephritis. The patient progressed to end-stage renal disease despite antibiotic and steroid therapy, whereas our subject showed a dramatic response to combination of antibiotic and steroid therapy and 23 days after admission, the renal function returned to normal.

Electron microscopy findings such as the presence of electron-dense paramesangial deposits supported this hypothesis that immunological mechanisms are involved in brucella glomerulopathies [14]. We didn't check the renal biopsy specimen by electron microscopy examination, but in IF study few C3 depositions in arteriolar walls (1+), and focal depositions of IgM in glomerular mesangium indicated negative immune reaction.

Some studies reported elevated serum IgM and IgG levels in patients with acute brucellosis [16-17], while other studies [18-19] found IgM brucella antibodies alone in acute infection. ELISA test is an effective method for diagnosis of brucellosis, particularly in sub-acute and chronic cases, when encounter with negative standard agglutination tests in presence of strongly suspected clinical settings [10, 20]. Treatment of

choice for brucellosis is administration of doxycycline and amino glycosides like streptomycin [21]. After antibiotic therapy the signs of the disease improve, but histologic findings, proteinuria, and hypertension may persist. Our case was received ceftriaxone 2gr/daily for 10 days in association with high dose steroid. We didn't recommend standard treatment for brucellosis since the results of wright and 2ME tests were not diagnostic. In our subject despite normal renal function and normal blood pressure (by using low dose furosemide and nifedipine), proteinuria and microscopic hematuria persisted after > 3 weeks.

In our case was brucella infection responsible for reversible acute kidney failure or the results of wright and 2ME tests just indicated previously un-diagnosed acute brucella infection which had recovered spontaneously?

Conclusion

In areas where brucellosis is endemic, acute brucella infection should be considered in the differential diagnosis of AKI when symptoms such as arthralgia or arthritis are present. As acute culture positive brucellosis can be associated with negative Wright and 2 ME tests [10], it can be attractive to conduct studies in order to define whether acute or chronic brucella infections may associate with lower titers of wright and 2 ME tests in non-immunocompromised cases (slightly -weakly positive titers)?

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