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Unusual Presentations of Pediatric Brucellosis: A Case Series from a Single Center

Pediatrik Brusellozun Sıra Dışı Sunumları: Tek Bir Merkezden Bir Vaka Serisi

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ÖZET
Amaç: Bu çalışma, nadir ve ciddi komplikasyonlarla ilişkili on pediatrik bruselloz vakasını bildirmeyi amaçlamaktadır.
Hastalar ve Yöntemler: Belgelenen klinik semptomlar, laboratuvar test sonuçları, tanı ve tedavi yöntemleri, 2018 ile 2021 yılları arasında brusellozun nadir komplikasyonlarıyla başvuran on pediatrik hasta için hastane dosyalarının retrospektif olarak incelenmesi ile elde edildi.
Bulgular: Çalışmaya dahil edilen hastalardan birinde diskit, üç hastada epididimo-orşit, iki hastada tek gözde ezotropya, bir hastada immün trombositopeni, iki hastada hemofagositik lenfohistiyositoz tanısı vardı ve bir hastaya da juvenil idiyopatik artrit tanısı yanlış olarak konmuştu. Tüm vakalarda ortak bulgu, tüm hastalarda ondulan olarak karakterize edilen ateşti. Tüm çocuklarda pozitif etiyolojik veya serolojik kanıt bruselloz enfeksiyonunu doğruladı ve Brucella için standart tüp aglütinasyon testi 1:160 veya daha yüksek titrede pozitifti ve iki hastada kan kültürleri de pozitifti. Tüm hastalar yaşa göre ayarlanmış dozlarda rifampisin (10-20 mg/kg/gün, oral) ile trimetoprim/sülfametoksazol (trimetoprim 10 mg/kg/gün ve sülfametoksazol 50 mg/kg/gün) veya doksisiklin (4,4 mg/kg/gün, oral) kombinasyonu ile tedavi edildi. Yedi hastaya gentamisin (5-7,5 mg/kg/gün, intravenöz) ile ek tedavi uygulandı ve iki hastada tedaviye seftriakson (100 mg/kg/gün) eklendi. Hemofagositik lenfohistiyositoz geliştiren iki hastadan biri yoğun bakım ünitesinde tedavi edildi ve her iki hastaya da bruselloz tedavisinin yanı sıra hemofagositik lenfohistiyositoz için önerilen ek tedavi (intravenöz immünglobulin 1 gr/kg/gün, 2 gün; deksametazon 10mg/m2/gün) uygulandı. Sonunda dokuz hasta sağlıklı bir şekilde taburcu edildi, bir hasta ise komplikasyonlar sonucu öldü.
Sonuç: Brucella enfeksiyonunun yaygın olduğu bölgelerde, alışılmadık komplikasyonlara sahip pediatrik hastalardaki klinik belirtilerin bruselloz ile ilişkili olabileceğini ve diğer hastalıklardan ayırt etmek için dikkatli bir ayırıcı tanı gerektirdiğini düşünmek önemlidir.

Anahtar Kelimeler: Bruselloz, çocuklar, diskitis, epididimo-orşit, hemofagositik lenfohistiyositoz, immün trombositopeni, juvenil idiyopatik artrit, nörobruselloz

ABSTRACT
Purpose: This study aims to report ten cases of pediatric brucellosis associated with rare and severe complications.
Patients and Methods: Documented clinical symptoms, laboratory test results, diagnosis, and treatment methods were retrospectively reviewed for 10 pediatric patients who presented with rare complications of brucellosis between 2018 and 2021.
Results: One of the patients included in the study had discitis, three had epididymo-orchitis, two had esotropia in one eye, one patient had immune thrombocytopenia, two patients had hemophagocytic lymphohistiocytosis, and one patient was misdiagnosed with juvenile idiopathic arthritis. A common finding in all cases was fever, which was characterized as undulant in all patients. All children positive etiological or serological evidence confirmed the brucellosis infection and the standard tube agglutination test for Brucella was positive at a titer of 1:160 or higher, and blood cultures were also positive in two patients. All patients were treated with age-adjusted doses of rifampicin (10-20 mg/kg/day, orally), in combination with either trimethoprim/sulfamethoxazole (trimethoprim 10 mg/kg/day and sulfamethoxazole 50 mg/kg/day) or doxycycline (4.4 mg/kg/day, orally). Seven patients received additional treatment with gentamicin (5-7.5 mg/kg/day, intravenously) and ceftriaxone (100 mg/kg/day) was added to the treatment in two patients. One of the two patients who developed hemophagocytic lymphohistiocytosis was treated in the intensive care unit, and both patients received additional treatment recommended for hemophagocytic lymphohistiocytosis [intravenous immunoglobulin 1 gr/kg/day, for 2 days; dexamethasone 10 mg/m2 /day] alongside brucellosis treatment. Eventually, nine patients were discharged in good health, while one patient died as a result of complications.
Conclusion: In regions where Brucella infection is prevalent, it is important to consider that clinical manifestations in pediatric patients with unusual complications may be associated with brucellosis, warranting a careful differential diagnosis to distinguish it from other diseases.

Keywords: Brucellosis, children, discitis, epididymo-orchitis, hemophagocytic lymphohistiocytosis, immune thrombocytopenia, juvenile idiopathic arthritis, neurobrucellosis

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INTRODUCTION

Brucellosis is the most prevalent zoonotic infection. In endemic areas, the reported prevalence of brucellosis in children ranges from 10% to 30%. Brucella melitensis is the species most commonly associated with human infections. In children, the infection is typically transmitted through the consumption of unpasteurized milk and dairy products, direct contact with infected animals, and less frequently, through aerosol inhalation. Clinical manifestations can vary widely, ranging from mild illness to severe disease complicated by life-threatening conditions (1). Clinically, brucellosis is manifested by nonspecific symptoms, including fever, profuse sweating, malaise, loss of appetite, testicular enlargement, epididymitis, joint pain, skin rash, and enlarged liver, spleen, and lymph nodes. Despite the diverse symptoms, fever and arthralgia are the primary clinical signs (2). Involvement of vital organs complicates the course of the disease and is a significant cause of morbidity and mortality, especially in endemic regions (3).

Brucellosis is a significant public health concern in developing countries. Due to the nonspecific nature of clinical symptoms, misdiagnosis is common, leading to life-threatening complications. This study aims to increase awareness of brucellosis among clinicians by describing pediatric patients with severe complications of brucellosis.

PATIENTS AND METHODS

A total of 183 patients diagnosed with brucellosis at the pediatric infectious diseases clinic of a tertiary training and research hospital between 2018 and 2021 were included in the study. The medical files of these patients were reviewed retrospectively. 173 patients were excluded for not meeting the inclusion criteria. Ultimately, the study focused on 10 patients with confirmed pediatric brucellosis who presented with rare complications. The clinical symptoms, laboratory test results, diagnosis, and treatment of these patients were reviewed. Informed consent was obtained from the parents of the patients for their participation in the study.

The inclusion criteria for the study were children aged between 1 month and 18 years (216 months), with a positive Brucella standard tube agglutination (STA) test with a titer of 1/160 or higher, and unusual brucellar complications. The exclusion criteria were age outside of the prespecified range, a STA test titer below 1/160, and parental refusal to provide consent for involvement of their children in the study.

Ethics Statement

Approval was obtained from the local ethics committee for the study (No: 2024/125).

CASE PRESENTATION

Case # 1

A 199-month-old male patient presented with complaints of back pain, limping while walking, high-grade (38.5º C) fever, loss of appetite, and malaise for one month. During the physical examination, the patient was able to walk with support but exhibited limping, and there was limited active or passive spinal movement. Severe pain was noted upon percussion and palpation in the lumbar region. No palpable mass was found. The neurological examination was unremarkable. The patient had a history of living in a rural area, consuming unpasteurized milk and dairy products, along with high-grade fever, loss of appetite, and malaise. Magnetic resonance imaging (MRI) of the lumbar spine and Brucella STA test were performed for the differential diagnosis of the patient, whose laboratory findings are shown in Table 2. The lumbar MRI revealed narrowing of the L4-L5 disc space and heterogeneous contrast enhancement in the endplates, but no mass was observed (Figure 1). The Brucella STA test result was positive at a titer of 1/1280. The patient was diagnosed with brucellosis-associated discitis with the current findings. The patient was started on treatment with doxycycline (4.4 mg/kg/day, orally) and rifampicin (10-20 mg/kg/day, orally) in combination with gentamicin (5-7.5 mg/kg/day, intravenously). Gentamicin was discontinued on the 14th day of treatment, and the patient received treatment for a total of 16 weeks. The patient improved without any sequelae, and no complications developed during follow-up.

Cases # 2,3, and 4

Three patients (aged 55, 110, and 190 months, respectively) presented with swelling, redness, and pain in the scrotum. On

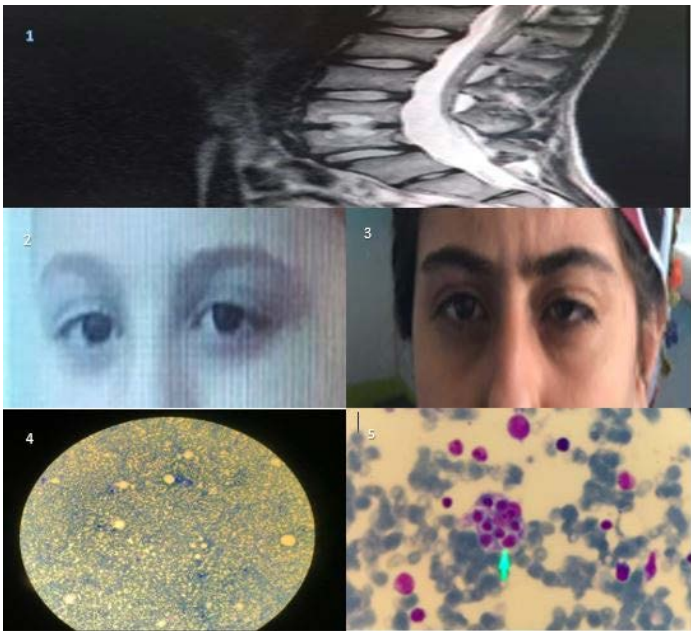

Figure 1A. Magnetic resonance imaging of the vertebra in a patient diagnosed with discitis **2A.** Image of the eyes of a patient diagnosed with neurobrucellosis. **3A** Image of the eyes of a patient diagnosed with neurobrucellosis. **4A.** Bone marrow aspiration smear image of a patient diagnosed with IT. **5A.** Bone marrow aspiration smear image of a patient diagnosed with HLH

Table 1. Epidemiological data, diagnosis and treatment of the patients

Case #	1	2	3	4	5	6	7	8	9	10
Diagnosis	Brucellosis	Brucellosis	Brucellosis	Brucellosis	Brucellosis	Brucellosis	Brucellosis	Brucellosis	Brucellosis	Brucellosis
Complication	Discitis	Epididymo-orchitis	Epididymo-orchitis	Epididymo-orchitis	Neuro-brucellosis	Neuro-brucellosis	Immune-mediated Thrombo-cytopenia	HLH	HLH	JIA
Age (months)	199	55	110	190	135	196	59	46	11	86
Sex	Male	Male	Male	Male	Female	Female	Female	Female	Male	Female
Presenting Symptoms	Fever, Loss of appetite, Malaise, Back pain, Limping	Fever, Loss of appetite, Malaise, Arthralgia, Scrotal swelling, Scrotal redness, Testicular pain	Fever, Loss of appetite, Malaise, Arthritis Testicular swelling, Testicular pain	Fever, Loss of appetite, Malaise, Arthralgia, Testicular swelling, Testicular pain	Fever, Headaches, Nausea, Malaise Diplopia, Ptosis	Fever Headaches, Nausea, Malaise Diplopia, Ptosis	Fever Weight Loss, Malaise, Knee Pain, Jaundiced Skin	Fever, Rash, Malaise Loss of appetite, Arthralgia	Fever, Malaise, Abdominal swelling	Fever, Malaise, Rash, Arthritis
Medications and Treatment Duration for Brucellosis	Doxycycline (16 weeks) Rifampicin (16 weeks) Gentamicin (2 weeks)	TMP-SMX (6 weeks) Rifampicin (6 weeks) Gentamicin (5 days)	Doxycycline (6 weeks) Rifampicin (6 weeks) Gentamicin (5 days)	Doxycycline (6 weeks) Rifampicin (6 weeks) Gentamicin (5 days)	Doxycycline (6 months) Rifampicin (6 months) Ceftriaxone (1 month)	Doxycycline (6 months) Rifampicin (6 months) Ceftriaxone (1month)	TMP-SMX (6 weeks) Rifampicin (6 weeks) Gentamicin (5 days)	TMP-SMX (6 weeks) Rifampicin (6 weeks) Gentamicin (5days)	TMP-SMX (17 days) Rifampicin (17 days) Gentamicin (5 days)	TMP-SMX (6 weeks) Rifampicin (6 weeks)

HLH, Hemophagocytic lymphohistiocytosis; JIA: juvenile idiopathic arthritis; TMP-SMX: Trimethoprim/Sulfamethoxazole

physical examination, the scrotum appeared red, painful to touch, and swollen, and body temperature was elevated. One patient had hepatomegaly, another had hepatosplenomegaly, while the third had no organomegaly. Scrotal color Doppler and ultrasound (US) examinations of the patients, whose laboratory findings are presented in Table 2, revealed heterogeneous structures of the testicles, expansion of the epididymis and spermatic cord, and increased echogenicity and vascularity. It was learned that all three had elevated fever, loss of appetite, malaise, symptoms of arthralgia and/or arthritis, along with a history of consuming unpasteurized milk and dairy products. For differential diagnosis, PPD skin test (for tuberculosis) and Brucella STA test were performed for the patients (Table 2). The patients were diagnosed with bilateral epididymo-orchitis associated with brucellosis. The patients were started on treatment for 6 weeks with age-appropriate doses of rifampicin (10-20 mg/kg/day, orally), in combination with either trimethoprim (TMP) /sulfamethoxazole (SMX) (TMP 10 mg/kg per day and SMX 50 mg/kg per day) or doxycycline (4.4 mg/kg/day, orally). Additionally, gentamicin (5-7.5 mg/kg/day, intravenously) was administered for 5 days (Table 1). Follow-up scrotal Doppler and US examinations were performed on the 15th and 42nd days of treatment, revealing resolution of all symptoms.

Cases # 5 and 6

Two female patients (aged 135 and 196 months, respectively) presented with complaints of headache, high-grade fever, nausea, malaise, diplopia, and ptosis. On physical examination, both patients had fever (38.7° C and 38.4 ° C), and the right and left upper (respectively) eyelids were ptotic, downward and inward deviation of the eyes, with limited outward gaze in both patients, while other eye movements were normal (Figures 2 and 3). Fundoscopic examination showed papilledema and abducens nerve palsy. Other systemic and neurological examination results were normal. Their laboratory results are shown in Table 2. Both patients had a history of living in areas where brucella is prevalent and consuming unpasteurized milk and dairy products. Brucella SAT test results were positive with a titer of 1/5120 for both patients. To exclude other potential causes of abducens nerve palsy, radiological imaging studies and lumbar puncture were performed. There were no remarkable findings in the orbital MRI and MR angiography of the patient (Case# 5), whose LP test results are given in table 2; however, cranial MRI showed several nonspecific hyperintense foci in the white matter of bilateral frontoparietal lobes on FLAIR imaging. The other patient's (Case# 6) orbital MRI, cranial MRI, and MR angiography were normal. In addition LP-specific laboratory results are presented in Table 2. With these findings, both patients were diagnosed with neurobrucellosis. The patients were started on treatment with ceftriaxone (100 mg/kg/day, intravenously), doxycycline (4.4 mg/kg/day, orally), and rifampicin (10-20 mg/kg/day, orally). On the 15th day of treatment, it was observed that eye movements were normal, except for mild limitation of outward gaze. Ceftriaxone was discontinued after four weeks. After two months, eye movements returned to normal in all directions. Treatment with the other medications (doxycycline and rifampicin) continued for six months, and by the sixth month, the Brucella agglutination tests were negative. No recurrence was observed during the one-year follow-up.

Table 2. Laboratory Investigations

Case #	1	2	3	4	5	6	7	8	9	10
Hemoglobin (g/dL)	13.2	10.5	12	12.8	11.7	13.06	7.05	8.1	5.5	8.3
Platelets (mm^3/uL)	322,000	9,800	103,000	554,000	275,000	355,000	62,720	109,000	59,000	705,000
WBC (mm^3/uL)	9131	3700	11500	22500	7167	8617	3500	4080	7700	25450
Neutrophils (10^3/uL)	5436	2730	7900	18400	3018	4126	890	3250	5320	18700
Lymphocytes(10^3/uL)	2460	954	2900	3680	3706	3769	2430	755	1990	4560
Urea(mg/dL)	51	29	19	34	23	15	21	51	39	11
Creatinine (mg/dL)	0.71	0.6	0.34	0.84	0.62	0.65	0.56	1.2	0.91	0.34
AST (U/L)	54	65	93	156	25	32	594	110	99	38
ALT (U/L)	49	94	80	221	22	35	251	174	86	45
LDH (U/L)	184	351	162	278	205	187	1414	421	895	301
Triglyceride (mg/dL)	98	-	-	-	-	-	-	511	304	-
Fibrinogen (mg/dL)	-	-	-	-	-	-	-	148	186	-
CRP (mg/dL)	18.2	42	32	66	17	29	11.5	78	57	71
ESR (mm/h)	51	40	21	53	7	32	28	63	48	98
Ferritin (ng/dL)	-	-	-	-	-	-	-	1295	>1500	-
Blood culture	Brucella spp.	No growth	No growth	No growth	No growth	No growth	No growth	Brucella spp.	No growth	No growth
Brucella STA Test	1/1280	1/640	1/640	1/1280	1/5120	1/5120	1/2560	1/5120	1/1280	1/320
CSF Protein (mg/dL)	-	-	-	-	145	37	-	-	-	-
CSF Glucose (mg/dL)	-	-	-	-	28 (blood glucose: 74)	39 (blood glucose: 86)	-	-	-	-
CSF Cellularity (/mm^3)	-	-	-	-	12 (lymphocytes)	8 (lymphocytes) 5-6 (erythrocytes)	-	-	-	-
CSF Culture	-	-	-	-	No growth	No growth	-	-	-	-
CSF Brucella Tube Agglutination Test	-	-	-	-	1/80	1/160	-	-	-	-
Toxoplasma Ig M	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Epstein-Barr Virus PCR	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Herpes Simplex Virus PCR	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Cytomegalovirus PCR	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Rubella IgM	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Parvovirus B19 PCR	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
HIV Ag/Ab	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Mumps Ig M	-	Negative	Negative	Negative	-	-	-	-	-	-
PPD	-	4 mm	0 mm	5 mm	-	-		-	-	-
ANA	-	-	-	-	-	-		-	-	Negative
RF (IU/mL)	-	-	-	-	-	-	-	-	-	Negative

ANA, anti-nuclear antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CSF, cerebrospinal fluid; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; PPD, purified protein derivative; RF, rheumatoid factor; STA, standard tube agglutination; WBC, white blood cell

Case # 7

A 59-month-old girl presented with symptoms of persistent high-grade fever (38.6º C), malaise, knee pain, weight loss, and jaundice for one month. Physical examination revealed jaundiced skin and sclera, as well as hepatosplenomegaly. Other systemic examinations were unremarkable. The patient had a history of consuming unpasteurized dairy products. STA with Coombs' antiserum showed a positive titer of 1/2560. Abdominal US findings of the patient, whose laboratory results are presented in Table 2, confirmed hepatosplenomegaly. Treatment was initiated with trimethoprim/sulfamethoxazole (TMP 10 mg/kg per day and SMX 50 mg/kg per day), rifampicin (10-20 mg/kg/day, orally), and gentamicin (5-7.5 mg/kg/day, intravenously) for five days. At the 15th-day follow-up, the patient's fever was under control, and all blood values were normal. However, on the 38th day of treatment, the patient returned with complaints of bruising and rash on various parts of her body. Aside from generalized ecchymoses and petechiae, no abnormal physical examination findings were noted. Laboratory tests revealed thrombocytopenia. Prothrombin time and activated partial thromboplastin time were normal. STA test was positive at a titer of 1/640. The bone marrow aspiration showed increased number of megakaryocytes and no hemophagocytosis was observed (Figure 4). Based on the aforementioned findings, the patient was diagnosed with immune-mediated thrombocytopenia (IT) induced by brucellosis and was treated with intravenous immunoglobulin (1 g/kg/day for 2 days). Following treatment, the platelet count rose to 240,000/mm^3. At the one-year follow-up, she received treatment once more for IT relapse, but no relapse related to brucellosis was observed.

Case # 8

A 46-month-old girl presented with high-grade fever (39º C), joint pain, malaise, and loss of appetite persisting for 2-3 weeks. On physical examination, the patient had a petechial rash that did not fade when pressed, and hepatomegaly. There was also swelling, increased temperature, and limited movement in the left knee. From the patient's history, it was learned that her mother had been diagnosed with brucellosis one month prior and that the patient also consumed unpasteurized dairy products. The patient's STA test was positive at a titer of 1/5120. Brucella spp. growth was observed on her blood culture. Given the patient's poor general condition, she was hospitalized and started on intravenous supportive therapy along with TMP (10 mg/kg per day and SMX 50 mg/kg per day), rifampicin (10-20 mg/kg/day, orally), and gentamicin (5-7.5 mg/kg/day, intravenously) for five days. However, fever persisted despite treatment, and the patient was re-evaluated on the sixth day of treatment. See Table 2 for the patient's laboratory results. Her clinical and laboratory findings led to the suspicion of Brucellosis-induced hemophagocytic lymphohistiocytosis (HLH), and a bone marrow aspiration was performed to confirm HLH (Figure 5). The results of bone marrow aspirate examination were consistent with HLH. While continuing the treatment for brucellosis, additional HLH-targeted therapies (intravenous immunoglobulin 1g/kg/day dose and 2 days, dexamethasone 10mg/m2/day for 2 weeks, then dexamethasone dose was tapered and stopped) were initiated, and fever control was achieved within 48 hours. After 14 days of in-hospital treatment, the patient was discharged for outpatient follow-up. At the third-week follow-up, her general condition was good, arthritis had completely resolved, and she had not had a fever for 15 days. Thereafter, the patient's treatment was continued on an outpatient basis for a total of 42 days.

Case # 9

An 11-month-old boy presented with complaints of persistent high-grade fever, malaise, yellowing of the skin, and abdominal swelling for two weeks. Physical examination revealed jaundiced skin and hepatosplenomegaly. Abdominal US imaging confirmed hepatosplenomegaly. The patient was fed unpasteurized dairy products by his mother. STA test was positive at a titer of 1/1280. Treatment was initiated with TMP (10 mg/kg per day and SMX 50 mg/kg per day), rifampicin (10-20 mg/kg/day, orally), and gentamicin (5-7.5 mg/kg/day, intravenously) for five days. Despite treatment with antibiotics, fever persisted and the patient developed pronounced hypotension, and required intensive care due to respiratory distress. His ferritin and triglyceride levels were elevated, and fibrinogen level was low (Table 2). Given the suspicion of Brucella-induced HLH, a bone marrow aspiration was performed; however, no evidence of hemophagocytosis was found. The patient, already receiving brucella treatment, was diagnosed with HLH due to the fulfillment of the other five (fever, bicytopenia, splenomegaly, hyperferritinemia, hypertriglyceridemia) criteria. Treatment for HLH (intravenous immunoglobulin at a dose of 1g/kg/day/IV, 2 day and dexamethasone 10 mg/m2/day/IV) was initiated but the patient didn't respond to the pharmacological treatment and passed away on the 17th day of treatment.

Case # 10

An 86-month-old girl presented with fatigue, widespread rash on her body, fever. She also presented with swelling, pain, redness and increased heat in her right knee. From her history, it was learned that her complaints had started approximately five weeks ago, that she lived in a rural area, and that her family was involved in animal husbandry. On physical examination, the right knee was swollen, red, and had limited mobility. Additionally, hepatosplenomegaly was present. The patient also had macular, erythematous rashes throughout her body that blanched with pressure, along with fever.

The patient was diagnosed with juvenile idiopathic arthritis (JIA) and had been on methylpredisolone 1 mg/kg/day treatment for eight days. Prior to methylpredisolone therapy, a bone marrow aspiration was performed, which did not reveal any findings suggestive of malignancy. Rheumatic tests were requested; however, treatment with corticosteroids had already begun before the results were available (Table 2). After the initiation of methylpredisolone therapy, her symptoms didn't resolve, and her STA test was positive at a titer of 1/320. The patient's methylpredisolone treatment for JIA was discontinued and TMP/ SMX (TMP 10 mg/kg per day and

SMX 50 mg/kg per day), rifampicin (10-20 mg/kg/day, orally) treatment was started. By the fourth day of treatment, fever control was achieved, and by the 17th day, all other clinical findings resolved. The patient received treatment for a total of 42 days. At the one-year follow-up, she was symptom-free and no relapse was observed.

DISCUSSION

Brucellosis is a zoonotic disease caused by Brucella, a gram-negative coccobacillus. Brucella can be transmitted directly through contact with infected animals or indirectly through the consumption of unpasteurized dairy products. In humans, brucellosis can affect any organ or system. The most common complication is osteoarticular involvement, which includes arthritis, spondylitis, and sacroiliitis, along with a multitude of nonspecific clinical symptoms such as fever and chills, muscle and joint pain, headaches, and sweating (4).

The treatment of brucellosis involves the use of rifampicin in combination with doxycycline or TMP-SMX, taking into account the patient's age. Depending on the severity of the disease and the presence of complications, gentamicin or streptomycin may also be added to the treatment regimen. The duration of treatment varies based on the presence of complications and the affected organs, ranging from six weeks to six months (4,5).

The most prevalent osteoarticular manifestation in children is monoarticular arthritis (usually in the knees and hips), while in adults, the sacroiliac joints (up to 80%) and spinal joints (up to 54%) are most commonly involved. In our patient (Case #10), JIA was initially considered due to the presence of fever and skin rash along with knee arthritis. After excluding malignancy, corticosteroid treatment was initiated. Although it was possible for the patient to receive a diagnosis of JIA based on the existing findings, it is essential to first consider brucellosis in an endemic region, as the likelihood of cure without sequelae is much higher with appropriate treatment. Studies on spinal brucellosis indicate that the predominant radiological finding is spondylitis or spondylodiscitis, followed by pre- or paravertebral abscesses. The most frequently affected area is at the L5-S1 level (6-9).

Spinal brucellosis typically manifests as back pain radiating to the legs, fever, sweating, and weight loss. Neurological symptoms may occur, and the severity of the symptoms depends on the extent of disk involvement, inflammation of the vertebral body, and the pressure effects on the spinal canal (10). Diagnosis is challenging due to symptom overlap with other chronic disorders, including tuberculosis and pyogenic osteomyelitis. The diagnosis of spinal TB primarily relies on the clinical manifestations of the disease, the history of exposure to the infectious source, spinal imaging findings, and laboratory investigations. MRI is the preferred imaging modality for diagnosing spinal brucellosis due to its high diagnostic sensitivity. Spinal MRI can reveal spondylitis, spondylodiscitis, or spinal canal stenosis along with epidural abscesses (11). Brucellar spondylitis requires a longer duration of antibiotic treatment compared to uncomplicated brucellosis and may necessitate surgical intervention. Delayed initiation of treatment can lead to long-term disability (4). A literature review revealed a lack of studies regarding brucellar discitis in children. In our patient (Case #1), lumbar MRI showed narrowing at the L4-L5 disc space and heterogeneous contrast enhancement in the endplates on T1- and T2-weighted images, which were suggestive of discitis. The STA test results also supported the diagnosis of brucellosis, and the patient was treated with oral doxycycline and rifampicin for four months. Additionally, gentamicin was administered during the first two weeks of treatment. The patient was followed at the pediatric infectious diseases clinic for six months. With early diagnosis and treatment, the patient recovered without sequelae.

Brucellar epididymo-orchitis, which occurs very rarely in children and adolescents, can present as the first sign of systemic disease or develop later on. The most common symptoms of the disease include pain and swelling in the testes, with less frequent occurrences of scrotal redness and increased temperature, as seen in our patient. Brucella species can cause granulomatous orchitis, which can mimic neoplasia in both clinical and ultrasound examinations. If the testis is focally involved, differential diagnoses should include testicular tumor, abscess, intratesticular hematoma. Early and accurate diagnosis of brucellar epididymo-orchitis is crucial to prevent severe complications and unnecessary orchiectomy due to misdiagnosis. In patients presenting with scrotal pain and swelling, brucellar epididymo-orchitis should always be considered among the differential diagnoses, especially when risk factors such as living in an endemic area and consumption of unpasteurized milk and dairy products are present. As with other forms of brucellosis, epididymo-orchitis should be treated for at least six weeks using a combination of rifampicin with TMP-SMX or doxycycline. Aminoglycosides may also be added for 5-7 days (4,12-14).

Neurobrucellosis occurs very rarely in the pediatric age group, accounting for approximately 0.8% of brucellosis cases. The involvement of the nervous system in brucellosis can lead to meningitis, encephalitis, meningoencephalitis, cerebellar dysfunction, radiculitis, myelitis, epidural abscess, meningovascular disease, cranial nerve involvement, seizures, brain abscess, and demyelination (16). Isolated cranial nerve involvement in neurobrucellosis is extremely rare, with only a few reports of isolated abducens nerve paralysis. The pathogenesis of abducens nerve paralysis involves the spread of meningeal infection and possible vasculitic process (17). Neurobrucellosis can develop at any stage of the disease. Due to the slow-growing nature of Brucella bacteria, cerebrospinal fluid (CSF) and blood cultures may yield negative results. Therefore, serological methods are typically used to optimize diagnosis. Definitive diagnosis is made upon detection of Brucella antibodies in CSF (18). Neurobrucellosis is a serious and rare complication of brucellosis, and although it is rare, it should be suspected in almost all neurological symptoms, particularly when they occur in individuals residing in endemic regions. The clinical and radiological manifestations of the disease are highly diverse and tend to mimic many other

diseases. Therefore, suspicion of brucellosis and investigation of the history of consuming unpasteurized dairy products are essential for early diagnosis with brucella-specific serological tests.

Active brucellosis may present with hematological findings including anemia, leukopenia, thrombocytopenia, and rarely, pancytopenia. Mild anemia and leukopenia are the most common hematological findings, while severe thrombocytopenia has been reported less frequently. The prevalence of thrombocytopenia ranges from 5% to 40%. (19,20). In our patient (Case #7), the initial decrease in platelet count occurred as a secondary effect of brucellosis and returned to normal shortly after the initiation of treatment. However, thrombocytopenia later re-emerged due to unidentified triggers. The Coombs' Controls test with antiserum and STA were performed due to the newly developed thrombocytopenia, and no increase in titer was observed. The Brucella IgM test was negative, while the Brucella IgG test was positive. The patient was diagnosed with IT as a result of bone marrow aspirate examination. The platelet counts returned to normal with appropriate treatment of IT. This case report highlights that thrombocytopenia in brucellosis may not always be part of the disease and can emerge in the form of IT, which requires entirely different treatment and management.

HLH is classified into primary and secondary types. Secondary HLH (sHLH) is associated with systemic viral, bacterial, fungal, or parasitic infections, malignancies, and autoimmune diseases (21,22).

Hyperactivation of the immune system in response to infections and the subsequent development of HLH are common triggers in patients with genetic predisposition as well as in sporadic cases without an underlying genetic cause. While the most common infectious triggers are viral infections, particularly Epstein-Barr virus, HLH can rarely develop due to infections like brucellosis (23). Although there are few reports on brucellosis-induced hemophagocytosis, it has been observed that HLH can be controlled with treatment targeting the triggering pathogen (24). Among our patients diagnosed with HLH based on clinical and laboratory findings (Cases # 8 and 9), one responded to treatment rapidly, while the other patient (Case 9) was unresponsive to HLH-targeted treatment added to the Brucella treatment, with no improvement in clinical symptoms. This suggests that there may be a genetic disorder in the patient that predisposes them to HLH. In patients with persistent high-grade fever in whom an infectious agent is identified, but treatment targeting the pathogen fails to achieve the expected improvement, HLH should be considered, and appropriate investigations should be conducted.

CONCLUSION

In children, brucellosis typically presents with characteristic clinical findings and is often accompanied by systemic symptoms. However, in regions where Brucella infection is prevalent, it is important to consider that clinical manifestations in pediatric patients with unusual complications may be associated with brucellosis, warranting a careful differential diagnosis to distinguish it from other diseases.

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