Rifampicin Hypersensitivity in a Pediatric Case of Brucellosis: A Case Report

Rifampisin Aşırı Duyarlılığı Olan Pediatrik Bir Bruselloz Olgusu: Olgu Sunumu

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Background: Brucellosis is a zoonotic infection that remains endemic in many regions, representing a significant public health problem. Clinical manifestations in children are often nonspecific, and musculoskeletal involvement is among the most frequent focal complications. Combination therapy with rifampicin and doxycycline or rifampicin and trimethoprim–sulfamethoxazole in pediatric patients is recommended as first-line treatment. However, drug hypersensitivity may complicate management and limit therapeutic options, particularly in cases where alternative medications are less effective or carry a higher risk of side effects.

Case Presentation: We report the case of a previously healthy 10-year-old boy who presented with fever and left knee pain following close contact with sheep. Brucellosis was confirmed by positive Rose Bengal, standard agglutination and Coombs tests. He was initially treated with doxycycline and rifampicin. After two weeks, the patient developed fever, vomiting, pruritus, conjunctivitis, eosinophilia, and elevated transaminases. Symptoms resolved upon discontinuation of rifampicin and recurred after re-initiation of anti-brucellosis therapy, strongly suggesting rifampicin hypersensitivity. Pediatric allergy consultation confirmed the suspicion, and rifampicin was permanently withdrawn. The patient was successfully treated with doxycycline and gentamicin (14 days of gentamicin and doxycycline for 6 weeks), leading to full clinical and laboratory recovery.

Conclusion: Rifampicin and doxycycline are essential first-line agents in the treatment of pediatric brucellosis in children older than 8 years, but hypersensitivity reactions, though rare, may mimic disease relapse or complications. To our knowledge, this instance is the first reported pediatric case of rifampicin hypersensitivity in brucellosis. Awareness of this possibility is crucial for timely recognition and appropriate management. Alternative regimens, such as doxycycline combined with aminoglycosides, can provide effective treatment in children unable to tolerate rifampicin.

Keywords: Brucellosis, child, drug allergy, hypersensitivity, rifampicin

Arka Plan: Bruselloz, birçok bölgede endemik olmaya devam eden ve önemli bir halk sağlığı sorunu oluşturan zoonotik bir enfeksiyondur. Çocuklarda klinik bulgular sıklıkla özgül değildir ve kas-iskelet sistemi tutulumu en sık görülen fokal komplikasyonlar arasındadır. Rifampisin ve doksisiklin kombinasyonu ya da pediatrik hastalarda rifampisin ve trimetoprim–sülfametoksazol kombinasyonu birinci basamak tedavi olarak önerilmektedir. Ancak ilaç aşırı duyarlılığı, tedavi sürecini zorlaştırabilir ve terapötik seçenekleri kısıtlayabilir.

Olgu Sunumu: Daha önce sağlıklı olan 10 yaşında bir erkek hasta, koyunlarla yakın temas öyküsünün ardından gelişen ateş ve sol diz ağrısı ile başvurdu. Standart aglütinasyon ve Coombs testlerinin pozitif olmasıyla bruselloz tanısı doğrulandı. Hastaya başlangıçta doksisiklin ve rifampisin tedavisi başlandı. İki haftanın sonunda hastada ateş, kusma, kaşıntı, konjonktivit, eozinofili ve transaminaz yüksekliği gelişti. Rifampisinin kesilmesiyle semptomlar geriledi ve anti-bruselloz tedavinin yeniden başlanmasının ardından bulguların tekrarlaması, rifampisin aşırı duyarlılığını güçlü şekilde düşündürdü. Çocuk alerji konsültasyonu sonrası bu tanı doğrulandı ve rifampisin kalıcı olarak tedaviden çıkarıldı. Hasta, doksisiklin ve gentamisin ile (14 gün gentamisin, 6 hafta doksisiklin) başarıyla tedavi edildi ve tam klinik ve laboratuvar iyileşme sağlandı.

Sonuç: Sekiz yaşından büyük çocuklarda bruselloz tedavisinde rifampisin ve doksisiklin temel birinci basamak ajanlar olmakla birlikte, nadir de olsa gelişebilen aşırı duyarlılık reaksiyonları hastalık nüksünü veya komplikasyonlarını taklit edebilir. Bildiğimiz kadarıyla bu olgu, brusellozlu bir çocukta rifampisin aşırı duyarlılığının bildirildiği ilk pediatrik vakadır. Bu olasılığın farkında olunması, zamanında tanı ve uygun yönetim açısından kritik öneme sahiptir. Rifampisini tolere edemeyen çocuklarda, doksisiklin ile aminoglikozid kombinasyonu gibi alternatif rejimler etkili bir tedavi seçeneği sunabilir.

Anahtar Kelimeler: Bruselloz, çocuk, ilaç alerjisi, hipersensitivite, rifampisin

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INTRODUCTION

Brucellosis is a common, prevalent zoonotic disease throughout the world, caused by *Brucella* species, transmitted to humans primarily through ingestion of unpasteurized dairy products or direct contact with infected animals and their secretions (Justman et al., 2018). It remains a significant public health problem, especially in endemic areas. Clinical presentations are highly variable, ranging from nonspecific symptoms such as fever, malaise, and sweats to focal organ involvement (Qasim et al., 2020). Musculoskeletal manifestations are among the most common focal complications, reported in 6% to 75% of cases, with sacroiliac and spinal joints being most frequently affected (Qasim et al., 2020; Çiftdoğan et al., 2020; Franco et al., 2007). In children, peripheral joint involvement, particularly of the knee and hip, may present as monoarthritis.

The cornerstone of treatment is prolonged combination antibiotic therapy, with rifampicin and doxycycline commonly used in children over 8 years, and rifampicin and trimethoprim-sulfamethoxazole in younger patients (Tanir et al., 2009; Young et al.,2019). However, drug-related hypersensitivity reactions make treatment more difficult and limit the number of available treatment options.

Here, we report a pediatric case of brucellosis with knee involvement complicated by rifampicin hypersensitivity. This case underscores the diagnostic and therapeutic difficulties in managing brucellosis in children with limited antibiotic options due to drug allergy.

To the best of our knowledge, rifampicin hypersensitivity in pediatric brucellosis has not been previously reported in the literature, making this case an important contribution for clinicians managing children with limited therapeutic options.

CASE PRESENTATION

A previously healthy 10-year-old male had been admitted to a hospital with a one-week history of posterior left knee pain and intermittent fever. He had a history of close contact with sheep, some of which had experienced stillbirths. He had no prior history of hospitalization, chronic illness, tuberculosis, rheumatologic disease, malignancy, travel, or known drug allergies. His vaccinations were complete according to the national immunization schedule, and his family history was unremarkable.

On examination, the liver was palpated 1.5 cm below the right costal margin. There was no lymphadenopathy, petechiae, or purpura. Joints exhibited a full range of motion without pain. Laboratory findings revealed erythrocyte sedimentation rate (ESR) 61 mm/h, C- reactive protein (CRP) 6 mg/L, aspartate aminotransferase (AST) 26 U/L, white blood cell (WBC) count 7.9 ($\times 10^3/\mu L$), hemoglobin 11.7 g/dL, platelets 257($\times 10^3/\mu L$), absolute lymphocyte count (ALC) 3.23 ($\times 10^3/\mu L$), absolute neutrophil count (ANC) 4.01 ($\times 10^3/\mu L$). Brucellosis was diagnosed based on positive Rose Bengal screening, followed by confirmatory Wright agglutination and Coombs Wright agglutination tests, with a titer of 1/320.. Abdominal ultrasound showed hepatomegaly (liver size 137 mm). Knee radiography was performed and was normal; magnetic resonance imaging was not performed due to the absence of clinical signs of arthritis. Doxycycline and rifampicin were initiated.

At the two-week follow-up, the patient presented with two days of fever, mild cough, vomiting, pruritus, and conjunctivitis. Vital signs: temperature 38.3°C, oxygen saturation 98%, and heart rate 124 beats per minute. Pulmonary auscultation revealed coarse breath sounds at the lung bases. Dermatologic exam demonstrated excoriated lesions secondary to scratching. Laboratory results: CRP 139 mg/L, procalcitonin 8.6 ng/mL, WBC 5.42 ($\times 10^3/\mu L$), platelets 153 ($\times 10^3/\mu L$), ALC 1.49 ($\times 10^3/\mu L$), ANC 3.57 ($\times 10^3/\mu L$), eosinophils 12%, AST 81 U/L, ALT 35 U/L, while GGT, ALP, and total bilirubin levels were within normal limits.

Both Wright agglutination and Coombs Wright agglutination tests were positive, with titers of 1/640. Serological tests for hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, Epstein–Barr virus, and cytomegalovirus were negative. Respiratory polymerase chain reaction results were also negative. An echocardiogram was performed to rule out multisystem inflammatory syndrome in children (MIS-C). The results were normal. Abdominal ultrasonography and chest X-ray were unremarkable. Blood and urine cultures were obtained. Empiric treatment with cefotaxime and azithromycin was started, and rifampicin and doxycycline were discontinued.

On the first day of treatment, the fever had resolved, the vomiting had subsided, and the skin lesions had faded. CRP decreased to 42 mg/L and procalcitonin to 2.9 ng/mL. Rifampicin and doxycycline were restarted after 48 hours of becoming afebrile. However, within hours, the patient developed recurrent fever, pruritus, and vomiting, leading to the discontinuation of both drugs. Antihistamines were administered, and antibiotics were continued.

The patient's blood cultures remained negative. Inflammatory markers normalized (CRP 4 mg/L, ESR 8 mm/h, procalcitonin negative). Given the temporal relationship between drug administration and recurrent symptoms, rifampicin hypersensitivity was strongly suspected. We consulted with the pediatric allergy clinic to determine whether rifampicin could be used for his treatment. Pediatric allergy consultation confirmed probable rifampicin hypersensitivity, and avoidance was recommended until formal testing and potential desensitization could be performed. Treatment was switched to doxycycline plus gentamicin (14 days of gentamicin; doxycycline continued to 6 weeks).

More importantly, doxycycline continued to be used for the remainder of the treatment without any recurrence of hypersensitivity symptoms; this supports the idea that the reaction was due to rifampicin, not doxycycline.

At discharge, the Brucella agglutination titer was 1/640. After completion of 6 weeks of doxycycline, the agglutination test titer decreased to 1/320. At follow-up, laboratory results showed CRP 2 mg/L, ESR 8 mm/h, and WBC 5.37 ($\times 10^3/\mu L$). The patient's joint pain had resolved, and no active complaints remained.

DISCUSSION

Brucellosis is a zoonotic infection that remains endemic in many regions where animal husbandry is common. In children, the disease often presents with nonspecific clinical manifestations, including fever, arthralgia, hepatosplenomegaly, and hematological abnormalities (Qasim et al., 2020). Diagnosis is supported by exposure history, clinical features, and serology (Wright agglutination and Coombs Wright agglutination tests). (Justman et al., 2018). In our patient, both a relevant exposure history and serological positivity supported the diagnosis.

The primary objective of treatment in pediatric brucellosis is to prevent relapse and long-term complications. Combination therapy with rifampicin plus doxycycline or rifampicin plus trimethoprim–sulfamethoxazole is generally recommended for at least six weeks (Tanir et al., 2009; Young et al., 2019; Editorial Board of Chinese Journal of Infectious Diseases, 2017). Nevertheless, adverse events such as intolerance, hepatotoxicity, and hypersensitivity reactions can complicate treatment and necessitate alternative regimens. Such reactions, though rare, have been described in adult brucellosis (Yilmaz et al., 2018).

Rifampicin hypersensitivity typically presents with fever, rash, gastrointestinal symptoms, and liver enzyme elevations, usually emerging after 7–10 days of therapy and resolving upon discontinuation (Yilmaz et al., 2018; Vodovar et al., 2014). Definitive diagnosis relies on drug provocation, but due to the risk of severe systemic reactions, re-exposure should be avoided outside controlled desensitization protocols.

Table I. Laboratory investigations during outpatient follow-up, hospitalization, and after discharge

	Day 1	Day 4	Day 14	Day 16	Day 18	Day 20	Day 33	6 week
Hb (g/dL)	11.7	12	13.4	12.8	-	13.3	12.5	13.3
WBC ($\times 10^3/\mu L$)	7.9	8	5.42	5.75	-	8.45	4.09	5.37
ANC ($\times 10^3/\mu L$)	4.01	3.87	3.57	2.08	-	4.37	2.01	2.17
ALC ($\times 10^3/\mu L$)	3.23	3.4	1.49	2.6	-	2.54	1.44	2.59
PLT ($\times 10^3/\mu L$)	257	310	153	181	-	295	295	298
Eosinophil %	-	0.3	2.7	12	-	9.1	4.4	2.8
ESR	61	29	17	-	-	8	28	8
Procalcitonin	-	-	8.6	2.9	1.2	0.23	0.03	-
CRP (mg/L)	6	7.8	139	42	17	4.7	2	2
Agglutination titer	1/320	-	1/320	-	-	1/320	1/640	1/320
AST	26	26	81	-	-	40	39	22

C-reactive protein (CRP), white blood cell (WBC), hemoglobin (Hb), absolute lymphocyte count (ALC), absolute neutrophil count (ANC), platelet (plt), Erythrocyte sedimentation rate (ESR), AST: aspartate aminotransferase

In the present case, the development of fever, vomiting, pruritus, conjunctivitis, eosinophilia, and elevated transaminases during the second week of rifampicin therapy, followed by the rapid recurrence of symptoms upon drug rechallenge, strongly suggested rifampicin hypersensitivity. The rapid normalization of clinical and laboratory parameters after discontinuation of rifampicin further reinforced the diagnosis in our patient. The fact that doxycycline was tolerated without any adverse effects for the remainder of the treatment further strengthens the causal relationship between rifampicin exposure and the observed hypersensitivity reaction.

In the absence of rifampicin, alternative regimens include doxycycline with aminoglycosides such as gentamicin or streptomycin, which have demonstrated effectiveness in children (Yilmaz et al., 2018; Maletskaia et al., 2002; Abramson et al., 1997). When rifampicin hypersensitivity is suspected, a definitive diagnosis can be established through a drug provocation test; however, such testing may be hazardous in the setting of severe systemic manifestations, particularly if the patient has experienced anaphylaxis or other serious reactions in the past.

For this reason, re-exposure is generally discouraged unless desensitization is undertaken in a controlled setting by pediatric allergy specialists. In our patient, rifampicin was permanently withdrawn, and therapy was successfully continued with doxycycline in combination with gentamicin. This regimen has been reported as an effective alternative, particularly in patients unable to tolerate rifampicin or in cases of resistant disease (Yilmaz et al., 2018). Clinical improvement was promptly achieved under this regimen.

In summary, this case highlights that rifampicin—an essential first-line agent in the treatment of pediatric brucellosis—can rarely provoke serious hypersensitivity reactions. Such adverse events may mimic disease relapse or complications, potentially confounding the clinical picture. Consequently, in pediatric patients receiving rifampicin who exhibit unanticipated clinical deterioration, drug hypersensitivity should be contemplated alongside infection progression and relapse in the differential diagnosis.

Although hypersensitivity to trimethoprim–sulfamethoxazole has been reported in pediatric brucellosis, to our knowledge, based on a PubMed/Medline search using the keywords ‘brucellosis’, ‘rifampicin’, ‘hypersensitivity’, and ‘child/pediatric’, there are no previously reported pediatric cases **(**Teker et al., 2014).

Our case, therefore, represents a novel observation and emphasizes the importance of considering drug allergy when evaluating treatment failure or relapse**.**

CONCLUSION

This case highlights the difficulties in diagnosing and treating pediatric brucellosis that are exacerbated by rifampicin hypersensitivity. Despite serological fluctuations and adverse drug reactions, the patient achieved clinical stabilization with an alternative antibiotic regimen. In endemic regions, when pediatric brucellosis patients under rifampicin develop unexplained fever or relapse-like symptoms, clinicians should also consider drug hypersensitivity.

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