



Doxycycline Associated Hyperpigmentation of The Tongue

Doksisiklin ilişkili Dilde Hiperpigmentasyon

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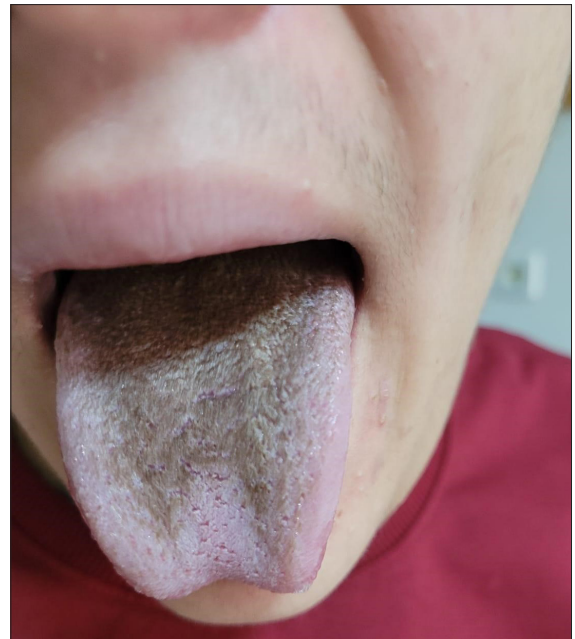
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Introduction

Brucellosis is widely prevalent all over the world and is still an important public health problem (1). Human brucellosis continues to be the most common zoonotic disease worldwide with more than 500.000 new cases annually (2). Türkiye is one of the countries where brucellosis is endemic. It is transmitted to humans through direct contact with secretions of infected animals and consumption of unpasteurized milk and dairy products (3). Brucellosis is a multisystemic disease that usually manifests itself with non-specific symptoms such as malaise, weight loss, fever, chills and joint pain (4). Combination therapy is used to reduce the risk of relapse and recurrence. The Centers for Disease Control and Prevention recommends the use of doxycycline and rifampicin for six weeks. If tetracyclines are contraindicated, combination therapy with trimethoprim-sulfamethoxazole can be employed (2). Doxycycline may cause diffuse skin hyperpigmentation (brown, bluish gray, black discoloration) in nails, hands, arms, legs, back of the feet, inside the mouth and around the lips (5). In this study, it was aimed to report a case of hyperpigmentation of the tongue due to doxycycline use during brucellosis treatment.

Case Report

A 16-year-old male patient with no previously known disease presented to our center with complaints of low back and



hip pain, intermittent fever and night sweats that had been lasting for three months. His medical history was unremarkable. His family was engaged in animal husbandry. There were no additional features in his family history. Physical examination revealed tenderness on deep palpation in the lumbar region, while other system examinations were normal. Blood

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tests revealed C-reactive protein= 38.7 mg/L, leukocyte= 5620/mm³, neutrophil= 1900/mm³, hemoglobin= 15.5 g/dL, platelet= 288000/mm³; other routine biochemical laboratory tests yielded normal results. No atypical cells or blasts were observed in peripheral smear. Brucella serum tube agglutination test was positive at 1/1280. Blood culture was negative. Hip and lumbar magnetic resonance imaging was reported to be normal. Oral doxycycline (4 mg/kg/day) and rifampicin (20 mg/kg/day) treatments were commenced upon diagnosis of brucellosis. On the 12th day of treatment, patient presented with a complaint of darkening of the tongue. There was no hyperpigmentation on other parts of the body including the skin and nails. Hemogram and routine biochemical tests were unremarkable. Doxycycline treatment was discontinued on the 12th day. Rifampicin treatment was continued and trimethoprim sulfamethoxazole (oral, 10 mg/kg/day, as per trimethoprim) was added to the treatment. Hospitalization was not considered, and outpatient follow-up was planned. Darkening of the tongue completely resolved nine days after discontinuation of doxycycline. Complete brucellosis treatment was continued for six weeks. Patient experienced no additional complaints in the subsequent periodic follow-up visits within the next six months.

Discussion

The goal of brucellosis treatment centers on controlling the disease and preventing complications, relapses, sequelae and mortality (6). The general principles of treatment strategies include the use of antibiotics that exhibit activity in acidic intracellular environments (such as doxycycline and rifampicin), use of combination therapy (given the high relapse rates with monotherapy) and prolongation of treatment duration (7). Drug-induced hyperpigmentation has been associated with various drug classes. Several antibiotics including doxycycline, erythromycin, amoxicillin-clavulanate, metronidazole and piperacillin-tazobactam have been reported to cause hyperpigmentation of the tongue. Clinical presentation of lingual hyperpigmentation is highly varied, with most cases being asymptomatic but aesthetically disturbing to patients. Its prevalence changes with geographical variation and ranges from 0.6% to 11.3%. Time of onset may range from a few weeks to five weeks. Diagnosis is based on clinical evaluation with a thorough patient history and physical examination. Absolute treatment remains uncertain, although the condition usually improves with identification and removal of the causative agent and adequate oral hygiene. Complications are rare and the prognosis is favorable (8).

Hyperpigmentation of the skin, nails, thyroid, oral mucosa, teeth and bones is a well-documented but rare side effect of long-term tetracycline exposure. There is no clear duration of use for the development of hyperpigmentation, though the risk increases with prolonged drug use (9). It develops within

days in some patients, whereas in others, the condition may last years to manifest itself. There may also be permanent changes in the skin after discontinuation of medication. For this reason, the duration of tetracycline use should be minimized, and patients be monitored for any possible skin findings (10). A study involving 18 patients aged between 11 and 87 years reported that the most common sites of involvement were the areas between the fingers, face, old acne scars, extremities and dorsum of the hands and feet. Skin darkening was observed as early as two days or as long as 144 months from the time doxycycline treatment was commenced. Doxycycline therapy was discontinued in most patients. Two pediatric patients (aged 11 and 17 years) were reported to have received doxycycline at a dose of 200 mg. The pediatric patients developed hyperpigmentation on days 15 and 20 after drug initiation. Hyperpigmentation occurred on the nails of both patients and on the thumb of one patient. In both patients, hyperpigmentation resolved within one month after discontinuation of doxycycline (10). In another case series, four patients with cutaneous hyperpigmentation due to therapeutic doses of doxycycline treatment were described. After discontinuation of treatment, hyperpigmentation decreased. The importance of identifying hyperpigmentation and timely discontinuation of treatment was emphasized (11). In our case, hyperpigmentation developed in a shorter period of time, and it resolved after discontinuation of the medication.

In conclusion, the need for doxycycline use is frequent in countries like Türkiye where brucellosis is endemic. It is important to monitor and evaluate patients in terms of possible complications.

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