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Case Report

Freiberg's Infraction in the Context of Systemic Lupus Erythematosus

Dilara Bulut Gökten [1,*], Rıdvan Mercan [1]

[1] Department of Rheumatology, Tekirdag Namik Kemal University, Tekirdağ, Turkey.

* Correspondence: dilarabulutgokten@gmail.com.

Abstract: Freiberg disease is a rare but clinically significant form of osteonecrosis that can affect the heads of all metatarsal bones, with a particular tendency to involve the second metatarsal. This disease was first identified in 1914, when Alfred Freiberg reported cases of infraction in the second metatarsal head. Several mechanisms have been proposed to explain the cause of the disease, with the most widely accepted being microtrauma, vascular insufficiency, and systemic diseases. Systemic lupus erythematosus (SLE), diabetes mellitus and hypercoagulability are the diseases most frequently cited as contributing to Freiberg's disease. This report discussed two female patients diagnosed with SLE and presented with pain and swelling in feet, following clinical examination and radiographic evaluation, the patients were diagnosed with Freiberg disease. An orthopedist was consulted, and a multidisciplinary treatment approach was prescribed. Following the treatment regimens, both patients are being stably followed up in our clinic. SLE is a complex autoimmune disease that can affect multiple organs. The disease course is often heterogeneous, and even in the same patient, it can vary over time. Bone tissue may be impacted, leading to conditions such as osteonecrosis. Among the osteonecroses associated with SLE, no studies specifically addressing Freiberg's disease have been found in the literature. This case differs from those in the literature as it specifically describes Freiberg infarction in two patients diagnosed with SLE. Freiberg disease remains a condition with an unclear pathogenesis. This rare condition can complicate the course of systemic diseases and diminish patients' quality of life. Early recognition by clinicians and ongoing monitoring may help slow disease progression.

Keywords: Freiberg disease; Systemic lupus erythematosus; Freiberg infraction.

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1. Introduction

Freiberg disease is a rare but clinically significant form of osteonecrosis that can affect the heads of all metatarsal bones, with a particular tendency to involve the second metatarsal [1]. This disease was first identified in 1914, when Alfred Freiberg reported six cases of infraction in the second metatarsal head [2]. Osteonecrosis in this bone leads to flattening and collapse as the disease progresses. Degenerative changes in the metatarsophalangeal joint further complicate the condition, and patients typically present with symptoms resembling arthritis [3]. While the second metatarsal bone is most affected (68%), the disease can involve any of the five metatarsal heads, including the third metatarsal (27%) and, less frequently, the fourth metatarsal (3%) [4].

Several mechanisms have been proposed to explain the cause of the disease, with the most widely accepted being microtrauma, vascular insufficiency, and systemic diseases [5]. Systemic lupus erythematosus (SLE), diabetes mellitus (DM), and conditions associated with hypercoagulability are the diseases most frequently cited in the literature as

contributing to Freiberg's disease. The condition predominantly affects women, with a female-to-male ratio of 5:1. It is most observed in adolescents aged 11 to 17, a period characterized by rapid bone growth [4].

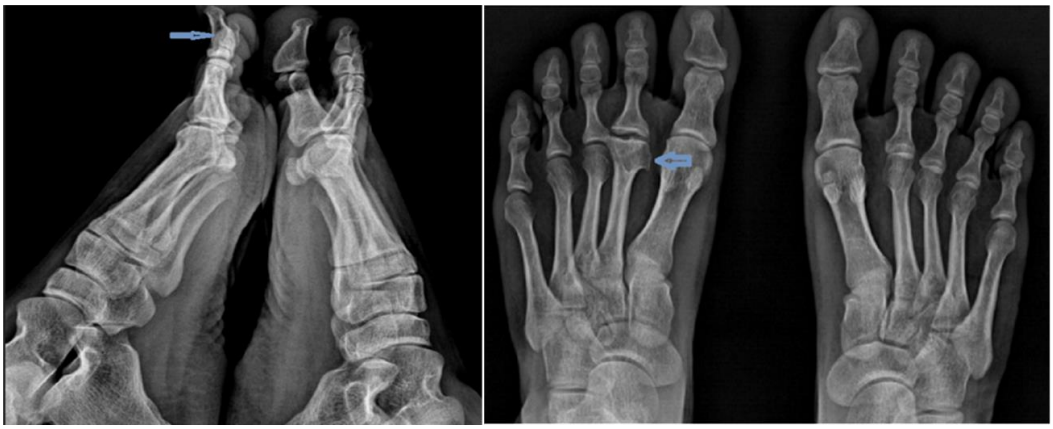
The diagnosis of the disease is based on the patient's medical history, physical examination findings, and radiographic changes, including joint space widening, which can typically be detected three weeks after symptom onset [6]. Clinically, this condition may present with pain, varying degrees of swelling, tenderness in the affected area, and a sensation of walking on a hard surface. Non-operative treatment approaches focus on alleviating symptoms and minimizing metatarsal head deformation. These methods include joint immobilization, shoe modifications, and pain management techniques, but they are only effective in the early stages of the disease. As the condition progresses, surgical interventions become crucial, with the choice of joint-preserving or joint-replacement approaches depending on the severity of the disease [7].

This report will discuss two female patients diagnosed with SLE who were followed in the rheumatology outpatient clinic and presented with pain and swelling in their feet.

2. Case Report

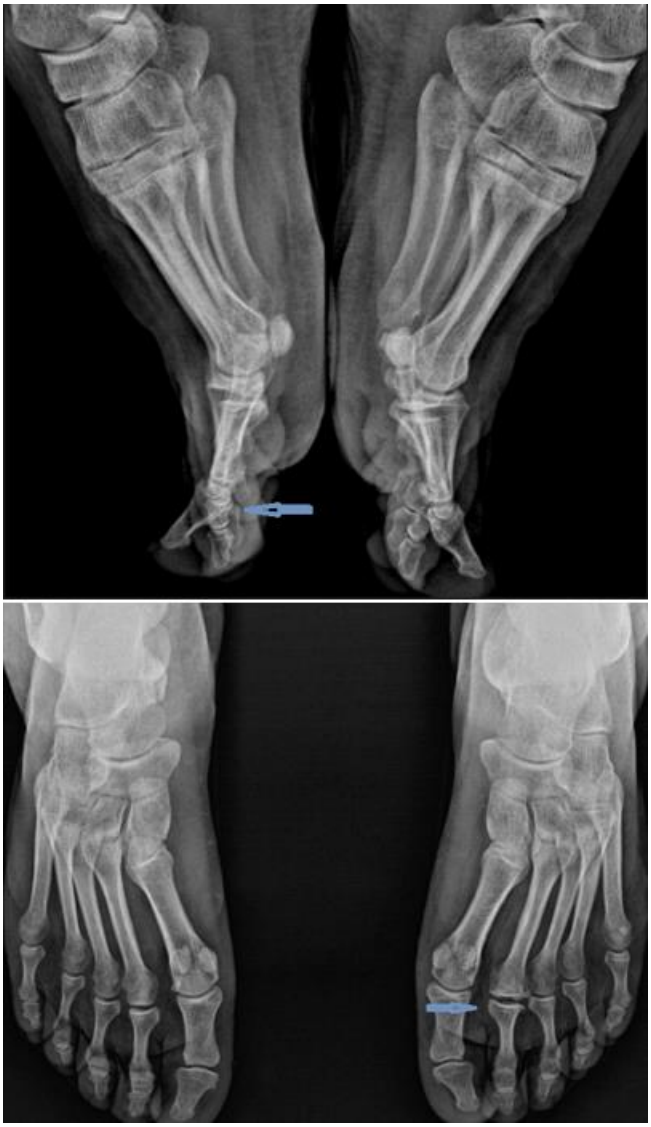
Two female patients, aged 22 and 33, had been followed for three and seven years, respectively, with a diagnosis of SLE based on the 2019 EULAR/ACR classification criteria [8]. Both were diagnosed due to the presence of SLE-specific and antiphospholipid antibodies, low complement levels, and other clinical features, including skin lesions, oral ulcers, pleural and pericardial effusions, and alopecia. Neither had accompanying diseases or relevant family history. The 22-year-old, managed with hydroxychloroquine and acetylsalicylic acid (ASA), presented with right foot pain lasting three months, initially suspected to be SLE-related arthritis or arthralgia. Examination revealed swelling and tenderness around the metatarsal, and X-ray findings showed collapse of the second dorsal metatarsal head, with the plantar articular portion remaining intact, consistent with Freiberg's disease (see Figure 1).

Figure 1. X-ray results revealed collapse of the second dorsal metatarsal head, with the plantar articular portion intact, consistent with stage two Freiberg's disease and areas of infraction in our 22-year-old female patient diagnosed with SLE. Blue arrows indicate areas of infarction.



Similarly, a 33-year-old patient, treated with hydroxychloroquine, corticosteroids, ASA, and mycophenolate mofetil, reported experiencing pain and stiffness in the metatarsal area during walking, which negatively affected her gait during routine check-ups. Plain radiographs showed the collapse of the second dorsal metatarsal head, with the plantar articular portion intact, consistent with Freiberg's disease (see Figure 2).

Figure 2. Plain radiographs showed collapse of the second dorsal metatarsal head, with the plantar articular portion intact, consistent with stage two Freiberg's disease and areas of infraction in our 33-year-old female patient diagnosed with SLE. Blue arrows indicate areas of infarction.



After the diagnosis, an orthopedist was consulted regarding the treatment of the patients. Given the first patient's young age and relatively short-term and mild clinical complaints, a symptomatic treatment plan was established for the 22-year-old. She was prescribed non-steroidal anti-inflammatory drugs (NSAIDs) both orally and locally. Over two years of follow-up, her symptoms have regressed, with no complications or recurrences observed. The second patient experienced significant walking difficulties due to severe pain while stepping. After consulting with an orthopedist, surgical treatment was deemed more appropriate, and surgery was recommended. The patient underwent a shortening metatarsal osteotomy, which was performed without complications. Postoperatively, the patient's pain subsided. In addition to the surgery, symptomatic NSAID treatment was provided. The patient has been followed up stably for about a year, with no recurrence observed.

3. Discussion and conclusions

Freiberg disease is a rare condition that can lead to complications significantly impacting patients' quality of life and daily activities [9]. Changes in foot mechanics and

inadequate blood flow contribute to the development of disease. The occurrence of the disease in identical twins suggests that a genetic component may also play a role [10]. It is the only type of osteochondrosis that is more common in women and is characterized by epiphyseal damage and irregularities of the joint surface, affecting endochondral ossification. When examining the pathological origins of general articular osteochondrosis, three stages are defined: in the first stage, intra-articular and periarticular soft tissues become swollen; in the second stage, irregularities develop at the epiphyseal margins; and in the final stage, necrotic tissue replaces healthy tissue [11]. Irregularities were observed at the edges of the epiphysis in the described cases, along with swelling in the surrounding soft tissues.

Throughout the course of the disease, pain intensifies with walking, and discomfort is particularly noted when barefoot or wearing high-heeled shoes. Physical examination reveals swelling in the affected toe, especially around the metatarsophalangeal joint [9]. In chronic and advanced stages, malalignment in the coronal or sagittal planes, hammer toes, decreased joint range of motion, and crepitations may be observed. Although swelling and pain were present in the affected area of the first case, there was no loss of function. However, in the second patient, gait disturbance developed, and her symptoms were more severe compared to the first.

Radiography is primarily used for diagnosing disease. In the early stages, widening of the joint space is observed; however, as the disease progresses, bone density increases in the subchondral region, and flattening occurs in the metatarsal head area. Oblique radiographs may also be preferred in mild cases. In the final stages, arthrosis is evident, characterized by depression in the joint center, loose bodies, sclerosis around the bone, narrowing of the joint space, and reactive thickening of the metatarsal body. The disease can also be staged radiographically. In addition to radiography, magnetic resonance imaging (MRI) is important; MRI can reveal signal changes resembling bone marrow edema in the affected metatarsal head area [12].

Conservative management is effective in the first stage of disease treatment. To minimize the need for surgery, load and pressure on the joint are reduced using NSAIDs, braces, and orthotic interventions. Early recognition of the disease and implementation of measures to reduce deformity are crucial, as they increase the likelihood of successful intervention. Surgical procedures can alter the anatomical structure and disrupt blood flow, leading to increased necrosis [13]. For this reason, although evidence regarding their success is limited, surgical interventions are reserved for cases with persistent pain, deformity, and disease progression [14]. Cases of early spontaneous recovery have also been reported in the literature. In the described cases, a mutual decision was made in consultation with the orthopedist to initiate symptomatic treatment, with further actions planned based on disease progression.

SLE is a complex autoimmune disease that can affect multiple organs. The disease course is highly heterogeneous, and it may vary over time, even in the same patient. Bone tissue can be affected by conditions such as osteoporosis and osteonecrosis, both of which are independent of the autoimmune pathophysiology of SLE. There are a limited number of studies in the literature addressing osteonecrosis that can occur during SLE. In the review article by Caramaschi et al., the frequency of osteonecrosis in SLE was reported to range from 2% to 30%, with the knee joint being the most affected [15]. In another study involving 72 SLE patients, osteonecrosis was detected on MRI in 44% (32 patients) of those receiving corticosteroids. In most cases, the condition was multifocal and occurred shortly after the initiation of corticosteroid therapy (within 1-2 months). The knee was identified as the primary joint affected by the osteonecrosis process in these cases as well [16].

In the cases described in the literature, osteonecrosis associated with SLE often involves multiple joints. In fact, 12 osteonecrotic lesions were identified in a single SLE case. While the most affected joints are the long bones, osteonecrosis can also involve the sternum, ilium, and vertebral bodies [17]. For this reason, when osteonecrosis is observed in one region in SLE patients, it is recommended to investigate other areas, as multifocal

involvement is frequently seen. A review of osteonecrosis cases reported during SLE indicates that symptomatic progression of lesions detected on MRI but remaining clinically silent is rare. In a prospective study following SLE patients receiving corticosteroids over three years, only 25% of those with MRI-detected avascular necrosis of the femoral head reported clinical symptoms [18]. In a study of 500 patients, 19 were reported to have undergone at least one joint replacement, and it was noted that most of these individuals had a course of SLE accompanied by rheumatoid arthritis (RA) [19].

The pathogenesis of non-traumatic osteonecrosis during SLE has not yet been fully elucidated. Proposed mechanisms include both intraluminal and extraluminal obliterations [20]. Intraluminal occlusion is thought to result from systemic inflammation and hyperlipidemia associated with SLE, fat emboli, glucocorticoid treatments, and the intravascular release of nitrogen gas bubbles following thrombosis. In a study by Glueck et al., it was reported that patients with osteonecrosis exhibited hypofibrinolytic 4G polymorphism of the plasminogen activator inhibitor-1 gene, a methylenetetrahydrofolate reductase gene mutation with elevated homocysteine levels, low protein S values, and elevated lipoprotein (a) levels compared to the control group [21]. Extraluminal obliteration is thought to occur due to increased pressure in the bone marrow, loss of bone elasticity, and decreased intraosseous blood flow. One proposed cause of this condition is bone marrow adipocyte hypertrophy, which develops following chronic glucocorticoid use [22]. In addition to these mechanisms, the literature indicates that thrombophilia's associated with antiphospholipid antibodies during the disease also disrupt blood flow [23]. The patients in this case were also positive for antiphospholipid antibodies, consistent with data from the literature. In the second case, corticosteroid use was an additional risk factor. Among the osteonecrosis associated with SLE, no studies specifically addressing Freiberg's disease have been found in the literature. This case differs from those in the literature as it specifically describes Freiberg infarction in two patients diagnosed with SLE.

In conclusion, Freiberg disease, though rare and with an unclear pathogenesis, should be considered in the differential diagnosis of patients presenting with unexplained foot pain, particularly in those with underlying conditions such as SLE. Early recognition is crucial, as timely diagnosis and intervention can prevent disease progression and preserve joint function. Clinicians should maintain a high index of suspicion for Freiberg disease in patients with persistent metatarsal pain, especially when accompanied by swelling or tenderness, and initiate appropriate imaging studies, including X-rays and MRI, to detect early-stage osteonecrosis. Multidisciplinary management, involving both rheumatologists and orthopedists, can help guide treatment decisions and improve patient outcomes. Prompt referral and the use of non-operative treatments in early stages may delay or avoid the need for surgical intervention.

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