Avascular Necrosis of the Foot and Ankle in a Patient with Systemic Sclerosis: A Case Based Review

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This review describes a case of atraumatic avascular necrosis in the foot and ankle in a patient with systemic sclerosis who did not receive corticosteroid therapy. Both avascular necrosis and systemic sclerosis are uncommon disease entities. This case demonstrates that vasculitis and secondary vasoconstriction in the pathogenesis of systemic sclerosis are important risk factors for the development of avascular necrosis of the foot and ankle. Therefore, if these patients develop chronic foot and ankle pain, avascular necrosis should be included in the differential diagnosis, even if they do not receive corticosteroids. For the diagnosis and follow-up of avascular necrosis MRI remains the gold standard. Thus, MRI should be used to diagnose avascular necrosis in an early stage.
Level of Clinical Evidence: 4.

***Key words:** Osteonecrosis; Scleroderma, Systemic; Tomography; Magnetic Resonance Imaging.*
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Introduction

Systemic sclerosis (SSc) is an autoimmune rheumatic disease characterized by fibrosis of the skin and internal organs due to excessive collagen production and vasculitis of small arteries. The prevalence of SSc is estimated between 3 and 24 cases per 100,000 people [1]. Female gender and African origin are risk factors for SSc [1].

Avascular necrosis (AVN) or osteonecrosis is bone death due to the disturbance of the vascular supply to the bone [2]. The incidence of AVN is approximately 3/100,000 [3], of which 3% involves the foot or ankle, whereas the hip is involved in 75.9% of cases [4]. AVN is often caused by a traumatic event but can also have an atraumatic cause such as the use of corticosteroids, alcoholism, hyperlipidemia, hemoglobinopathies/thrombophilia or diabetes mellitus.

As the treatment of systemic causes often includes corticosteroids, determining the exact cause can prove to be challenging. We present a case in which SSc can be identified as the causal factor in AVN since the patient did not receive any treatment with corticosteroids or had other concurrent pathology that may induce AVN.

Case Report

A 67-year-old woman complained of invalidating pain in the left foot that started spontaneously one year ago. She had a history of peripheral polyneuropathy, abdominal pain, acrosclerosis and pulmonary hypertension in the context of systemic sclerosis. She was treated with pulmonary vasodilators (macitentan, tadalafil), asaflow, bumetanide (Burinex), spironolactone, rosuvastatin and analgesics. She had not previously received any glucocorticoids.

On examination there was a pronounced swelling of both the ankle and the foot. The alignment was neutral, but weight bearing was not possible. There were inflammatory signs of dolor and calor, but no erythema. The functional assessment was limited due to pain. Palpation showed pronounced non-specific tenderness. The neurovascular examination showed limited hyporeflexia and mild deep sensory disturbance without clearly abnormal electromyogram.

Previous radiographs showed no other structural abnormalities but mild osteopenia and limited subchondral sclerosis (Fig. 1A). A Tc-99m HDP bone scintigraphy one month after the onset of the symptoms (one year before consultation) showed a hot spot in the talus, which was interpreted as a stress fracture (Fig. 2A). Supportive treatment with a walker boot provided initial symptom relief. However, due to ongoing discomfort 6 months later, a new bone scintigraphy was performed, which showed an active arthropathy mainly in the calcaneocuboid and subtalar joints (Fig. 2B). Finally, an additional MRI was performed seven months after the radiographs, which showed extensive AVN of different bones in the hind-, mid- and forefoot and of the tibia (Fig. 1B; Fig. 1C).

Maximum conservative treatment was opted for with limited weightbearing, a walking boot and pain medication. One year after the onset of the symptoms, the mobility and function of the joints is intact, and she has weaned off the walking boot.

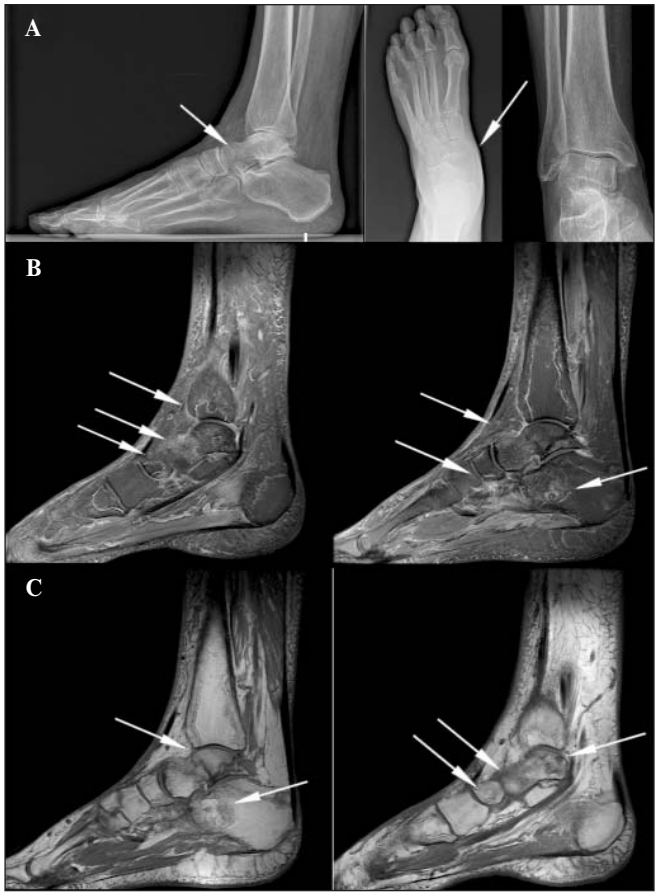

Fig. 1. *Radiographic and MRI Images of the Left Foot and Ankle. (A) Lateral and Anteroposterior Radiographic Images of the Left Foot and Ankle: the arrows indicate areas of limited osteopenia and subchondral sclerosis, which corresponds to stage II of avascular necrosis. (B) Sagittal T2-Weighted MRI Images and (C) Sagittal T1-Weighted MRI Images of the Left Foot and Ankle with arrows indicating extensive avascular necrosis of the hind-, mid- and base of the forefoot and the tibia, corresponding to stage II/III of AVN*

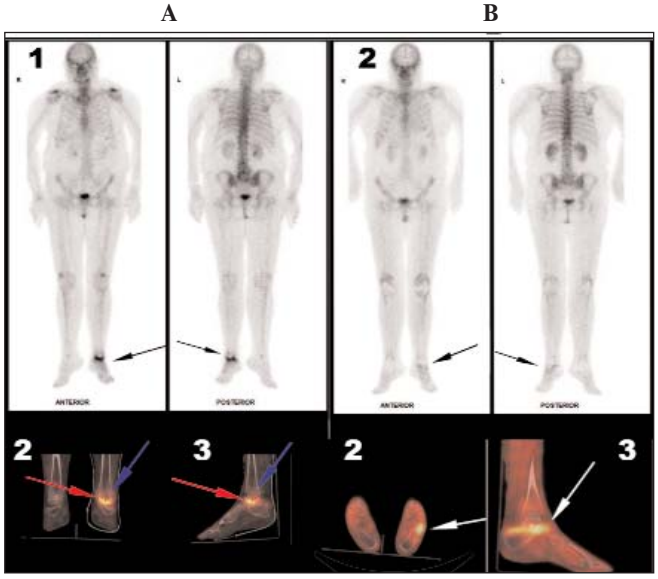

Fig. 2. *Three-phase HDP-99m bone scintigraphy. (A) One month after the onset of atraumatic pain in the left ankle, possibly corresponding to stage II/III of avascular necrosis. (1) Whole body scintigraphy showing increased bone turnover of the left ankle (black arrows). (2) Coronal and (3) sagittal SPECT/CT reconstructions of the feet in the same patient showing a hot spot (red arrows) in the base of the talus, and a relatively colder zone (blue arrows) in the cranial pole of the talus. (B) 18 months after the onset of atraumatic pain in the left ankle, possibly corresponding to a late phase of avascular necrosis. (1) Whole body scintigraphy no longer showing increased bone turnover of the left ankle (black arrows). (2) Transverse and (3) sagittal SPECT/CT reconstructions of the feet in the same patient showing active calcaneocuboid (2) and subtalar (3) arthropathy (white arrows), characterized by degenerative changes of the joints involved in the disease process*

Discussion

This case highlights the importance of considering AVN in the differential diagnosis in patients with chronic foot and ankle pain. AVN is caused by a disruption of the blood flow to the bone. This can be caused by a variety of processes including traumatic or compressive arterial inflow disruption, venous outflow obstruction or intraluminal vascular occlusion [2]. Trauma is a frequent cause of AVN in the femoral head, humeral head, scaphoid and talus. Besides trauma, AVN can also have an atraumatic cause such as the use of corticosteroids, alcoholism, hyperlipidemia, hemoglobinopathy/thrombophilia, diabetes mellitus or irradiation. If there is a systemic cause, such as systemic lupus erythematosus (SLE), multifocal infarctions of the foot and ankle can occur [2, 5, 6]. There are several case reports that describe an association between SSc and AVN, which is most commonly observed in the hip [7–9] and lunate bone [10–12]. However, only two cases of SSc with AVN of the foot are briefly mentioned in literature [13, 14]. In both cases, the talus was affected. In one of these cases multiple joints were affected, namely both hips and both taluses, and the patient never received any corticosteroids either [13]. In the second case, no specific information was given about concurrent AVN in other bones of the foot or other joints, on the use of corticosteroids or on the use of MRI for the diagnosis of AVN [14].

In systemic sclerosis (SSc), the characteristic changes in blood vessels are well known and are caused by three separate processes [15]. First, autoantibodies are produced, and cell-mediated autoimmunity is activated by abnormalities in the innate and adaptive immune system. Second, defective endothelial cells and fibroproliferative vasculopathy of small blood vessels develop. The damage to the endothelial cells leads to vasoconstriction (influenced by endothelin) and to obliteration of the micro-and macrovasculature. Finally, because of fibrogenic characteristics of endothelin and the abnormal fibroblast growth, qualitatively normal collagen is excessively produced. These three mechanisms affect all blood vessels in the body. For instance, vasculitis induced vasoconstriction can cause pulmonary hypertension and abdominal angina. Both the macro- and microvascular effects of vasculitis could be the cause of sporadic occurrence of AVN in SSc, similarly to the pathogenesis of acral osteolysis in SSc. Treatment with corticosteroids is also a known risk factor for developing AVN, but vasculitis itself and vasoconstriction are separate risk factors for AVN development and play an important role in its pathogenesis. Therefore, the

Table 1. Imaging Features of Different Stages of Avascular Necrosis

Stage	Symptoms	RX / CT	MRI	Bone scintigraphy
0	None	Normal	Bone marrow edema	Cold spot
I	Pain on weight support	Osteopenia	Osteosclerosis (double-line sign)	Hot spot surrounding cold spot
II	Continuous pain	Osteopenia, osteosclerosis	Osteosclerosis (double-line sign)	Hot spot surrounding cold spot
III	Irradiating pain	Bone collapse	Bone collapse	Hot spot
IV	Severe pain	Bone collapse, joint destruction	Bone collapse, joint destruction	Bone collapse (CT)

diagnosis of AVN should also be considered in patients with SSc who are not receiving corticosteroids.

In atraumatic AVN, vasculopathy disrupts the blood flow to the bone and causes oxygen deprivation in the bone tissue (stage 0). The affected bone attempts to repair itself via reossification, revascularization and resorption of necrotic bone (stage I-II). In severe cases the bone can collapse which causes severe pain and inability to use the affected joint (stage III). The collapsed bone often results in damage the cartilage surface and causes osteoarthritis in the long term (stage IV). The time between the onset of the first symptoms and bone collapse can take several months to over a year. The processes of reossification and resorption in the bones affected by AVN can be visualized using different medical imaging techniques: radiography, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)(2). The different stages of AVN and their corresponding findings on clinical examination, radiography/CT, MRI and Tc-99m HDP bone scintigraphy with Single Photon Emission Computed Tomography (SPECT) are summarized in Table 1.

AVN appears similarly on radiography and CT. In stage 0 of AVN, radiography and CT will not show any abnormalities of the affected bones. This time lag between the vascular insult and visible radiographic manifestations mirrors the underlying pathophysiology. The interruption of the blood supply induces hyperemia in the portions of the bone that are still perfused. This results in resorption of healthy bone and causes a relative osteopenia. As the bone is further resorbed, the contrast with the remaining necrotic bone increases. In stage I and II, the necrotic bone appears sclerotic since it cannot be reabsorbed anymore due to the lack of perfusion. Nevertheless, during reossification, new bone is laid down over the necrotic trabeculae which leads to further sclerosis and enlargement of the contrast with the healthy bone. Revascularization and resorption tend to occur around the area of osteonecrosis, which can result in a lucent rim around the necrotic bone. In stage III signs of bone collapse are visible and in stage IV changes towards osteoarthritis, such as joint space narrowing, sclerosis and osteophytosis, are visible.

While different stages of AVN can be recognized on CT, MRI is considered the gold standard for the radiographic diagnosis of AVN. Even in stage 0, early signs of AVN, namely bone marrow edema, can be detected, which is not possible using CT imaging. The bone marrow edema corresponds to a low intensity zone on T1-weighted images and to a high intensity zone on T2-weighted images. Histologically, bone marrow edema corresponds to ischemic death of hematopoietic cells, endothelial cells and lipocytes. This induces an elevated amount of extracellular fluid in the bone. Edema can be detected two weeks after the disruption of the blood supply. In stage I and II of AVN, MRI shows sclerosis of the bone, both on T1- and T2-weighted images. The double-line sign is described as a typical sign in these stages. It represents the necrotic bone and the viable granulation tissue as a low intensity edge and a high intensity center on T2-weighted images. The double-line sign is rarely observed in the foot and ankle and is more frequently observed in AVN of the humeral head and femur. Yet, in this patient the MRI of the foot does depict the double line sign. In stage III and IV of AVN, collapse of the bone and late changes in the affected joint are also clearly visible on MRI.

Another type of imaging that can be used to visualize different stages of AVN is bone scintigraphy where Tc-99m HDP uptake represents the zones of decreased, normal or increased bone turnover. Therefore, in stage 0 of AVN only a zone of decreased bone turnover will be visible, the so-called «cold spot». Nonetheless, this image is rarely captured. In stage I and II the cold spot is still visible, representing the necrotic bone, but is now surrounded by a zone of increased bone turnover, representing an attempt of the body to reconstruct the bone. In stage III the cold spot is no longer visible and is replaced by the zone of increased bone turnover. In stage IV the bone is deformed and there is no longer new bone formation. These imaging features for each stage of AVN have not yet been described in the foot.

In conclusion, AVN should be considered in the differential diagnosis of foot and ankle pain in a patient with SSc, even in the absence of corticosteroid therapy. MRI remains the gold standard to diagnose AVN.

Key points:

- Atraumatic avascular necrosis of the foot is a possible complication of systemic sclerosis.
- Avascular necrosis should be suspected in patients with systemic sclerosis who develop chronic joint pain.
- Literature suggests that vasculitis and vasoconstriction in systemic sclerosis play an important role in the pathogenesis of avascular necrosis.
- MRI is the gold standard for the radiographic diagnosis of AVN of the foot.

REFERENCES

1. Ranque B, Mouthon L. Geoepidemiology of systemic sclerosis. *Autoimmun Rev.* 2010 Mar;9(5):A311-8. doi: 10.1016/j.autrev.2009.11.003. Epub 2009 Nov 10.
2. Couturier S, Gold G. Imaging Features of Avascular Necrosis of the Foot and Ankle. *Foot Ankle Clin.* 2019 Mar;24(1):17-33. doi: 10.1016/j.fcl.2018.10.002. Epub 2018 Nov 26.
3. Cooper C, Steinbuch M, Stevenson R, et al. The epidemiology of osteonecrosis: Findings from the GPRD and THIN databases in the UK. *Osteoporos Int.* 2010 Apr; 21(4):569-77. doi: 10.1007/s00198-009-1003-1. Epub 2009 Jun 23.
4. Moon DK. Epidemiology, Cause, and Anatomy of Osteonecrosis of the Foot and Ankle. *Foot and Ankle Clinics.* Vol. 24. W.B. Saunders; 2019. P. 1-16.
5. Gontero RP, Bedoya ME, Benavente E, et al. Osteonecrosis in Systemic Lupus Erythematosus. *Reumatol Clin.* May-Jun 2015;11(3):151-5. doi: 10.1016/j.reuma.2014.05.005. Epub 2014 Nov 22.
6. Ekinci RMK, Balc S, Celik G, et al. Symptomatic multifocal avascular necrosis in an adolescent with neuropsychiatric systemic lupus erythematosus. *Reumatologia*. 2019; 57(3):182-7.
7. Wilde AH, Rodnan GP, Mankin HJ. Avascular necrosis of the femoral head in scleroderma. *Arthritis Rheum.* Jul-Aug 1970; 13(4):445-7. doi: 10.1002/art.1780130414.
8. Buslau M, Spitzenberger D. Unklare Hü ftschmerzen bei systemischer Sklerodermie: Osteonekrose. *Z Rheumatol.* 2013 Aug;72(6):601-5. doi: 10.1007/s00393-013-1152-7.
9. Shah AA, Wigley FM. Often Forgotten Manifestations of Systemic Sclerosis. *Rheum Dis Clin North Am.* 2008 Feb;34(1):221-38; ix. doi: 10.1016/j.rdc.2007.10.002.
10. Frerix M, Kröger K, Szalay G, et al. Is osteonecrosis of the lunate bone an underestimated feature of systemic sclerosis? A case series of nine patients and review of literature. *Semin Arthritis Rheum.* 2016 Feb;45(4):446-54. doi: 10.1016/j.semarthrit.2015.07.010. Epub 2015 Aug 4.
11. Zegarra-Mondragon S, Llop-Vilaltella M, Sifuentes-Giraldo WA, de la Puente Bujidos C. Osteonecrosis of the Lunate Associated With Systemic Sclerosis: Report of 4 Cases. *Reumatol Clin.* Sep-Oct 2019;15(5):e70-e71. doi: 10.1016/j.reuma.2017.10.010. Epub 2017 Dec 16.
12. Bruni C, Guiducci S, Bellando-Randone S, et al. Avascular bone necrosis: An underestimated complication of systemic sclerosis. *Semin Arthritis Rheum.* 2017 Aug;47(1):e3-e5. doi: 10.1016/j.semarthrit.2017.03.015. Epub 2017 Mar 21.
13. Fossaluzza V, Peressini A, De Vita S. Multifocal ischemic necrosis of bone in scleroderma. *Clin Rheumatol.* 1991 Mar;10(1): 95-7. doi: 10.1007/BF02208044.
14. Delanois RE, Mont MA, Yoon TR, et al. Atraumatic Osteonecrosis of the Talus. *J Bone Joint Surg Am.* 1998 Apr;80(4):529-36. doi: 10.2106/00004623-199804000-00009.
15. Pattanaik D, Brown M, Postlethwaite, Bradley C. Postlethwaite AE. Pathogenesis of systemic sclerosis. *Front Immunol.* 2015 Jun 8; 6:272. doi: 10.3389/fimmu.2015.00272. eCollection 2015.

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