CASE REPORT

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Failure of internal fixation for ankle joint Charcot neuroarthropathy with beta(2)-microglobulin amyloidosis: a case report

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ABSTRACT

Charcot neuroarthropathy (CN) is a serious diabetic complication with a poor prognosis and a high rate of misdiagnosis. Furthermore, beta(2)-microglobulin amyloidosis (Abeta2M) makes the diagnosis and therapy more difficult and complex. This case report highlights the pathophysiology, clinical evaluation, treatment, and prevention of the major diabetic complications associated with CN and Abeta2M that cause poor quality of life, limit the patient's ability to walk independently, and are directly or indirectly linked with a high risk for lower limb amputation. Ankle CN was discovered in a 36-year-old single female with a history of type 1 diabetes mellitus and diabetic nephropathy. We performed early internal fixation. However, because she lived alone and needed hemodialysis three times a week, wearing a brace and non-weight-bearing were extremely inconvenient. Furthermore, she did not experience any pain and only some edema; thus, she proceeded to bear weight ahead of schedule without authorization. Due to the premature weight-bearing and poor compliance, the patient suffered severe bone resorption and infection and eventually had to undergo amputation. Abeta2M was suggested by bone pathological sections. We present a case of failed internal fixation of ankle CN with Abeta2M, emphasizing the importance of social factors and postoperative management.

Keywords: Charcot neuroarthropathy, ankle fracture, diabetic nephropathy, beta(2)-microglobulin amyloidosis

Abbreviations:
CN: Charcot neuroarthropathy
Abeta2M: beta(2)-microglobulin amyloidosis
CT: computed tomography
ORIF: open reduction and internal fixation

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INTRODUCTION

Charcot neuroarthropathy (CN) is a chronic, progressive, and destructive arthropathy caused by long-term diabetes in the majority of patients. The clinical manifestations typically include a unilateral, localized, inflammatory reaction in a focal area of the foot or ankle with erythema, warmth, and swelling.[1] CN is frequently misdiagnosed as cellulitis, deep vein thrombosis, or osteomyelitis and causes further bony destruction, the development of neuroarthropathy, and an increased risk of complications.[2] Joint disorganization can be severe and irreversible in patients who present later in the disease course. Ulceration and infection are prevalent, wreaking havoc on life, and leading to amputation in some cases.[3]

Beta(2)-microglobulin amyloidosis (Abeta2M) is an important cause of morbidity in patients with chronic renal failure and those on dialysis. The precursor protein of the Abeta-2M-amyloid fibril is beta(2)-microglobulin (beta2M), and an elevated serum level is the main cause of Abeta2M in patients with kidney failure.[4]

We share a case of ankle CN combined with Abeta2M that has not been reported and speculate whether the two are associated.

CASE PRESENTATION

A 36-year-old single female with no history of trauma presented with a 15-day history of progressive right ankle swelling but little discomfort while walking. She had type 1 diabetes for 23-years and diabetic nephropathy with hemodialysis for 5 years.

A distal tibial fracture with concurrent fibular fracture and valgus malalignment were discovered in radiographs and computed tomography (CT) scans (Figs. 1 and 2). Deep vein ultrasound of both lower extremities indicated no obvious thrombosis. Table 1 lists the laboratory parameters. The beta2M level was 20,071.6 μg/L. According to the detailed examination results, infection and lower deep venous thrombosis were excluded. We performed open reduction and internal fixation (ORIF).

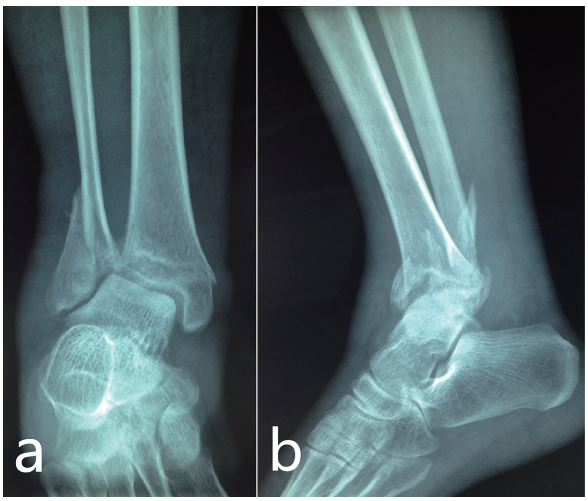

Fig. 1 A distal tibial fracture with a concomitant fibular fracture and valgus malalignment in preoperative radiographs

Fig. 1a: Anteroposterior radiograph
Fig. 1b: Lateral radiograph

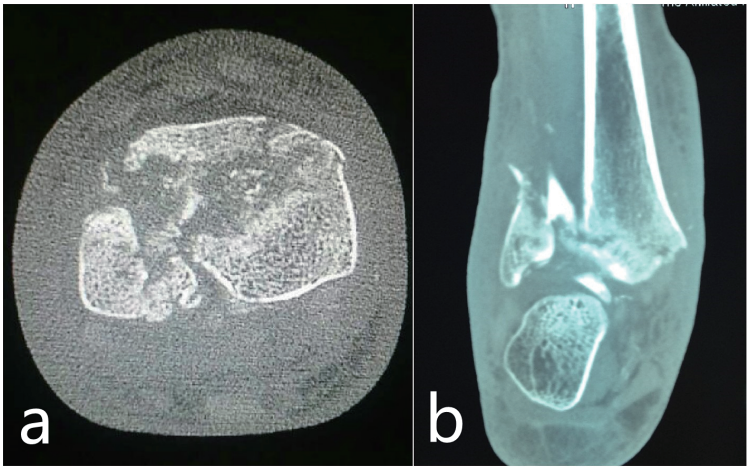

Fig. 2 Comminuted intraarticular fracture of the distal tibia with concurrent fibular fracture and valgus malalignment in preoperative CT sections
Fig. 2a: Axial CT section
Fig. 2b: Coronal CT section

Table 1 Laboratory parameters

Parameter	Result (normal range)	Unit	Parameter	Result (normal range)	Unit
beta2M	20071.6 (100.0–300.0)	ug/L	FPG	8.96 (3.89–6.11)	mmol/L
HbA1c	6.7 (4.0–6.3)	%	UA	493 (208–428)	μmol/L
Cre	203 (59–104)	μmol/L	AST	1004 (5–40)	U/L
BUN	23.4 (2.9–8.2)	mmol/L	ALT	1216 (10–42)	U/L
ALP	483 (40–150)	U/L	BNP	639.6 (0.0–100.0)	pg/mL
WBC	6.6 (3.5–9.5)	$10^{\wedge 9}$/L	CRP	<1.00 (1–8)	mg/L
Neutrophil	68.9 (50.0–70.0)	%	RBC	3.32 (3.68–5.13)	$10^{\wedge 12}$/L
Lymphocyte	18.2 (20.0–40.0)		PLT	243 (125–350)	$10^{\wedge 9}$/L
Monocyte	9.9 (3.0–10.0)		Hb	96 (130–175)	g/L
Eosinophil	2.6 (0.5–5.0)		Blood culture	Neg	
Basophil	0.4 (0.0–1.0)				

beta2M: beta(2)-microglobulin
BUN: blood urea nitrogen
ALP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
Cre: creatinine
BNP: brain natriuretic peptide
FPG: fasting plasma glucose
UA: uric acid
HbA1c: glycated hemoglobin
WBC: white blood cells
PLT: platelets
Hb: hemoglobin

The postoperative radiographs (Fig. 3) revealed almost anatomic restoration of the articular surface and corrected limb alignment. The patient was discharged with an ankle brace after the incision healed well and she was told not to bear weight on the leg for 3 months.

Follow-up radiographs 3 months after ORIF showed separation of the inferior tibiofibular syndesmosis, articular surface subsidence of the distal tibia, and a periosteal reaction (Fig. 4). The patient confirmed that she had started to load-bear walk less than 2 months after ORIF. Because

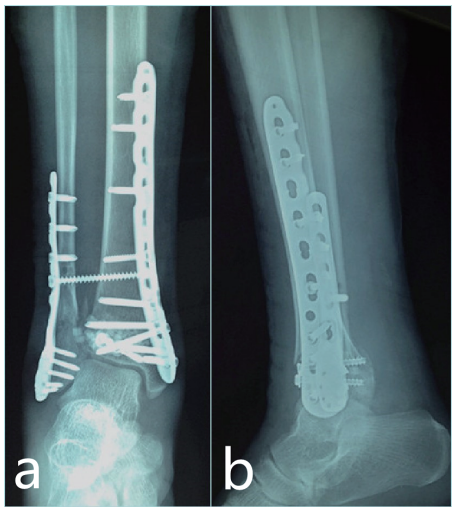

Fig. 3 Radiographs taken the day following ORIF (open reduction and internal fixation) reveal near-anatomic repair of the articular surface as well as corrected limb alignment
Fig. 3a: Anteroposterior radiograph
Fig. 3b: Lateral radiograph

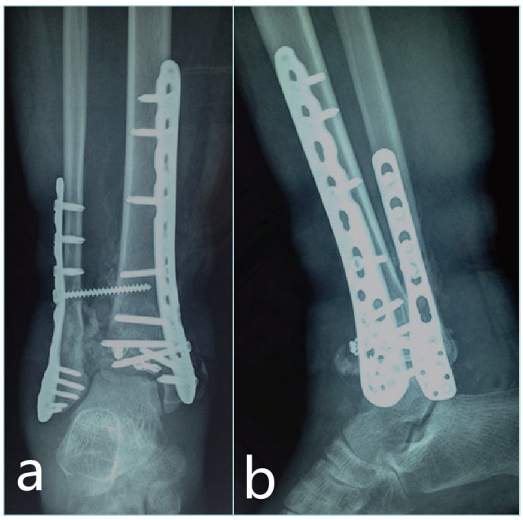

Fig. 4 Radiographs taken 3 months after ORIF (open reduction and internal fixation) showing separation of the inferior tibiofibular syndesmosis and subsidence of the distal tibia articular surface, accompanied by the periosteal reaction
Fig. 4a: Anteroposterior radiograph
Fig. 4b: Lateral radiograph

she lived alone and needed hemodialysis three times a week, wearing a brace and not being able to bear weight were extremely inconvenient. Furthermore, she did not experience any pain, only some edema; thus, she proceeded to bear weight ahead of schedule without authorization.

The patient presented with right limb edema and a normal skin temperature 5 months after ORIF. She did not experience any pain, even while walking, and her ankle remained active (Fig. 5). A deep vein ultrasound was normal as before. Radiographs (Fig. 6) showed bone resorption of

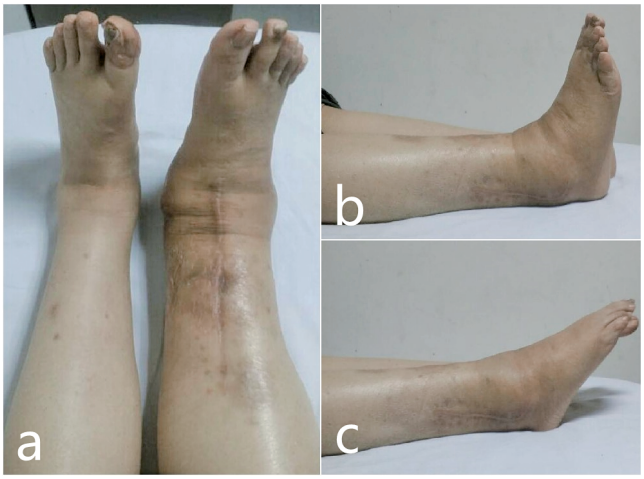

Fig. 5 The patient presented with right limb swelling 5 months after ORIF (open reduction and internal fixation), but the ankle was active

Fig. 5a: Right limb swelling
Fig. 5b: Extension of the ankle joint
Fig. 5c: Flexion of the ankle joint

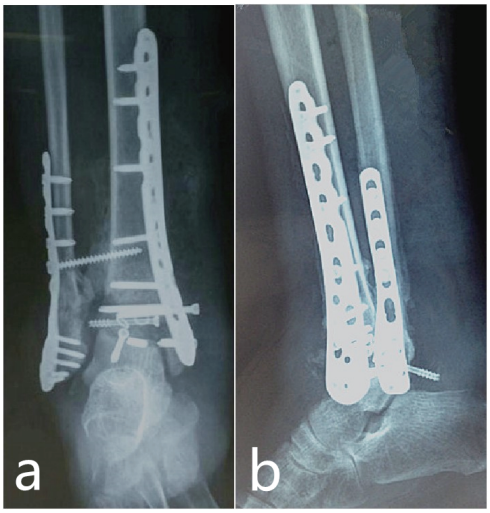

Fig. 6 Radiographs taken 5 months after ORIF (open reduction and internal fixation) showing bone resorption of the distal tibial articular surface, the looseness of internal fixation, and fracture of a locking screw

Fig. 6a: Anteroposterior radiograph
Fig. 6b: Lateral radiograph

the distal tibial articular surface and failure of the internal fixation. Although we had repeatedly warned the patient that weight-bearing was not allowed, she was more inclined to walk with weight-bearing because she did not feel any pain.

The swelling in the right limb had worsened 3 weeks later, particularly near the pretibial

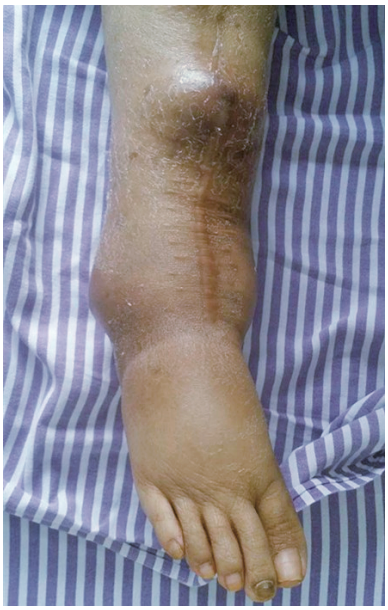

Fig. 7 Limb photograph taken 6 months after ORIF (open reduction and internal fixation), showing significant swelling, particularly near the pretibial incision, accompanied by a fluctuating mass

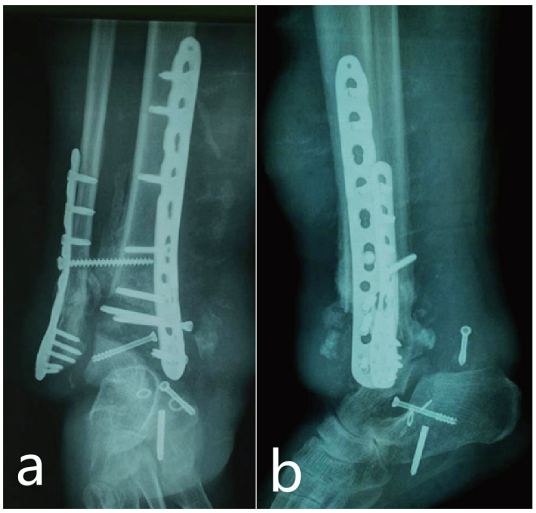

Fig. 8 Radiographs 6 months after ORIF (open reduction and internal fixation) showing bone resorption of the distal tibial articular surface and talus, significantly looseness of internal fixation, and fracture of a locking screw

Fig. 8a: Anteroposterior radiograph

Fig. 8b: Lateral radiograph

incision, and she could not walk without pain (Fig. 7). Gray pus was extracted from the anterior tibial swelling, and a bacterial culture revealed *Staphylococcus aureus*. Radiographs showed more severe bone resorption of the distal tibial articular surface and talus, as well as displacement of the internal fixation (Fig. 8).

We finally performed a sub-knee amputation as a reasonable option for the severe bone damage and infection. The postoperative limb anatomy revealed hyperemic gray pus from the middle tibia to the ankle, as well as distal tibial and talus bone resorption (Fig. 9).

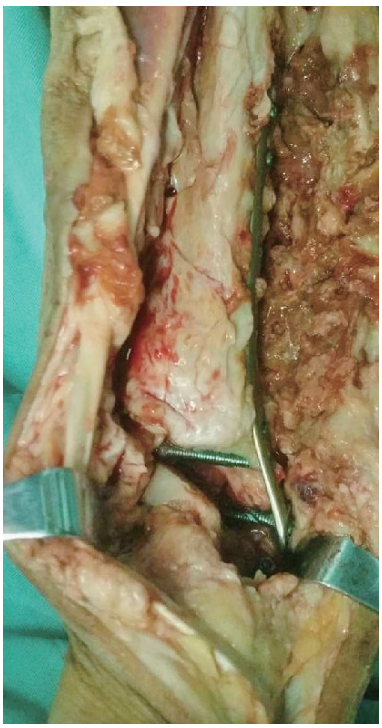

Fig. 9 Limb photograph at autopsy showing the infection from the middle part of the tibia to the ankle The distal tibial articular surface and most of the talus were resorbed.

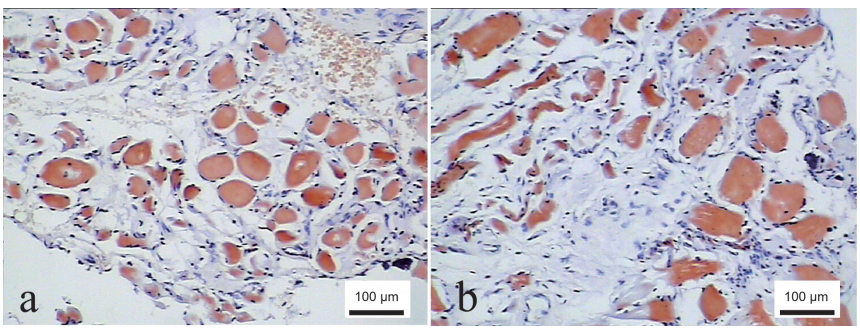

Fig. 10 Distal tibial biopsy: higher magnification (Congo red stain, 400×) showing amyloidosis
Fig. 10a: Congo red staining was positive.
Fig. 10b: Congo red staining was positive.

Pathological slices of bone tissue revealed inflammatory cell infiltration. Congo red staining was positive, indicating Abeta2M (Fig. 10).

The patient received intravenous Cefotiam antibiotic therapy for 7 days. She was discharged from the hospital 2 weeks after the amputation, and the incision healed well. Unfortunately, the patient died of a severe lung infection 6 months later.

DISCUSSION

CN is divided into four stages in the modified Eichenholtz classification, including "active" (stages 0, 1, 2) and "inactive" (stage 3) stages to indicate whether the process is in the acute or reconstructive stage, which is related to the method and timing of the operation.[2,5-7] Despite the fact that our patient did not exhibit "vanishing bone" in radiographs or a CT scan at the first appointment, the pathological fractures had already developed, placing her in stage 1 (active stage) of the classification system.

CN treatment should be managed by a multidisciplinary team, including strict unloading, casting, and surgical reconstruction. The goals are to achieve osseous stability, maintain the integrity of the foot and ankle, and prevent ulceration.[8] There is no universal agreement on the best time or method for surgical intervention.

Many studies have reported that surgical treatment should be considered during stage 3 (inactive CN) when the acute inflammatory changes have subsided.[9-11] Less edema, less inflammatory products, and fewer soft tissue and wound complications are all advantages of surgical intervention at this stage.[10] Similar to high-energy trauma to the foot and ankle, high levels of edema and inflammation increase the risk for postoperative wound complications. Waiting for the later stages of CN may provide a better physiological mechanism for bone and skin healing. However, the CN process can take several months to resolve. Waiting for later stages makes it more difficult to reduce consolidated deformities, increasing the possibility that an osteotomy may be required to rectify the bone deformities. In addition, many deformities progress during the waiting period, and soft tissues can break down and become infected. Therefore, some experts believe that active CN may be the best time for surgery, as the deformities are fresh and flexible and are easy to reduce, similar to other acute fractures.[3,12,13] Active disease may also offer the best bone quality compared to later stages of CN.

Most experts believe that ankle CN seems more likely to fail during non-surgical correction and has a higher risk for severe deformity, necessitating early surgical intervention.[14] Experts concur that direct ankle joint expansion fusion should be performed for first-stage ankle joint CN.[15] In addition, some authors suggest that ORIF can be employed as the primary operation for patients with inactive CN and no wound or infected tissue.[16] We performed surgery at the "active" stage, as the present patient had a substantial ankle fracture with instability. We adopted ORIF to preserve the function of the ankle joint and prevent additional aggravation of the deformity.

Many studies have shown that health education is important, and poor adherence to treatment recommendations, particularly off-loading, may negatively affect outcomes.[17] Patients with suboptimal compliance have a longer duration of acute Charcot syndrome and a higher risk for foot ulceration and amputation than those with better compliance, according to a long-term retrospective study.[18] Although we repeatedly reminded this patient that weight-bearing was forbidden within 3 months, her compliance was poor, and she began bearing weight without authorization in less than 2 months. Eventually, she experienced severe bone loss and infection.

Abeta2M is a type of systemic amyloidosis that is specifically seen in patients with chronic renal disease. However, the precise mechanism of Abeta2M remains unclear. The precursor

protein of Abeta2M-amyloid fibril is beta2M, and an increase in the serum level is the primary cause of Abeta2M in patients with kidney failure.[19] Osteolytic lesions are often found around the synovial membrane with deposits of Abeta2M-amyloid. Osteoclastogenesis and active osteoclastic bone resorption are found, while osteoblastic bone formation is absent in the lesion most likely associated with the inflammation caused by infiltrating macrophages/monocytes into the Abeta2M-amyloid deposits. The precise mechanism of this inflammatory change is unknown. More research is required to elucidate the association between Abeta2M-amyloid accumulation and progressive bone destruction.[4] Our patient's laboratory results indicated that beta2M was quite high (20,071.6 μg/L). The pathological bone biopsy showed positive Congo Red staining, suggesting that the patient had bone amyloidosis. We speculate that there is a relationship between CN and Abeta2M in patients with diabetic nephropathy, but this requires further studies to confirm.

In conclusion, we believe that poor compliance, premature weight-bearing, and missed identification of Abeta2M were the primary causes of this patient's failure. Given that the patient was a single woman who required hemodialysis three times a week, and wearing a non-weight-bearing brace was inconvenient, we should have thought twice before choosing surgical treatment.

AUTHOR CONTRIBUTION

YZ and JDZ served as co-first authors.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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REFERENCES

1 Schmidt BM, Holmes CM. Updates on Diabetic Foot and Charcot Osteopathic Arthropathy. *Curr Diab Rep*. 2018;18(10):74. doi:10.1007/s11892-018-1047-8.
2 Womack J. Charcot Arthropathy Versus Osteomyelitis: Evaluation and Management. *Orthop Clin North Am*. 2017;48(2):241–247. doi:10.1016/j.ocl.2016.12.011.
3 Ramanujam CL, Stuto AC, Zgonis T. Surgical treatment of midfoot Charcot neuroarthropathy with osteomyelitis in patients with diabetes: a systematic review. *J Wound Care*. 2020;29(Sup6):S19-S28. doi:10.12968/jowc.2020.29.Sup6.S19.
4 Lonnemann G, Koch KM. Beta(2)-microglobulin amyloidosis: effects of ultrapure dialysate and type of dialyzer membrane. *J Am Soc Nephrol*. 2002;13 Suppl 1:S72-S77. doi:10.1681/ASN.V13suppl_1s72.
5 Marmolejo VS, Arnold JF, Ponticello M, Anderson CA. Charcot Foot: Clinical Clues, Diagnostic Strategies,

and Treatment Principles. *Am Fam Physician*. 2018;97(9):594–599.
6 Trieb K. The Charcot foot: pathophysiology, diagnosis and classification. *Bone Joint J*. 2016;98-B(9):1155–1159. doi:10.1302/0301-620X.98B9.37038.
7 Holmes C, Schmidt B, Munson M, Wrobel JS. Charcot stage 0: A review and consideratons for making the correct diagnosis early. *Clin Diabetes Endocrinol*. 2015;1:18. doi:10.1186/s40842-015-0018-0.
8 Lowery NJ, Woods JB, Armstrong DG, Wukich DK. Surgical management of Charcot neuroarthropathy of the foot and ankle: a systematic review. *Foot Ankle Int*. 2012;33(2):113–121. doi:10.3113/FAI.2012.0113.
9 Botek G, Figas S, Narra S. Charcot Neuroarthropathy Advances: Understanding Pathogenesis and Medical and Surgical Management. *Clin Podiatr Med Surg*. 2019;36(4):663–684. doi:10.1016/j.cpm.2019.07.002.
10 Schneekloth BJ, Lowery NJ, Wukich DK. Charcot Neuroarthropathy in Patients With Diabetes: An Updated Systematic Review of Surgical Management. *J Foot Ankle Surg*. 2016;55(3):586–590. doi:10.1053/j.jfas.2015.12.001.
11 Kroin E, Schiff A, Pinzur MS, Davis ES, Chaharbakhshi E, DiSilvio FA. Functional Impairment of Patients Undergoing Surgical Correction for Charcot Foot Arthropathy. *Foot Ankle Int.* 2017;38(7):705–709. doi:10.1177/1071100717701233.
12 Armstrong DG, Lavery LA. Acute Charcot's arthropathy of the foot and ankle. *Phys Ther*. 1998;78(1):74–80. doi:10.1093/ptj/78.1.74.
13 Yates TH, Cooperman SR, Shofler D, Agrawal DK. Current concepts underlying the pathophysiology of acute Charcot neuroarthropathy in the diabetic foot and ankle. *Expert Rev Clin Immunol*. 2020;16(8):839–845. doi:10.1080/1744666X.2020.1804869.
14 Hartemann-Heurtier A, Van GH, Grimaldi A. The Charcot foot. *Lancet*. 2002;360(9347):1776–1779. doi:10.1016/S0140-6736(02)11671-0.
15 Wukich DK, Raspovic KM, Hobizal KB, Sadoskas D. Surgical management of Charcot neuroarthropathy of the ankle and hindfoot in patients with diabetes. *Diabetes Metab Res Rev*. 2016;32 Suppl 1:292–296. doi:10.1002/dmrr.2748.
16 Wukich DK, Sung W. Charcot arthropathy of the foot and ankle: modern concepts and management review. *J Diabetes Complications*. 2009;23(6):409–426. doi:10.1016/j.jdiacomp.2008.09.004.
17 Bullen B, Young M, McArdle C, Ellis M. Charcot neuroarthropathy patient education among podiatrists in Scotland: a modified Delphi approach. *J Foot Ankle Res.* 2018;11:54. doi:10.1186/s13047-018-0296-8.
18 Nilsen FA, Molund M, Hvaal KH. High Incidence of Recurrent Ulceration and Major Amputations Associated With Charcot Foot. *J Foot Ankle Surg*. 2018;57(2):301–304. doi:10.1053/j.jfas.2017.10.008.
19 Heegaard NHH. beta(2)-microglobulin: from physiology to amyloidosis. *Amyloid*. 2009;16(3):151–173. doi:10.1080/13506120903151775.