Annals of Diagnostic Pathology 47 (2020) 151509

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Original Contribution

Novel FEMASK-score, a histopathologic assessment for destructive Charcot neuropathic arthropathy, reveals intraneural vasculopathy and correlates with progression and best treatment

Jesse King[a,1], Ben Murie[a,b,1], Julie C. Fanburg-Smith[a,b,c,d,*], Chris Michael Stauch[a,c], Don Flemming[a,e], Michael J. Klein[f], Elizabeth E. Frauenhoffer[a,b,c], Madelaine Fritsche[a], Jessica D. Smith[g], John Elfar[a,c], Michael Aynardi[a,c]

[a] Penn State College of Medicine, Penn State Health, Milton S. Hershey Medical Center, Hershey, PA, USA
[b] Department of Pathology, Hershey, PA, USA
[c] Department of Orthopedic Surgery, Hershey, PA, USA
[d] Department of Pediatrics, Hershey, PA, USA
[e] Department of Radiology, Hershey, PA, USA
[f] Hospital for Special Surgery, Pathology, New York, NY, USA
[g] Georgetown University, Washington DC, USA

ARTICLE INFO

Keywords:
Charcot
Neuropathy
Diabetes
Midfoot
Amputation
Eichenholtz
Vasculopathy
Neurotraumatic
Neurovascular
Inflammatory
Cytokine

ABSTRACT

Background: Charcot neuropathic arthropathy is a debilitating, rapidly destructive degenerative joint disease that occurs in diabetic, neuropathic midfoot. Clinicoradiologic assessment for Charcot neuropathic arthropathy previously relied on Eichenholtz stage. There is limited histopathologic data on this entity. We wanted to independently develop a histopathologic scoring system for Charcot neuropathic arthropathy.

Design: Retrieval of surgical pathology midfoot specimens from Charcot patients (2012–2019) were analyzed to evaluate joint soft tissue and bone. Considering progression from large (≥half 40× hpf) to small (<half 40× hpf) periarticular bone fragments to resolution, we devised and applied a Charcot neuropathic arthropathy novel FEMASK-score (named after coauthors: Fanburg-Smith, Frauenhoffer, Flemming, Fritsche, Elfar, Murie, Aynardi, Stauch, Smith, King, and Klein): 0 (initial) = the observed intraneural arteriolosclerosis in all diabetic neuropathic patient specimens (not observed in other diabetic nerves); and finally scored with the most destruction observed: 1 = large bone fragments without host histiocytic response; 2 = mixed bone fragments with host histiocytic response; 3 = small minute bone spicules resorption to fibrosis. Eichenholtz stage and outcome were then compared.

Results: Forty-eight cases of Charcot neuropathic arthropathy included 34 males and 14 females, mean age 60.3 and age range 28–83 years, with clinical diabetes mellitus (predominantly Type II) and longstanding neuropathy. Elevated HbA1C, Eichenholtz stage, American Society of Anesthesia score, and Charlson comorbidity index indicated initial clinical amputation. Pathologic specimens varied from fixation tissue to amputation. In addition to neurotraumatic, neurovascular and inflammatory findings, a distinctive intraneural hyalinized arteriolosclerosis was observed. FEMASK-scores: 1 = 10%, 2 = 58%, and 3 = 32%. Score comparisons were 98% accurate compared with Eichenholtz and 98% reproducible among pathologists. FEMASK 2 and 3 correlate with clinical need for amputation.

Conclusions: Our novel Charcot neuropathic arthropathy FEMASK-score classification, derived from the largest cohort of diabetic neuropathic specimens, is reproducible, explains pathophysiologic progression of destructive phase of Charcot, correlates with Eichenholtz, and predicts progression to or clinical need for amputation. The unique intraneural vasculopathy observed contributes to Charcot neuropathic arthropathy etiology.

* Corresponding author at: Penn State Health, Milton S. Hershey Medical Center, Hershey, PA 17033, USA.
E-mail address: fourxjs@cox.net (J.C. Fanburg-Smith).
[1] These authors share first authorship.

https://doi.org/10.1016/j.anndiagpath.2020.151509

1. Introduction

Neuropathic arthropathy (Charcot joint) is a destructive, degenerative joint disorder that occurs in patients with longstanding diabetes and insensate neuropathy. This can lead to rapidly progressive fragmentation of the joint, collapse of the midfoot, contraction deformity, secondary ulceration with osteomyelitis, and limb amputation [1]. While the original description of "Charcot" 1868 [2] applied to tertiary syphilitic tabes dorsalis, "Charcot joint" is currently most often associated with peripheral neuropathy and diabetes mellitus [3].

The literature on histopathologic changes of neuropathic arthropathy is limited. There is no large histopathologic series or previous pathologic classification system for destructive neuropathic joint (arthropathy), nor one that correlates with disease progression or pathophysiology. Traditional clinicoradiologic assessment for Charcot includes the modified Eichenholtz stage [4,5] originally designed by orthopedic surgeon Sidney N. Eichenholtz in 1966, a three-tiered system that describes 1) development or fragmentation, 2) coalescence or callus and 3) resolution or consolidation. Patients with diabetes and early neuropathy are often undiagnosed and histopathologic material from these patients is frequently unavailable.

This paper delineates a classification and histopathologic scoring system for Charcot osteoarthropathy, based our consideration of the typical pathophysiology of this disease. Without prior knowledge that there is a clinicoradiologic Eichenholtz stage, we microscopically observed progression of large to small (cellular breakdown) bone and cartilage fragments to host response, then to resolution (fibrosis). We independently reviewed the histopathology of our patients who had surgical intervention for Charcot neuropathic arthropathy and, afterwards, clinicians disclosed to us the modified Eichenholtz stage and clinical data for correlation.

This novel FEMASK-score for Charcot neuropathic arthropathy, named after the coauthors, Fanburg-Smith, Frauenhoffer, Flemming, Fritsche, Elfar, Murie, Aynardi, Stauch, Smith, King, and Klein, is reproducible and subsequently correlates with (modified) Eichenholtz clinicoradiologic stage. To date, this series represents the largest cohort of patients with histopathologic evaluation of Charcot arthropathy. Higher FEMASK-scores of 2 and 3 are associated with a clinical progression to amputation. We believe that this seminal pathology FEMASK-score for Charcot neuropathic arthropathy may aid in the clinical management of these diabetic neuropathic patients.

2. Design

With prior IRB approval, surgical pathology specimens and reports, obtained from our list of our neuroarthropathic (Charcot) midfoot clinic patients cohort of senior author from 2012 to 2019, including of joint, bone and soft tissue, were reviewed and analyzed. Additional clinical, radiology, and laboratory records were later correlated. Patient selection was based on clinically known diabetic neuropathic surgical patients within this time frame, searched by CPT and ICD-10 codes. Neuropathic arthropathy (Charcot) midfoot surgery specimens, included surgical debridement, reconstruction and/or amputation, including rare Syme, Chopart or more likely below-knee-amputation, when amputation was required, from our surgical clinical patients with available pathology. These specimens required adequate periarticular/synovial tissue, as well as nerve, vessel, skeletal muscle, often bone, for complete evaluation. Microscopic assessment included morphology, inflammation, joint soft tissue, bone, and especially synovial or periarticular embedded bone or cartilage fragments and detritus and host response. CD68 immunostaining was used in select cases to highlight histiocytes. Patient demographics, laboratory values, clinical indices, and radiologic evaluation were reviewed together and interpreted by subspecialty coauthors.

First, a neuropathic arthropathy scoring system (FEMASK-score 0–3) was devised based upon our understanding of disease progression and pathophysiology, from large (> half 40× hpf) to small (< half 40× hpf) fragments of detritus, host response, and resolution. A scoring system (below) was applied to each case by pathologists (including subspecialty orthopedic pathologist) and trainees. Afterwards, the FEMASK scoring system for each patient was compared with all revealed clinical data and the clinicoradiologic (modified) Eichenholtz stage (0–3) [5].

Finally, additional independent observers, including additional orthopedic pathologists and trainees, were given the sections and instructed in the FEMASK scoring system to assess its reproducibility; these results were statistically compared and correlated.

3. Design FEMASK score

FEMASK-score 0 was assigned when review of glass slides of neuropathic diabetic patients revealed a distinctive intraneural arteriolosclerosis (hyalinized vasculopathy, neurotraumatic), associated with neural hypertrophy, mild intraneural myxoid changes, and perineural fibrosis.

FEMASK-score 1 is defined as the first stage of Charcot joint destruction, with large embedded bone or cartilage fragments within periarticular soft tissue without a host response. Focal fibrinoid and mild acute inflammation in the soft tissue near the large fragments of FEMASK-score 1, not necessarily associated with acute cellulitis or acute osteomyelitis, was recorded.

FEMASK-score 2 is defined as the second stage of Charcot joint destruction, observed as mixed large and small bone fragments embedded in periarticular soft tissue with a host histiocytic response, with occasional granulation tissue.

FEMASK-score 3 is considered the end stage of Charcot joint destruction, with either small minute residual bone spicules to complete absence or resorption of bone fragments and/or rare to absent histiocytes, often replacement by extensive fibrosis.

4. Results

Forty-eight cases of (diabetic) neuropathic arthropathy were included. There were 34 males and 14 females, with an age range of 28–83 years; the mean age was 60.3 years. Selection of cases via clinically known patients over the past decade separately revealed clinical midfoot deformity and clinicoradiologic Eichenholtz stage, afterwards revealed to pathologists (see clinicoradiologic results in Section 6). Fig. 1A–D demonstrates midfoot (modified) Eichenholtz stages 0–3 and Fig. 1E clinical Eichenholtz stage 3. Surgical procedures performed included soft tissue ulcer excision or debridement with reconstruction as fixation placement or removal (55%) and rarely Chopart or Syme amputation (4%) or clinical need for below-the-knee amputation (41%). Most of the amputation cases had attempted fixation first and both specimens revealed the same FEMASK score. The preoperative American Society of Anesthesia score and Charlson comorbidity index were initial predictors of amputation specimens, for pathologic review (see Section 7).

5. Microscopic pathology and FEMASK-score results

Histopathologic review of these specimens foremost revealed notable vascular changes, importantly intraneural arteriolosclerosis, an eosinophilic hyalinization of the vessels within enlarged nerve with perineural fibrosis and minimal intraneural edema, vacuolar change, irregular neural fibres, assigned as precursor FEMASK 0, in all cases (100%). Additional vascular changes in all cases with available larger vessels included medial calcification and atherosclerosis. There was widespread moderate to marked skeletal muscle atrophy in all cases (100%). Lymphoplasmacytic or lymphoid aggregates were not prominent features of the synovial soft tissue. The pathologic specimens also revealed superficial epidermal ischemic ulceration, dermal fibrosis,

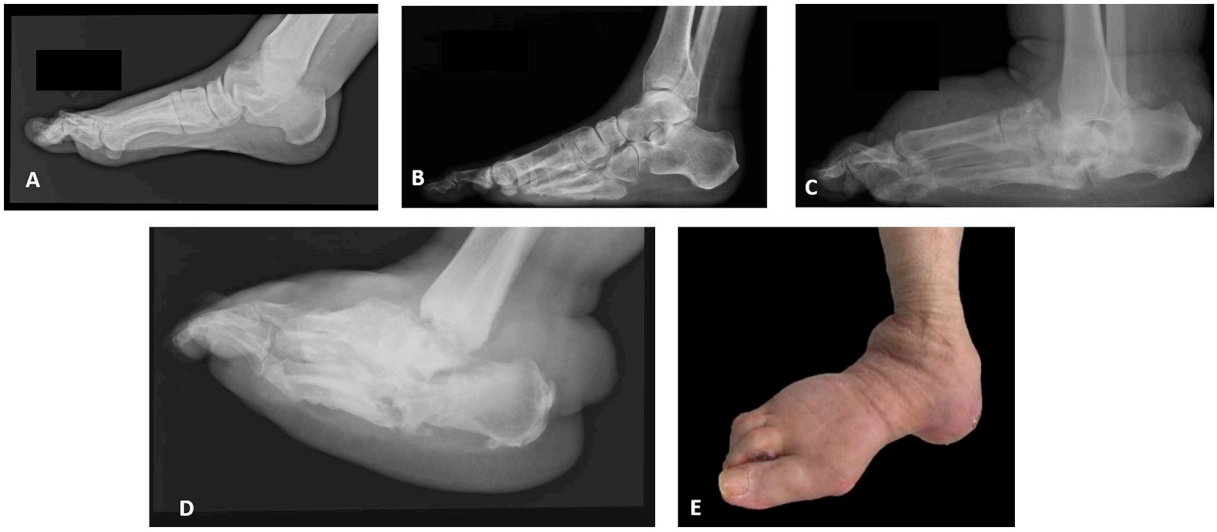

Fig. 1. Charcot neuropathic arthropathy: radiologic Eichenholtz stages, progressive 0 (A. clinical warmth, swelling and joint instability without abnormal radiologic appearance of bone and joints); 2 (B. development, fragmentation or joint dislocation); 2 (C. coalescence); 3 (D. resolution, consolidation, or ankylosis); and clinical Eichenholtz stage 3 (E).

acute and chronic cellulitis, and those cases with bone for intraosseous assessment, demonstrated acute and/or chronic osteomyelitis in half (50%) of cases. Cultures in infectious cases yielded rare cases of *Staphylococcus epidermidis*, *Streptococcus B*, or single cases of *Pseudomonas* sp. or methicillin-resistant *Staphylococcus aureus*.

Crucial analysis of synovial and periarticular tissue, particularly examining for embedded bone and cartilage fragments, detritus, and host inflammatory, histiocytic or fibrosis response, was performed to assign a final FEMASK-score. The histiocytes were additionally highlighted in select cases by CD68+ immunostaining (6/6+, 100%). Cases were assessed as follows:

FEMASK-score 0 (distinctive intraneural arteriolosclerosis, i.e. hyalinized vasculopathy) was present in all (100%) cases, as depicted (Fig. 2A1 low power and A2 higher power). While all cases demonstrated this finding, cases were also scored by the highest score reached, as below, and therefore all cases demonstrated intraneural arteriolosclerosis as a "precursor" finding and then were better classified as a later FEMASK-score.

FEMASK-score 1 (first stage of Charcot joint destruction, with periarticular soft tissue large embedded bone or cartilage fragments, mild acute inflammation, no significant histiocytic response) represented 10% of our cohort of patients with surgical specimens for evaluation (Fig. 2B).

FEMASK-score 2 (second stage of Charcot joint destruction, observed as mixed large and small bone fragments embedded in periarticular soft tissue with a host histiocytic response and occasional granulation tissue) represented the majority, 58%, of our cohort of patients with surgical specimens for evaluation. (Fig. 2C).

FEMASK-score 3 (considered the end stage of Charcot joint destruction with small minute residual bone spicules to complete absence or resorption of bone fragments or rare to absent histiocytes, often replacement by extensive fibrosis) represented 32% of our cohort of patients with surgical specimens for evaluation. (Fig. 2D1 and D2).

6. Clinicoradiologic, Eichenholtz-stage, clinicopathologic correlation results

Clinical risk factors for Charcot arthropathy included diabetes mellitus (predominantly Type II, with rare Type I) and longstanding clinical neuropathy in all cases. Patients presented clinically with elevated CRP and elevated (treated) glycated hemoglobin HbA1c, mean 8.2%, range 5.4 to 12.2% (normally below 5.7%, 39 mmol/mol). Surgical personal observations that the patients with FEMASK 2 or 3 on their biopsy/excision (fixation) material failed fixation and subsequently required amputation.

In retrospect, the (modified) Eichenholtz stage correlated exactly case for case with our FEMASK score, with the exception of one case that differed clinicoradiologically as an Eichenholtz-stage 2 rather than FEMASK-score 3 due to insufficient synovial tissue submitted for surgical pathology evaluation of the radiologically-apparent detritus. Overall, there were 10% Eichenholtz-stage 1 (development or fragmentation or joint dislocation), 56% Eichenholtz-stage 2 (coalescence), and 30% Eichenholtz-score 3 (resolution, consolidation, or ankylosis of Charcot neuropathic arthropathy).

Score comparisons were 98% accurate of FEMASK with respect to (modified) Eichenholtz (due to inadequate periarticular soft tissue to evaluate) and inter and intra-observer FEMASK-scores were 98% reproducible among three expert bone pathologists and three trainees. A single case differed early in classification between FEMASK 2 versus 3 between independent reviewers, because small fragments of bone and retention of histiocytes was in a grey zone between the two scores; this was then clarified in the scoring system as an early FEMASK 3 for later reviewers. In both cases of Eichenholtz-FEMASK evaluation and inter-observer FEMASK-score, the differences were between FEMASK-score 2 and FEMASK-score 3 and both of these higher scores correlated with a resultant failure of fixation and clinical need for amputation (see Table 1. Comparison of Eichenholtz and FEMASK-scores).

7. Discussion

In this study, we present a pathologic classification and scoring system for (Charcot) midfoot neuropathic arthropathy to explain pathophysiology and correlate with clinical outcome. This is based on the largest available cohort of evaluable surgical pathology specimens from patients with neuropathic arthropathy due to diabetes mellitus and neuropathy. The findings are significant based on sufficient and reproducible data that this classification accurately describes the pathophysiology of Charcot neuropathic arthropathy. This FEMASK-score is reproducible among trainees to experts, correlates with the clinicoradiologic (modified) Eichenholtz stage, [5] and appears to be related, at higher scores FEMASK-score 2 or FEMASK-score 3, that corresponds with a clinical need for amputation. Notably, all cases in this cohort with available nerve for review revealed novel intraneural arteriolosclerosis (vasculopathic neuropathy) that appears to precede and may

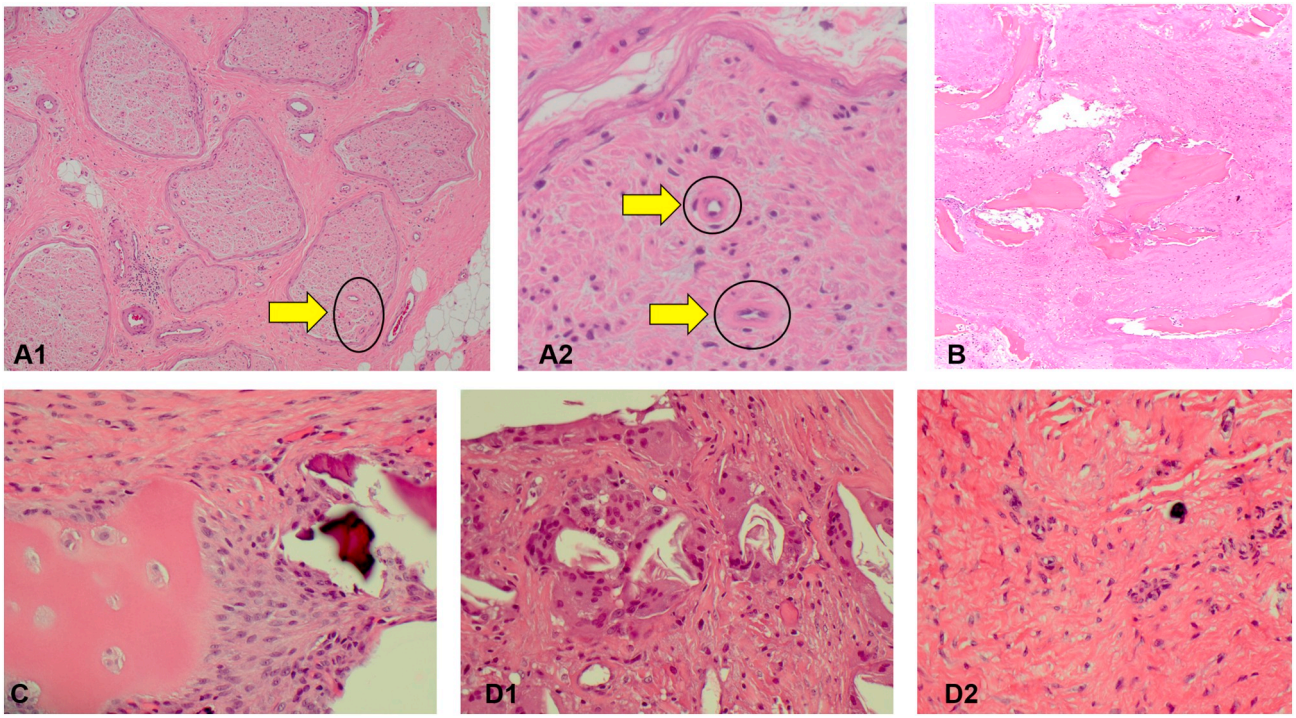

Fig. 2. Charcot neuropathic arthropathy, progressive midfoot FEMASK scores: FEMASK-score 0 (A1. Lower power and A2. Higher power of hyalinized vasculopathy) (intraneural arteriolosclerosis, yellow arrows and black-circled); FEMASK-score 1 (B. large fragments of embedded periarticular bone within fibrinoid focal acute inflammation); FEMASK-score 2 (C. mix of large and small fragments with host histiocytic response and non-depicted occasional granulation tissue); and FEMASK-score 3 (D1. Early minute spicule of bone with few residual histiocytes and D2. Late near complete resorption of bone and replacement by fibrosis). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

be an etiologic factor for development of neuropathic arthropathy.

"Charcot" was first coined by Dr. Jean-Martin Charcot in his seminal paper on syphilitic neuropathic arthropathy in 1868 [2]. At this time, there were fewer diabetic patients with neuropathic arthropathy, most likely because type I diabetes was a uniformly fatal wasting disease and patients did not live long enough to develop long term sequela. Now, the term is expanded to include any joint destruction resulting from a neuropathy, most commonly referring to neuropathy in diabetes mellitus [3]. Dr. Jean-Martin Charcot [2] gave credit to Dr. John Kearsley Mitchell, an American surgeon, who depicted it with tuberculosis in 1831 [6]. Both Charcot and Mitchell recognized denervation and altered biomechanics and an *inflammatory* element to this disease.

The etiology of neuropathic arthropathy has been conventionally theorized as *neurotraumatic*, caused by repetitive overuse trauma to an unprotected insensate distal lower extremity [7-9]. More recent observations support a *neurovascular* theory, autonomic denervation of the periarticular circumflex system, as well as sensory and motor denervation, abnormal vascular reflex and unrestricted chronic hyperemia (neurovascular shunting) around the involved joint, with subsequent change in sympathetic tone. The regional increased bone resorption, mechanical weakening, osteoclastogenesis, osteopenia, fracture and resultant rapidly progressive fragmentation of the joint are concurrent with genetic predisposition [10-14].

Our findings confirm that Charcot neuropathic arthropathy has multifactorial etiologies, combinations of neurotraumatic and neurovascular alterations as well as an inflammatory response. It is known that cytokine-driven IL-1B mediation or TNF-alpha through RANK-L [11,15] with inflammation-induced mutations of the OPG-RANKL-RANK pathway, previously measured by single nucleotide polymorphism (SNP) mutational analysis [11,15-17]. These factors explain a reduction in bone mineral density, bone microarchitecture, and marrow space with late thin trabeculae, as previously described [7-9,12,14,18-21]. These findings correlate with our findings of acute inflammation during early fragmentation, FEMASK-score 1. Clinically, we believe the most important factor that contributes to neuropathic arthropathy, common to traumatic, vasculopathic and inflammatory theories, is the loss of sensation to pain. There is resultant neuropathic lack of proprioception or sensation, chronic microtrauma (neurotraumatic etiology), ligament laxity, joint instability, cytokine release, and finally arthropathic destruction. In our pathologic specimens we observed both an early fibrinoid mild acute inflammation (inflammatory etiology) present in the soft tissue with the large fragments of detritic bone (FEMASK-score 1) and we identified a preceding vasculopathic intraneural arteriolosclerosis (neurovascular etiology, FEMASK-score 0), consistent with proposed etiologic theories.

While some authors have compared the similarities between rapidly-progressive Charcot neuropathic arthropathy in the midfoot and rapidly-progressive osteoarthritis (coxarthrosis) in the hip joint, [10,22] we believe that these changes are radiologically, anatomically, and etiologically different entities. Rapidly progressive osteoarthritis may exhibit morphologic joint detritus in the intertrabecular spaces and numerous microfractures. Other changes of alternate arthritis are not present in these patients, including no evidence for osteomalacia, conventional osteoarthritis, osteoporosis, osteonecrosis or lymphoplasmacytic aggregates of inflammatory arthropathy. Essentially there is no overlap between these two entities and rapidly progressive Charcot (diabetic) and rapidly progressive coxarthrosis (osteoarthritis) are distinct pathophysiologic entities.

The pathologic information on Charcot neuropathic arthropathy is indeed limited and there is no former large series or pathologic classification system developed for this entity. Available data regarding gross or histopathologic changes considers both 1) productive changes and then 2) destructive changes. This second phase of destructive changes in our patients with available surgical specimens are rapidly progressive with extensive fragmentation with resultant periarticular soft tissue or synovial embedded bone and cartilage fragments then bone

Table 1
Comparison of clinicoradiologic Eichenholtz-stage to pathologic FEMASK–score.

Eichenholtz	STAGE	Clinicoradiologic	FEMASK - Score	Pathologic Score
0		Diabetic patient with peripheral neuropathy, dislocation, warm, swollen ankle sprain without radiologic change	0	Early Charcot without surgical changes, intraneural arteriolosclerosis
1	Fragmentation	Acute inflammation, edema, hyperemia, erythema, bone fragmentation on radiograph	1	Acute fibrinoid inflammation with large fragments (> 1/2 40x hpf per fragment) of bone and cartilage embedded within synovium
2	Coalescence	Edema, hyperemia, erythema, coalescing new bone at fracture or dislocation on radiograph	2	Large and small (< 1/2 40x hpf) fragments of bone and cartilage embedded in periarticular soft tissue with host giant cell histiocytic response.
3	Resolution	Resolution of clinical inflammation, bone consolidation on radiologic imaging (9-12 months post symptom onset).	3	a) Threads of bone to absence of bone with rare residual histiocytic response or b) Replaced by fibrosis with absence of bone or histiocytes

resorption in weeks to months. A radiologic productive or osteosclerotic form of early Charcot joint was not histologically sectioned in our series. This early finding may produce dramatic joint deformity, large osteophyte formation, subluxation, joint space narrowing, and profound bone osteosclerosis at the articular surfaces; we are concurrently working on a mouse model that simulates these early findings. Later Charcot features of subarticular (geode) cyst formation, intraarticular bone and cartilage loose bodies, as debris within synovium, and acute inflammation followed by histiocytic and granulation tissue have been observed [10] and correlate independently with our findings.

In our current cohort of midfoot Charcot arthropathy patients, we notably identify adjacent intraneural arteriolosclerosis (designated as FEMASK-score 0) that in our experience (personal observations) while not entirely specific is not typically observed in diabetic patients with surgery for non-neuropathic etiology or infection-alone. We do not believe that this distinctive hyalinized intraneural arteriolosclerosis is a reduplication of the basal lamina in endoneurial capillaries, although we do concur that this endoneurial microvascular abnormality is associated with hypoxia and ultimately fibrosis in the affected nerves. We propose “FEMASK 0” because this histopathologic finding appears to be associated with neuropathy and suggests a vasculopathic neuropathic etiology for neuropathic arthropathy in our cases. Our concurrent mouse model for neuropathic arthropathy involving obesity-induced neuropathy and inclined treadmill-induced trauma reveals early histopathologic parameters that theoretically precede our FEMASK-score of 0 or 1, pathologic predictive pre-destructive changes. Early data suggests that productive weak aberrant periarticular osteosclerosis may precede fragmentation, destructive phase.

The FEMASK-score was designed to correlate with sequential pathophysiologic neuropathic destruction. Neurotraumatic, neurovascular and inflammatory multifactorial etiology with osteoclast activation and resorption would suggest to us that bone and/or cartilage fragments would be initially large, without immediate host histiocytic response; there may be a mild fibrinoid to acute inflammatory stroma. Then, histiocytic response, depending on the para-articular neovascularity, and possibly a mortar-pestle effect on the large pieces may break these bone and cartilage fragments into small pieces. Therefore, a histiocytic or later granulation tissue response would be associated with a mixture of size of small, medium, and large soft tissue embedded fragments of bone or cartilage. Finally, when the histiocytic response is complete, and the detritus fragments are near pulverized and essentially become powdery, there would be little to no bone fragments left, and therefore fewer histiocytes, and the remaining tissue would be replaced by chronic stromal fibrosis. We devised a pathologic staging system and score to parallel sequential destruction, FEMASK 0–3.

Radiologic change in Charcot neuropathic arthropathy is characterized by complete derangement of the joint with joint swelling, articular debris, joint instability, subluxation and disarticulation. Periarticular osteopenia and bone loss with fracture, as well as hyperostosis with large osteophytes, are readily apparent. Our pathologic classification was designed without a priori knowledge of the (modified) Eichenholtz staging system [5] as many orthopedic pathologists are not familiar with this clinicoradiologic staging system. The Eichenholtz stage was originally designated by orthopedic surgeon Dr. Sidney N. Eichenholtz in 1966 [5] to assess the following stages: 1) development, fragmentation or joint dislocation, 2) coalescence and 3) resolution, consolidation, or ankylosis of Charcot neuropathic arthropathy, and we independently validated this previously subjective clinicoradiologic staging system. Shibata added a stage 0 that corresponds to clinical warmth, swelling and joint instability without abnormal radiologic appearance of bone and joints [4]. With the exception of one case without sufficient material for review, our FEMASK score correlated with the (modified) Eichenholtz score in the majority of cases.

The clinical presentation for neuropathic arthropathy is often painless and may be subclinical for long time periods, although the progression of disease is often rapidly destructive clinically. Patients will first present with painless soft tissue and joint swelling or effusion, deformity, weakness and instability, subluxation and dislocation. Our cohort of patients and those in the literature often have elevated HbA1c, Eichenholtz stage, preoperative American Society of Anesthesia score, and Charlson comorbidity index [23]. The American Society of Anesthesia physical status classification system is a system for assessing the fitness of patients before surgery. It has been predictive of patient risk for adverse outcomes in the perioperative period [24]. The Charlson Comorbidity Index predicts the ten-year mortality for a patient who may have a range of comorbid conditions [25].

Clinicoradiologic findings will reveal Lisfranc and Chopart joint destructive arthropathy, with bone erosion of the first metatarsal joint, dislocation of the second metatarsophalangeal joint and collapse of the talus with ankle instability. Early surgical management is often considered as a prophylactic measure to temporize disease progression; however, preoperative consideration of bony structural involvement and the presence or absence of inflammation could play a role in surgical outcomes [26,27]. With incidence as high as 13.6% among patients with diabetic neuropathy, the management of neuropathic arthropathy has a significant impact on diabetic patients [27-30]. Amputation in our study is associated with FEMASK-scores of 2 and 3. Patients who have 2 or 3 on their biopsy/excision material failed fixation and required amputation, anyways. Thereby, a higher FEMASK score could alert the surgeon to progress to amputation initially, without trying fixation that would fail, reducing patient risk from increased surgeries, infection, and increased costs.

Additional studies on pre-destructive earlier changes, including initial weakly productive subchondral osteosclerosis observed radiologically would complete our understanding of the process. Often, we are only able to review Charcot joint specimens due to concurrent gangrene and infection. One drawback of our study is the limited availability of earlier stage neuroarthropathic specimens from patients who did not have reason to or did not yet seek clinical or surgical attention. Nonetheless, this series represents the largest cohort of patients with available histopathologic evaluation of neuropathic arthropathy,

with discovery of intraneural arteriolosclerosis, in the literature to date, and these findings are significant.

In summary, our FEMASK-score is highly reproducible among pathologists, from trainees to experts, explains the pathophysiology of progression of neuropathic arthropathy, and correlates well with the clinicoradiologic (modified) Eichenholtz in all cases with adequate synovial tissue for evaluation. A high FEMASK-score (2 or 3) predicts clinical progression and need for amputation. Early mild acute inflammation and distinctive demonstrable intraneural arteriolosclerosis confirm that inflammatory cytokines and neurovascular etiology, as well as neuromicrotrauma, plays a role in the development of neuropathic arthropathy. Foot and Ankle surgeons may make assessment to amputate early if there is already a FEMASK-score of 2 or 3 because these patients often fail fixation and require amputation. We believe that this novel pathologic classification scoring system, the FEMASK-score, can be used on tissue specimens and may be useful to aid in the clinical management of these diabetic and neuropathic patients, predict initial need for amputation and result in best clinical outcome.

Author contributions

All named authors contributed to concept design, ideas, research data collection, literature review, materials, tissue acquisition and processing, slide review, radiologic, pathologic and clinical data, rearview, editing, and approval of the final project and manuscript. Trainees were mentored by subspecialty surgeons, radiologist and pathologist in their specific disciplines of musculoskeletal expertise.

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