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# Overlapping features of rapidly progressive osteoarthrosis and Charcot arthropathy

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ABSTRACT

Nerve growth factor (NGF) is the primary neurotrophin in the skeleton and a central mediator of skeletal pain. Recent trials of anti-NGF neutralizing antibodies have resulted in infrequent but well-described incidence of rapidly progressive osteoarthrosis (RPOA). Neuropathy, whether from syphilis or diabetes, is also associated with severe joint destruction, known as neuroarthropathy or Charcot joint. These commonalities of severe joint destruction with either loss of a neurotrophin (anti-NGF) or a deficit of functional skeletal innervation led us to examine our institutional case files for potential radio-pathologic overlap between RPOA and Charcot joint.

## 1. Introduction

Charcot arthropathy, first described as a complication of neurosyphilis, is most commonly encountered in the diabetic population. A diverse group of peripheral or central neuropathies may also cause Charcot joints, including leprosy, polio, chronic alcoholism or syringomyelia.[1] Charcot arthropathy typically presents with a warm, swollen joint (usually foot and ankle), and a diagnosis of cellulitis or osteomyelitis is often entertained due to antecedent trauma or ulceration.[1] Two primary and potentially combinatorial theories have been entertained regarding the pathophysiology of Charcot arthropathy: the 'neurotraumatic' and the 'neurovascular' theories.[2–4] In the 'neurotraumatic' theory, an insensate joint is exposed to inappropriate overuse, resulting in fracture and progressive joint degradation. In the 'neurovascular' theory, change in sympathetic tone results in increased blood flow, osteoclastogenesis, osteopenia, fracture, and progressive degradation. Giving credence to altered osteoclast activity, recent SNP analysis have showed mutations in *OPG* associated with diabetic neuroarthropathy.[5] In sum, the pathophysiologic underpinnings of neuropathic joints have long been a subject of debate.[6] With recent pharmaceutical breakthroughs, neutralizing antibodies to the primary neurotrophin NGF (Nerve growth factor) have been developed to inhibit the sensation of skeletal pain (Tanuzemab and Fasinumab).[7–10] Notably, development of anti-NGF therapies were temporarily halted by the FDA due to an increased incidence of rapidly progressive osteoarthritis (RPOA), observed especially at higher dosages and in older female patients.[11] This connection led us to query the histopathologic overlap between Charcot arthropathy and RPOA.

RPOA is described as a significant loss of joint space and an abnormal loss or destruction of bone within short time period (within a year).[12] RPOA occurs in an about 2–18% of patients with severe OA per year in case series analyses and is common in the hip joint.[12–18] Other terms for RPOA include rapidly destructive coxopathy, rapidly destructive hip disease, rapidly destructive arthritis, erosive arthritis or analgesic hip. Similar rapidly destructive arthropathies have been described in the knee,[19–21] shoulder (Milwaukee shoulder syndrome)[22,23] and lumbar spine.[24] Their association with subchondral insufficiency fractures have been well described.[20,25–28]

In our clinical experience, overlapping features of Charcot arthropathy and RPOA were observed, including key pathologic features. In this Johns Hopkins University institutional case file review, all cases of Charcot joint and RPOA with pathologic material available were examined to identify distinguishing and overlapping features.

## 2. Methods

11 cases of Charcot joint and 7 cases of RPOA were identified in our surgical pathology archives (dated 2002-2018). IRB approval was obtained, which included a waiver of informed consent for this retrospective case series. The clinical, radiographic, and histological data of the cases were compiled. Two pathologists (EFM, AWJ) independently verified the diagnoses.

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**Table 1**
Patient demographics and other data.

| No | Age | Sex | Location |
|---|---|---|---|
| Charcot joints | | | |
| 1 | 42 | F | Right subtalar joint |
| 2 | 31 | M | Left midfoot |
| 3 | 71 | M | foot |
| 4 | 32 | M | Left forefoot |
| 5 | 58 | M | Left ankle joint |
| 6 | 54 | M | Left hallux |
| 7 | 74 | M | Foot |
| 8 | 74 | M | Left hallux |
| 9 | 39 | M | Right foot |
| 10 | 71 | M | Left hallux |
| 11 | 70 | M | Right ankle joint |
| RPOA | | | |
| 11 | 66 | F | Right Hip |
| 12 | 69 | F | Left Hip |
| 13 | NR | F | Right Hip |
| 14 | 50 | F | Left Hip |
| 15 | 68 | F | Right Hip |
| 16 | 57 | F | Right Hip |
| 17 | 60 | F | Right Hip |

Abbreviations: M: male; F: female; NR: Data not recorded; NA: Not available; RPOA:Rapid Progressive osteoarthritis.

## 3. Results

### 3.1. Features of Charcot joints

Eleven available cases of Charcot joints were reviewed, with demographics summarized in Table 1. The majority were male (10/11 patients) with a wide age range (31–74 yrs). All specimens were obtained from the foot (two from ankle joint, one from subtalar joint, one from forefoot, one from midfoot, three from hallux, three were not specified). Bone erosions, joint dislocations and joint destructions are typical findings. (Fig. 1A–C). In some patients, severe osteophytes formation were also found (Fig. 1D). On pathology review, all cases showed detritic bone and/or cartilage, often embedded in synovium (Fig. 2A). Reactive changes were present in all cases and included exuberant granulation tissue in 7 cases (Fig. 2B), reactive bone formation in 5 cases (Fig. 2C), synovial hyperplasia in 5 cases. Acute inflammation to raise the possibility of osteomyelitis was present in 4 cases.

### 3.2. Features of rapidly progressive osteoarthrosis (RPOA)

Seven available cases of RPOA were reviewed, with demographics summarized in Table 1. All were female with an older age range than seen in Charcot arthropathy (50–69 yrs). All specimens were obtained from the femoral head. In the initial radiograph. right hip joint with slight joint narrowing (Fig. 3 A, B). One month later, both acetabulum and femoral head destructions were seen (Fig. 3C, D). A large portion of femoral heads were disappeared rapidly in RPOA cases. (Fig. 4 A-G). Pathology showed all cases to have prominent detritic bone and/or cartilage, often embedded in granulation tissue (Fig. 5). Co-existent osteonecrosis was seen in one case. Acute inflammation was not a prominent feature in any case.

## 4. Discussion

In sum, the recent observation of anti-NGF induced RPOA led us to review our case files for similarities between Charcot arthropathy and RPOA. Basic features differ, including the anatomic site most commonly affected (hip versus foot), demographics (older women versus more diverse demographic group), and clinical presence of pain (Table 2). Nevertheless, strong radiographic and histopathologic features are common between these entities. Radiographic similarities are present, including bone erosion, joint dislocation and severe joint destruction. Histopathologic similarities are present, including prominent bone and cartilage detritus, often embedded in synovium and granulation tissue. The presence of prominent acute inflammation is a distinguishing feature of Charcot joint. It is not clear if acute inflammation within this subset of Charcot joints may solely reflect concurrent osteomyelitis.

The time course for progression is another distinguishing feature between RPOA and Charcot joints. RPOA is by definition a rapid, destructive process that worsens within a year.[16] On the other hand, it often takes more than 6 years to get worse in Charcot joint associated with diabetes.[29,30] In addition, the known precipitating factors for

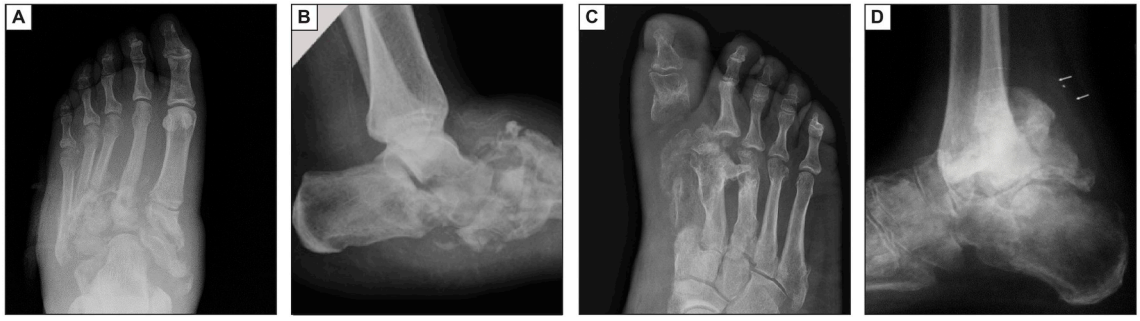


**Fig. 1.** Radiographic appearance of Charcot arthropathy. (A) Severe destructive arthopathy in both Lisfranc and Chopart joints of the left foot are seen. (B) Lateral view of the X-ray of the ankle joint as seen in A. (C) Bone erosion in the first metatarsal bone and dislocation of the second metatarsophalangeal joint are seen in the right foot. (D) Lateral view of the X-ray of the ankle joint in another case. The talus is collapsed and the ankle joint is anteriorly dislocated. Severe osteophytes are also seen.

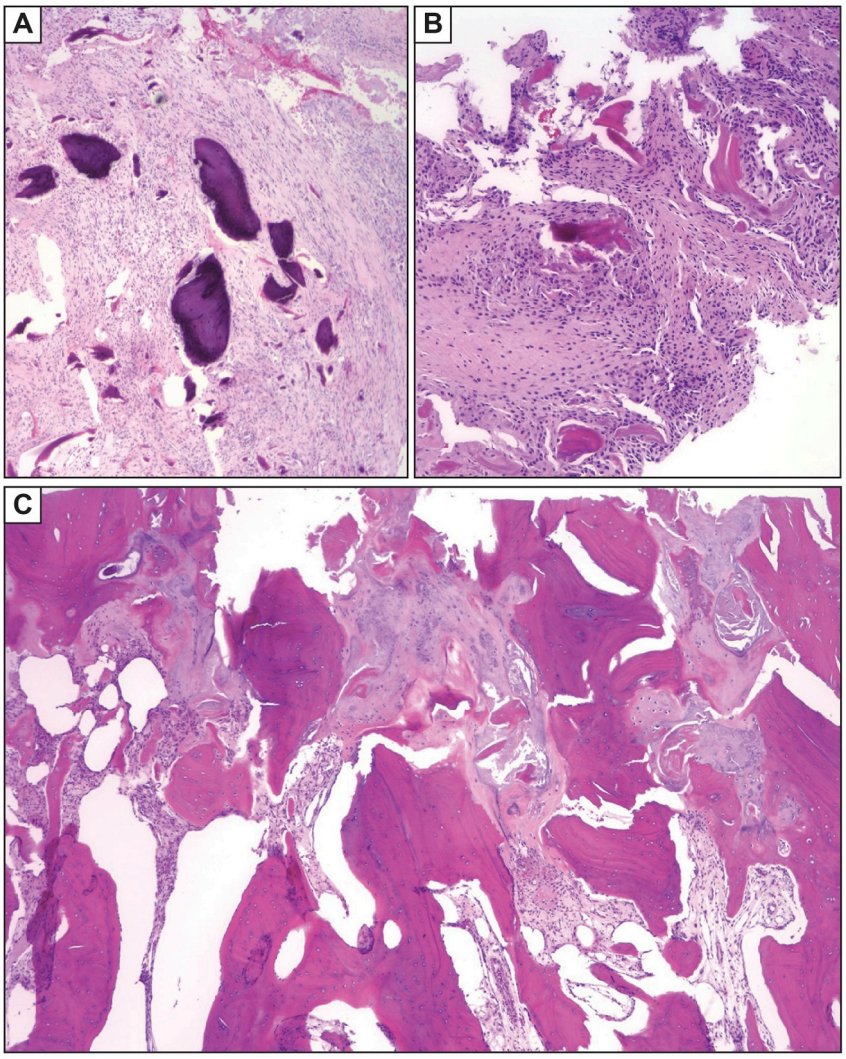


**Fig. 2.** Representative histologic appearance of Charcot arthropathy. (A,B) Prominent granulation tissue with bone detritus – a feature of both Charcot arthropathy and RPOA. (B) Histiocytic inflammation surrounding fragments of devitalized bone. In this case, acute inflammatory cells were not conspicuous. (C) Bone detritus, granulation tissue and acute inflammation involving subchondral bone.

RPOA and Charcot joints differ. Subchondral insufficiency factors are well established precipitating factor for RPOA and related entities,[26] while infection is not. In contrast, osteomyelitis and trauma are known to precipitate, co-exist or worsen Charcot joints.[1,6]

The central mediator of skeletal pain sensation is NGF (Nerve growth factor), which transmits nociceptive signals either by directly activating TrkA (tropomyosin receptor kinase A) sensory neurons or through indirect mechanisms, which enhance the response of other nociceptive pathways. To better address osteoarthritic pain, anti-NGF neutralizing antibodies are currently in Phase 3 clinical trials and are on the cusp of clinical availability. However, with RPOA now as a known side effect of anti-NGF therapy, understanding the NGF-TrkA signaling axis in severe joint disease is more critical now than ever before.

Several earlier studies have indirectly supported the neurotraumatic theory of Charcot joint – pointing to the central role of sensory nerves. Loss of sensory innervation to the joint results in abnormal joint

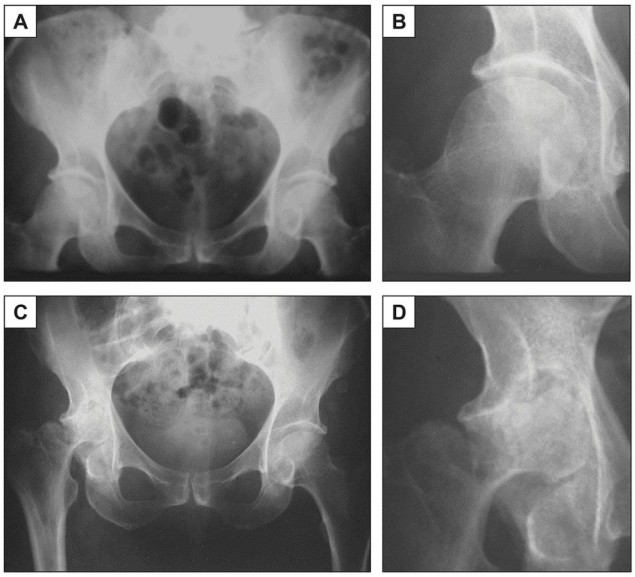


**Fig. 3.** Radiographic appearance and interval progression of RPOA. 66 year-old with a history of right hip pain. (A,B) Initial radiograph. Right hip joint with slight joint narrowing. (C,D) One month later. End-stage osteoarthritis of the right hip joint in the same patient as A. Severe destructive changes to both the acetabulum and femoral head can be seen.

loading.[3,31,32] Age-related loss of knee joint sensory nerves has been observed in C57BL/6 mice, at timepoints preceding osteoarthritic changes.[33] However, older surgical denervation models have wide ranging results published in mouse,[34] rabbit,[35] cat,[36] and dog,[37,38] which range from no evidence of spontaneous arthropathy[37,38] to rapid onset cartilage degeneration.[36] These older surgical models of denervation include dorsal root ganglionectomy and articular neurectomy which both have significant limitations, including lack of specificity for sensory nerves, as well as incomplete denervation with either approach. Importantly, no available experimental models of joint denervation recapitulate the features of neuropathic arthropathy.

In summary, Charcot arthropathy and RPOA have many common features in radiographic, histopathologic features and underlying circumstance. Further study is necessary to understand the basic pathophysiology of these two severe arthropathies.

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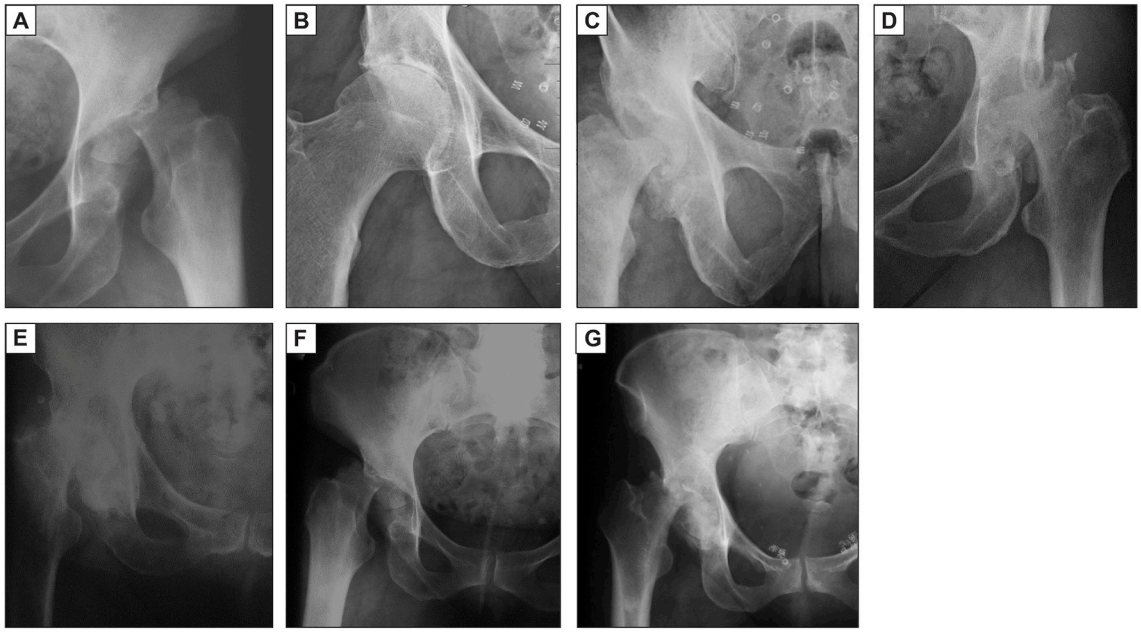


**Fig. 4.** Radiographic appearance of additional cases of RPOA. All images are taken of individual patients (with the exception of B and C which are obtained from the same patient at one month intervals). Age range is 50–69 years old, and all patients are female.

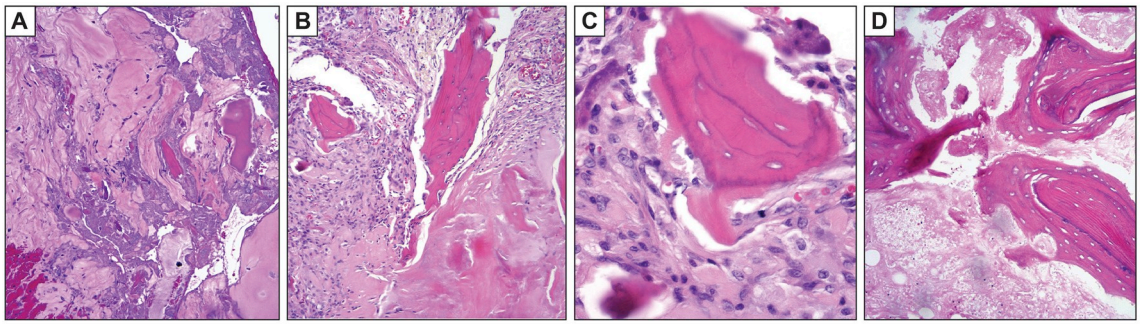


**Fig. 5.** Representative histologic appearance of RPOA. Histology from Fig. 3 case. (A) Extensive fragments of detritic bone and cartilage. (B) Detritic bone embedded in granulation and fibrous tissue. (C) Histiocytic inflammation surrounding detritic bone. (C) Granulation tissue response. (D) Rare foci of classic osteonecrosis, with necrotic bone and marrow space. Prominent repair is not seen.

**Table 2**
Comparison of features in Charcot joint and RPOA.

| Features | Charcot joint | RPOA |
|---|---|---|
| Association with innervation | Neuropathy | Anti-NGF therapy |
| Symptom | Weak pain | Severe pain |
| Common Site | Ankle<br>Foot | Hip<br>Knee<br>Shoulder |
| Pre-existing OA | No | Yes |
| Bone metabolism | Upregulated osteoclast activity<br>Osteopenia | Upregulated osteoclast activity<br>Osteoporosis<br>Osteomalacia |
| Local inflammation | Yes | Yes |
| Infection | Possible | None |
| Age | Middle age | Elderly |

RPOA: Rapid Progressive osteoarthritis; OA: Osteoarthritis; NGF: Nerve Growth Factor.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jor.2019.02.015.

## Author disclosure/conflict of interest statement

None.

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