Open Journal of Internal Medicine, 2012, 2, 27-30 **OJIM**
http://dx.doi.org/10.4236/ojim.2012.21006 Published Online March 2012 (http://www.SciRP.org/journal/ojim/)

Neuropathic arthropathy of the shoulder: Two cases of syringomyelia with cocaine use

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Received 3 August 2011; revised 6 December 2011; accepted 29 January 2012

ABSTRACT

Neuropathic arthropathy (NA) is a progressive, degenerative disorder associated with decreased sensory innervation of the involved joints. The shoulder joint is an uncommon presentation for NA, although syringomyelia is the most common cause for this joint. Two cases are presented of NA of the shoulder, with both patients having a history of syringomyelia and cocaine use. In both cases a work up for malignancy was negative, but imaging was consistent with NA. Although syringomyelia has been linked with this presentation in prior publications, the role of cocaine use may not be incidental, with complex biochemical interactions in bone metabolism. Cocaine has been shown to involve the Leptin, Neuromedin U (NmU), Cocaine and amphetamine-regulated transcript (CART), and Receptor activator of nuclear factor kappa-B ligand (RANKL) pathways of bone remodeling. Treatment can be challenging, involving concurrent use of pharmacotherapy, surgical correction, and protective bracing.

Keywords: Neuropathic Arthropathy; Charcot; Syringomyelia; Cocaine; RANKL

1. INTRODUCTION

Neuropathic arthropathy (NA), also known as Charcot Joint, is a progressive, degenerative disorder that is associated with decreased sensory innervation of the involved joints. Charcot Joint is most commonly associated with diabetes mellitus (DM), syringomyelia, and tabes dorsalis. In patients presenting with shoulder involvement, syringomyelia is the most common association [1]. Herein we present two cases of advanced Charcot Joint and their associated radiologic findings.

2. CASE REPORT 1

A 44 year old male patient, with history of cocaine use, was admitted through our Emergency Department with a complaint of right shoulder swelling and pain. He described an acute change in the right shoulder, moderate shoulder pain and paresthesias of the right hand. His symptoms progressed over one week's time, prompting his visit to the Emergency Room. His past medical history is significant for T3-11 syrinx, myxopapillary ependymoma resection, and multiple neurosurgical procedures. He was dependent on crutches for ambulation.

On examination, there was noted to be deformity of the right shoulder and bicep with significant swelling, and limited abduction and extension of the right shoulder. Sensation was diminished as compared to the left. Strength was graded as 4/5 for the shoulder joint as well as for grip. Right upper extremity reflexes could not be elicited. Joint position was preserved.

There was significant sclerosis of the right humeral head with soft tissue swelling noted on radiographs of the right shoulder. CT revealed right humeral sclerosis, with several heterogeneous masses extending over the region of the pectoralis, with the largest mass noted in the right bicep. MRI revealed fractures of the proximal humerus with erosion of the glenoid, as well as fracture of the coracoid process. There were significant inflammatory changes with soft tissue swelling. All images, therefore, were compatible with some destructive lesion involving the humeral head, with associated pathologic fractures with significant fluid collection.

A CT-guided biopsy was obtained, which was non-diagnostic. The patient was therefore brought to the operating room for open biopsy, with multiple specimens obtained. Pathology revealed no evidence of malignancy.

3. CASE REPORT 2

A 55 year old female patient, also with a history of cocaine, presented to our Emergency Department with a complaint of chest pain as well as right shoulder pain. She was admitted to evaluate acute coronary syndrome (ACS). Her past medical history is significant for uncontrolled DM, Hepatitis C, sickle cell trait, asthma, pancreatitis and chronic pain, with a history of a right hu-

meral bony lesion, that was biopsied several years earlier at another hospital. Once ACS was ruled out, the patient began to focus her complaints more on her right shoulder pain. The patient denies any history of trauma to the right upper extremity. Review of her hospital records revealed some evidence of bony destruction of the right humerus from ten years earlier.

On examination, the patient was noted to have an obvious deformity of her right upper extremity, with an apparent area of swelling extending from approximately the right shoulder to the distal aspect of the right deltoid. Range of motion was grossly limited, especially involving abduction, and extension. She also had grossly diminished strength to 3/5 for both flexion and extension. Sensation was grossly diminished when compared to the left.

Chest x-ray showed destruction of the right humeral head and anterior glenoid. CT revealed an expansile right axillary soft tissue mass with adjacent bony destruction, most consistent with a neoplasm. The prior biopsy report was obtained, and demonstrated a low grade spindle cell neoplasm most consistent with a low grade neoplasm of the bone. Given this history, her physical exam and radiographic findings, it was arranged for an open bone biopsy. Destruction of the osseous structures and joint was obvious. Multiple samples were sent to pathology, with no evidence of malignancy.

Based upon the pathologic results, as well as the clinical picture of the patient, it was determined she was likely suffering from neuropathic arthropathy. An MRI of the cervical spine was obtained, which revealed a syrinx extending from approximately C1 through T2, with gliosis at the C2-3 level.

4. DISCUSSION

4.1. Background/History

Neuropathic arthropathy (NA), also known as Charcot Joint, is associated with decreased sensory innervation of the involved joints. Although Mitchell was the first to describe this entity in 1831, Charcot brought attention to the disorder in 1868 [2].

4.2. Theories of Pathogenesis

Both Charcot and Mitchell speculated that the changes in the involved joint were secondary to damage in the trophic centers of the central nervous system (CNS), later known as the French Theory. Shortly thereafter, the German theory, proposed by both Volkmann and Virchow contended that NA was the result of multiple years of repeated, insensible trauma results in total joint destruction [2]. This theory has limitations, as NA is known to develop in bedridden patients, with no history of trauma. In addition, the neurotraumatic theory proposes that when the CNS is damaged, the joint exceeds the safe limits of normal range of motion due to decreased proprioception, resulting in the aforementioned repeated microtrauma, similar to the German theory, and ultimately total joint destruction [2]. The neurovascular theory holds that CNS damage results in a loss of vascular reflex, which produces locally increased blood flow, with bone resorption due to increased osteoclast activity. Although not performed in the two cases above, this can be correlated with increased uptake in nuclear bone scans and angiography demonstrating hypervascularity of the joint [2].

4.3. Clinical Features

NA has been reported to occur with a variety of diseases including: diabetes, tabes dorsalis, leprosy, syringomyelia, poliomyelitis, rheumatoid arthritis, multiple sclerosis, congenital neuropathy, traumatic injury, iatrogenic causes, and tertiary syphilis [3]. Both upper motor neuron (UMN) and lower motor neuron (LMN) lesions can potentiate sensory impairment and lead to NA [1].

The majority of cases of NA are seen in patients with underlying DM, usually accompanying peripheral neuropathy [4], and a painless monoarthritis. Currently, prevalence of NA is estimated to range from 0.08% in the general diabetic population to 13% in high-risk diabetic patients [4]. The development of arthropathy in this subset of patients with diabetes is likely multifactorial with a complex interaction between mechanical and vascular factors, vasomotor changes, and cytokine related changes to osteoclastic activity [5].

As demonstrated by both of our patients, NA can also be associated with syringomyelia [1,6], of which 20% to 25% of patients with syringomyelia developing NA, with a predilection for upper extremity joints [3]. An uncommon process, syringomyelia is characterized by a longitudinal cavitation of the spinal cord, leading to the loss of pain and sensory innervation of the involved joint, predisposing the patient to the development of NA. The involvement of a single joint helps categorize this arthritis in the group of monoarthropathies. The clinician should keep in mind that the differential diagnosis for a monoarthopathy is diverse, and appropriate history and examination is needed to distinguish (see **Table 1**).

4.4. Role of Cocaine

Of interest both patients reported in this series had a history of cocaine use. Whether cocaine use has contributed to the unusual findings in these two cases is unclear. It has been well documented that cocaine use can cause clinically significant vasospasm and ischemia [7]. It may be possible that a similar vaso-occulusive process can

Table 1. The differential diagnosis of acute monoarthropathies.

Adapted from Kelley's Textbook of Rheumatology 8*th ed.* 2008 [3]

- Acute Monoarthritis:
  - Infectious Arthritis
  - Crystal-induced Arthritis
- Other Causes of Acute Monoarthritis:
  - Patients without Systemic Manifestations:
    - Juvenile Idopathic Arthritis
    - Rheumatoid Arthritis
    - SeronegativeSpondyloarthropathies
    - **Neuropathic Arthropathy**
    - Hemarthroses
    - Lyme Arthritis
  - Patients with Signs of Systemic Illness:
    - Enteropathic Arthritis
    - Systemic Autoimmune Disease

potentiate neurovascular derangement, changes to blood flow, and eventual increased local osteoclast activity. In addition, cocaine's role as a neuropeptide, particularly in the regulation of Neuromedin U (NmU) may contribute to NA [8].

NmU is a is a neuropeptide found in the brain of humans and other mammals, with a number of diverse functions including bone growth and hormone release [1]. Recombinant NmU receptors have been found to increase the internal calcium concentration [9]. Previous work has shown that neuronal control of bone remodeling is mediated by leptin, and that leptin inhibits bone formation [10]. Like leptin, NmU is an anorexigenic neuropeptide that acts downstream and independently of leptin to regulate bone formation [10]. NmU-deficient (Nnm-/-) mice have high bone mass owing to an increase in bone formation (both trabecular and cortical bone) compared to Wild-Type (WT) mice [10,11].

NmU has been shown to modulate bone remodeling through a mechanism known as the *molecular clock*. In the hypothalamus, NmU stimulates the sympathetic nervous system, leading to anti-osteogenic activities without affecting bone resorption [10]. Sympathetic signaling in osteoblasts is gated by transcriptional factors referred to as the molecular clock (MC) [11]. MC genes are mediators of the inhibition of bone formation by leptin. These genes contribute to daily variation in bone marrow proliferation. Taken together, NmU, acting through the CNS affects the negative regulator of bone remodeling via leptin, that is, the MC in bone. One can infer that cocaine, therefore, as a sympathomimetic agent acting via NmU and through the CNS, can affect the MC in bone remodeling. In addition to bone formation, sympathetic signaling also regulates bone resorption. For example, Isoproterenol, a surrogate of sympathetic signaling, increases expression of Receptor activator of nuclear factor kappa-B ligand (RANKL) in osteoblasts, which results in the activation of osteoclastogenesis [11].

Besides NmU, leptin is reported to interact with other various hypothalamic neuropeptides, such as cocaine and amphetamine-regulated transcript (CART) and neuropeptide Y, all of which may modulate the effects of leptin on bone [11]. CART is a central mediator of leptin's action on bone resorption, and CART's expression is increased in NmU-/- mice as compared to WT, suggesting a protective activity of CART on bone resorption [10]. Thus, through CART, leptin leads to inhibition of bone resorption by decreased RANKL expression. Indeed, mice lacking CART have low bone mass due to an increase in bone resorption stimulated by RANKL [11].

It is difficult to say that cocaine was primarily responsible for the NA observed in the above cases, as cocaine's biochemical affect on the NmU-CART pathway is paradoxical. NmU stimulates sympathetic outflow and ultimately leads to decreased bone mass while CART, conversely, leads to sparing of bone mass. Furthermore, recent work shows that Leptin has a dose dependent effect: initial increases in leptin stimulate bone formation, however higher levels result in inhibition of bone formation [11]. Despite the complexity of this pathway, one can say that cocaine use leads to dynamic effects on bone remodeling.

4.5. Treatment of NA

The aim of NA treatment is to treat the underlying disease and decrease the rate of deformity to the lowest level [1]. It entails early diagnosis, proper management, and includes reducing further articular damage by prevention of repetitive trauma when it has a traumatic/physical etiology [12]. When present, the aspiration of large effusions and splinting will prevent further ligamentous laxity. When there is synovial inflammation, nonsteroidal anti-inflammatory drugs can be used [1]. Other therapeutic and conservative options include functional orthosis, physical therapy, and bisphosphonates, which have been found to be quite beneficial in reducing disease activity and bone turnover [12]. However, when these options prove not to be successful, procedural and surgical interventions should be considered. Surgical procedures require careful patient selection [12]. Surgical treatment options include: prosthetic replacement, resection arthroplasty or arthrodesis [1]. Surgical treatment options are not without risks due to the lack of protective pain sensation and reflexes, the presence of osteopenic

bone, and the weakness of the surrounding ligamentous and muscular tissues. The high stresses put on the implanted components leads to a high failure rate, in part by septic loosening and periprosthetic fractures [12]. Despite the occasional good result after surgical treatment, a non-operative treatment with the use of braces is probably the best solution for long-term management of these cases.

5. CONCLUSION

Charcot Joint can present a confusing clinical picture for the physician. It can often present with the sudden onset of pain in the involved joint without trauma. The clinical picture can be confusing for malignancy as well, as there is often concern for a lytic process. Although DM is the most common cause of NA, in cases of upper extremity NA it is imperative to screen for the presence of syringomyelia. Other patient factors, such as cocaine use, through complex biochemical mechanisms on bone physiology, may potentiate the development of NA. The radiologic findings, as outlined above, can be quite impressive, demonstrating total destruction of the involved joints and a dramatic soft tissue mass.

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