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Gouty Arthritis of the Spine in a Renal Transplant Patient: A Clinical Case Report

An Unusual Presentation of a Common Disorder

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Abstract: Axial gout is a well-documented but uncommon manifestation of gout. Its mimicking nature and the impracticality of axial joint aspiration might considerably delay its diagnosis. We report a case in a normouricemic renal transplant recipient, whereby the primary symptom of severe neck pain suggested pyogenic spondylodiscitis as an initial tentative diagnosis. Clinical findings included a high C-reactive protein concentration and elevated body temperature. The patient did not respond to empiric antibiotic treatment and suffered consecutive attacks of severe wrist and ankle pain in conjunction with a persistent fever. Blood and joint cultures were negative, but analysis of aspirated ankle joint fluid revealed monosodium urate crystals. A dual-energy computed tomography scan confirmed the presence of monosodium urate crystals in the costovertebral joints. Colchicine treatment dramatically improved the patient's clinical condition.

Axial gout should be considered in transplant recipients with severe neck or back pain, fever, and increased inflammatory parameters with a high likelihood of an infectious etiology, despite the presence of paradoxically normal or even decreased serum urate concentrations. Dual-energy computed tomography is a noninvasive technique of possible benefit in the detection of axial gout when joint fluid aspiration is not deemed safe.

(*Medicine* 94(13):e676)

Abbreviation: DECT = dual-energy computed tomography.

INTRODUCTION

Gout is characterized by the deposition of monosodium urate crystals in the synovial fluid of joints and soft tissue. It is an increasingly common cause of inflammatory arthritis affecting almost 2% of the population in industrialized countries and is even more common in kidney transplant recipients,[1,2] in whom it is associated with both decreased patient and death-censored graft survival.[3] Gout usually affects the peripheral joints, but involvement of the axial spine has been documented.[4] The prevalence of axial gout is largely unknown, but computed tomography (CT)-graphic evidence was observed in 35% of the patients with a history of long-standing, poorly controlled gout.[5] Hyperuricemia is the main risk factor for recurrent gout flares and is associated with a mature male population in conjunction with diuretic and alcohol, especially beer and spirits, intake.[6] Serum uric acid concentrations above 6.8 mg/dL might lead to supersaturation and formation of monosodium urate crystals, with subsequent deposition into joints and soft tissue causing gout attack.[3,4] Transplant recipients are even more at risk due to kidney dysfunction and exposure to cyclosporine, both of which increase the serum uric acid concentration.[3] Additionally, both cyclosporine and tacrolimus interact with colchicine, increasing its half-life and thereby potentiating toxicity.[7,8]

Clinical features of axial gout encompass a broad spectrum ranging from radiculopathy, neurologic compression, or acute back pain to a complete absence of symptoms. Its prevalence is probably underestimated as this extensive array of symptoms mimic other conditions such as spondylodiscitis, discogenic disease, and osteoarthritis.[4]

The gold standard for diagnosing gout is the detection of monosodium urate crystals in the joint fluid using polarized light microscopy. Additionally, dual-energy CT (DECT) is a highly specific and sensitive imaging modality, used increasingly in the detection of crystal deposits in the joint.[9]

METHODS

Informed consent was obtained.

CASE REPORT

A 51-year-old white male laborer developed a febrile syndrome of unknown origin, 2 months after renal transplantation. He presented with a history of gouty arthritis and end-stage kidney disease due to reflux nephropathy, for which he received a second graft in June 2014; this was after the development of end-stage kidney disease due to biopsy-proven interstitial fibrosis and tubular atrophy in his first graft. He was taking tacrolimus and mycophenolate mofetil as maintenance immunosuppressive treatment after withdrawal of corticosteroids a few weeks before admission, following the development of serous central chorioretinopathy. At presentation, he complained of acute-onset severe dorsal pain, radiating to both shoulders. Both active and passive mobility of his lower cervical spine were reduced and upon palpation was tender. His body temperature was elevated (37.9°C), but vital signs and clinical examination were unremarkable. Blood tests showed an elevated C-reactive protein (CRP) concentration (146.2 mg/L, normal range < 5.0 mg/L) and a serum creatinine

Editor: Pavlos Malindretos.
Received: December 24, 2014; revised: February 26, 2015; accepted: February 28, 2015.
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The authors have no funding and conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000676

of 1.48 mg/dL (baseline 1.3 mg/dL) with an estimated glomerular filtration rate of 54 mL/min/1.73 m^2. White blood cell count, liver function tests and serum uric acid concentration were unremarkable. Neurological investigation and lumbar puncture results were negative. Radiographic and CT-graphic imaging of the cervical spine showed degenerative lesions. We initiated intravenous analgetics and amoxicillin-clavulanic acid, and his general condition improved slightly, with diminished pain and a decline in CRP.

Seven days after admission, he suddenly reexperienced severe neck pain. Urgent magnetic resonance imaging (MRI) of the spine disclosed degenerative lesions, consistent with the earlier findings on CT- and radiographic imaging. No signs of spondylodiscitis were visualized, and MRI offered no explanation for his febrile syndrome; MRI of early vertebral osteomyelitis and discitis may, however, show nonspecific lesions.[10] We subsequently conducted a positron emission tomography (PET)-CT scan in order to find a focus of infection. The PET-CT scan showed increased glucose metabolism at thoracic vertebrae levels 1 and 2 (Figure 1). These findings on PET-CT caused us to suspect spondylodiscitis, despite the negative MRI imaging. We upgraded the antibiotic treatment to piperacillin/tazobactam and teicoplanin in response to spiking fever with repeated negative blood, urine, and stool cultures. Nevertheless, he developed severe wrist and ankle pain over the following days and remained febrile. During his hospital stay, we did a thorough workup to uncover the focus of his assumed infection. Repeated transthoracic and transesophageal ultrasonography of the heart did not reveal endocarditis. Culture and/or polymerase chain reaction of bronchoalveolar lavage fluid results were negative, including mycobacteria, fungi, and yeasts, and we did not detect galactomannan antigen. Serologic testing for brucella antibodies was negative. Bone marrow puncture showed no abnormalities and Ziehl–Neelsen staining was negative. We did not observe any location of increased glucose metabolism on PET scans, other than the above-mentioned localization. Culture and Ziehl–Neelsen staining of the joint fluid of both wrist and ankle were negative. However, we did confirm the presence of monosodium urate crystals in association with leukocytes (43000/μL and 95% polymorphonuclear), on polarized light microscopy of the ankle joint fluid. Serum uric acid was as low as 1.9 mg/dL (normal range 3.4–7 mg/dL) during the acute phase of his axial and peripheral pain attacks (Figure 2).

Despite treatment with broad-spectrum antibiotics, the patient remained febrile with a further CRP increase up to 276.7 mg/L. This caused us to radically change our perspective. We now considered axial gout as an explanation for the sudden-onset axial pain and peripheral arthritis in this patient, as well as his history of gout, the presence of monosodium urate crystals in the ankle joint fluid, and recent interruption of corticosteroids. Reminiscent of this, a DECT scan finally confirmed axial gout (Figure 3) at the costovertebral joints of thoracic vertebrae 1 and 2, consistent with the location on PET/CT scan (Figure 1). Only after we initiated colchicine at a dose of 1 mg daily in 2 separate doses did our patient completely recover; he was discharged in good health with a normalized CRP. We started him on a 150 mg daily dose of prophylactic allupurinol 2 weeks later.

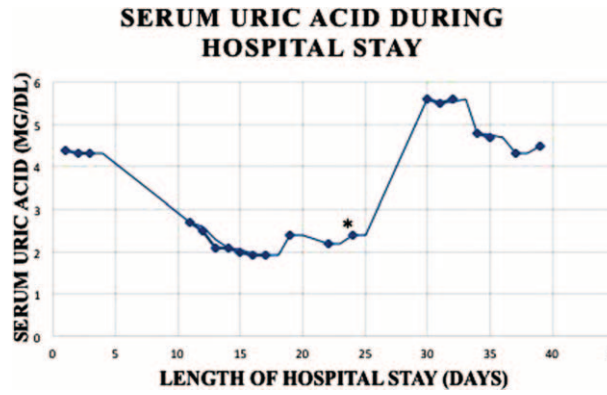

FIGURE 2. Serum uric acid during the course of the patient's hospital stay with sudden decrease during the acute phase of the arthritis episode and recovery after colchicine treatment. *, Start colchicine treatment.

Figure 4 depicts the patient's clinical course and treatment during the hospital stay. The serum CRP remained high despite broad-spectrum antibiotic coverage. The course of the patient's clinical manifestations with the development of consecutive attacks of severe neck, wrist, and ankle pain is outlined. Only after initiation of colchicine, the CRP concentration reached the normal range (<5 mg/L) and the patient's symptoms resolved.

DISCUSSION

In this case history, we initially suspected pyogenic spondylodiscitis as the primary culprit. Despite a history of gout, the index of suspicion for a gout attack was very low following the initial localization, the findings on MRI, the spiking fever, the low-to-normal uric acid, despite kidney dysfunction and the use of tacrolimus instead of cyclosporine.

The incidental detection of monosodium urate crystals in the ankle joint fluid urged us to confirm the diagnosis of axial gout on DECT as we did not consider spinal aspiration safe. The gold standard in diagnosing gout, at least in atypical cases, is to

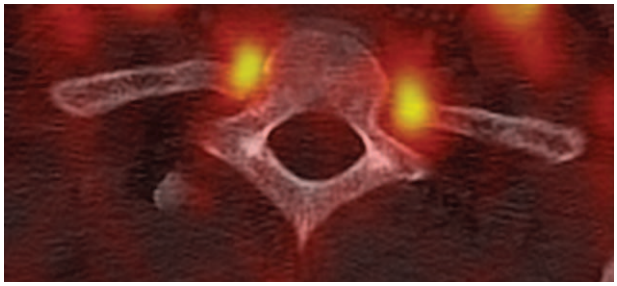

FIGURE 1. PET/CT scan showing an increased glucose metabolism on the level of thoracic vertebrae 1 and 2. CT = computed tomography, PET = positron emission tomography.

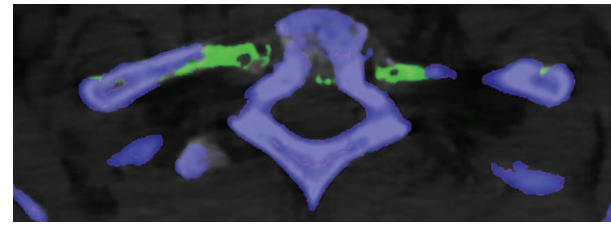

FIGURE 3. DECT images showing costovertebral deposition of monosodium urate crystal deposition (in green) at the level of thoracic vertebrae 1 and 2 (axial projection). DECT = dual-energy computed tomography.

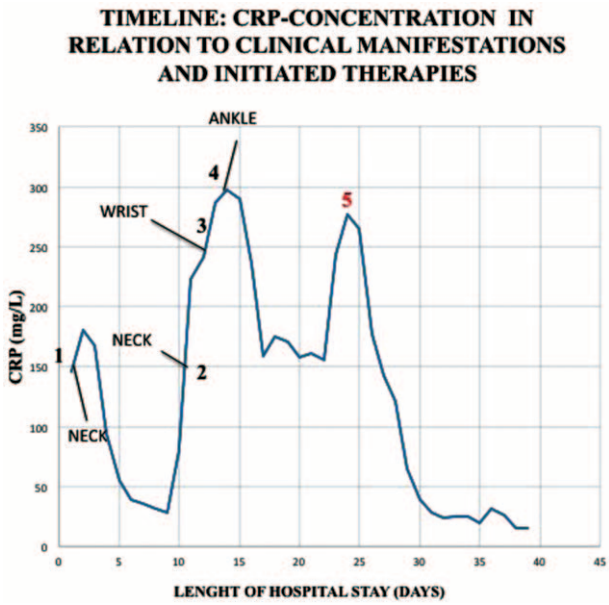

FIGURE 4. Timeline: CRP concentration in relation to clinical manifestations and initiated treatment. , CRP (mg/L); 1, amoxicillin-clavulanic acid (day 0); 2, upgrade to piperacillin-tazobactam (day 10); 3, upgrade to piperacillin-tazobactam + teicoplanin (day 12); 4, upgrade to piperacillin-tazobactam + teicoplanin + ketoconazole (day 13); 5, Stop antibiotics, Start colchicine (day 24). CRP = C-reactive protein.

confirm monosodium urate crystals in the aspirated joint fluid.[6] As this procedure is not always feasible, DECT might be of use. In a recent diagnostic accuracy study, sensitivity of DECT in the detection of monosodium urate crystals was 90%, and specificity was 83%.[9]

In this patient, the CT and MRI scans disclosed no abnormalities other than degenerative lesions, and as such they could not offer us an explanation for the patient's febrile syndrome. However, PET/CT scan showed an increased glucose metabolism on the level of thoracic vertebrae 1 and 2, consistent with the localization on DECT scan (Figures 1 and 3). PET/CT scan is a highly sensitive technique to detect inflammation, and this technique has recently been described as an imaging technique in spinal and sacroiliac gout.[11]

During the acute phase of the gout attacks, our patient's serum uric acid dropped from within the normal range to 1.9 mg/dL (normal range 3.4–7 mg/dL) and normalized after initiation of colchicine. Approximately 80% to 90% patients with gout are hyperuricemic,[12] but a normal serum uric acid concentration at presentation does not exclude the disease.[13] During the acute phase of the attack, serum concentrations of uric acid are often decreased, possibly due to increased renal urate excretion associated with the inflammatory reaction.[6,14] The exact mechanism, however, remains elusive. It is possible that antioxidant uric acid becomes increasingly consumed through its scavenging of free radicals, produced in the inflammatory process.[15]

Both diagnosis and treatment in this patient were quite a challenge. Corticosteroids were contraindicated considering his central chorioretinopathy, and nonsteroidal anti-inflammatory drugs were avoided because of the potential risk of graft dysfunction. Nonsteroidal anti-inflammatory drugs can potentiate calcineurin inhibitor toxicity.[16] Although, by definition, nonsteroidal anti-inflammatory drugs are not contraindicated in a renal transplant patient with mild-to-moderate chronic kidney disease, we were reluctant to prescribe them. We therefore considered colchicine as the preferable treatment option. Hepatic CYP3A4 is involved in the metabolism of colchine, which is a substrate for P-glycoprotein, a transmembrane protein that excretes the drug from the hepatocyte cannicular membrane into the bile. Tacrolimus inhibits both the CYP3A4 enzyme and the P-glycoprotein, potentiating the risk of toxic concentrations of colchicine.[7] The Food and Drug Administration suggests dose reduction or even interruption of colchicine if treatment with a P-glycoprotein or strong CYP3A4 inhibitor is required. Severe colchicine-induced myopathy in tacrolimus-treated renal transplantations has been reported.[17] We failed, however, to detect any serum creatinine kinase concentration increases during low-dose colchicine treatment in our patient.

Interestingly, interleukin-1 inhibitors are an alternative option in the control of an acute gout attack. Interleukin-1 is a proinflammatory cytokine that plays a major role in the inflammatory process during acute flares. To date, 3 interleukin-1 inhibitors, anakinra, canakinumab, and rilonacept, are currently under investigation for their use in the treatment of gout. However, the efficacy of these interleukin-1 inhibitors has yet to be further investigated. At present, the European Medicines Agency has approved canakinumab for the treatment of acute gout in adults who have undergone 3 or more attacks within 12 months, in whom nonsteroidal anti-inflammatory drugs and colchicine are either contraindicated or do not provide an adequate response to first-line options, and in whom repeated courses of corticosteroids are not appropriate.[18] However, a recent Cochrane review highlighted the fact that there are currently no trials comparing canakinumab to colchicine or nonsteroidal anti-inflammatory drugs.[19]

Despite the patient's normal serum uric acid concentrations, we prescribed allopurinol as prophylaxis. Urate-lowering therapy is indicated for patients with recurrent gout attacks, chronic arthropathy, tophi, and gout with uric acid stones. The aim of urate-lowering therapy is to maintain the urate concentration below the saturation point of monosodium urate. Target serum uric acid concentrations <6 mg/dL are advised, but in severe gout even lower concentrations are recommended as the rate of tophus disappearance is inversely related to uricemia.[1]

We conclude that, despite the fact that gout typically involves peripheral joints, axial gout should be considered in every patient with severe axial pain, inflammation, and fever, especially those with a history of gout. Diagnostic pitfalls are its mimicking clinical nature, difficulties in joint aspiration, and normal-to-low serum uric acid concentrations. Joint aspiration and detection of monosodium urate crystals on polarized light microscopy is superior to DECT in the diagnosis of gout in atypical cases; however, DECT might be extremely helpful when joint puncture and fluid aspiration are neither easy nor safe to perform.[9] Colchicine toxicity should be monitored in renal transplant recipients receiving cyclosporine or tacrolimus. Of key importance, early recognition of the atypical nature of spinal gout might save time, money, and, most importantly, greatly reduce a patient's suffering and pain.

ACKNOWLEDGMENTS

We thank Sarah Knapp for her linguistic review of the manuscript.

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