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Clopidogrel-Associated Migratory Inflammatory Polyarthritis

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Case series
Patients: Male, 54 • Male, 77
Final Diagnosis: Clopidogrel associated migratory inflammatory arthritis
Symptoms: Joint pain • joint swelling
Medication: Clopidogrel
Clinical Procedure: —
Specialty: Rheumatology

Objective: Challenging differential diagnosis

Background: Clopidogrel is an antiplatelet medication that plays an important role in primary management and secondary prevention of thrombotic vascular events in patients with acute coronary syndrome. It is generally well tolerated by most patients, but rare adverse effects such as inflammatory arthritis has been noted. A very few cases of migratory polyarthritis secondary to clopidogrel have been reported in the literature.

Case Report: We describe 2 cases of acute migratory polyarthritis associated with clopidogrel that resolved with discontinuation of clopidogrel and did not recur after prasugrel initiation. In the first case, the patient presented with migratory polyarthritis approximately 2–3 days after initiating clopidogrel, and the symptoms lasted in each joint for 1–2 days. In the second case, the migratory polyarthritis started 1 week after initiating clopidogrel, and the symptoms lasted in each joint for approximately 2–3 days. The symptoms completely resolved after discontinuing clopidogrel in both the cases, which is typical of an immune-mediated drug reaction. A diagnosis of acute migratory inflammatory polyarthritis related to clopidogrel was determined in both cases by excluding other conditions causing inflammatory arthritis. In both cases, the eosinophil count was within normal limits, thereby differentiating the disease process from an acute allergic reaction.

Conclusions: Identifying the etiology of inflammatory arthritis in a patient on clopidogrel needs extensive evaluation. The diagnosis of clopidogrel-related inflammatory arthritis is often missed due to lack of awareness. Early diagnosis and timely intervention are essential, as the symptoms completely resolve after discontinuing clopidogrel.

MeSH Keywords: Arthritis • Platelet Aggregation Inhibitors • Thienopyridines

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Background

Clopidogrel is a thienopyridine, selective, irreversible ADP receptor/P2Y12 inhibitor. As clopidogrel has antiplatelet activity, it plays an important role in primary management and secondary prevention of thrombotic vascular events in patients with acute coronary syndrome [1,2]. The most common adverse effect of clopidogrel is increased risk of gastrointestinal bleeding [3]. Clopidogrel is well tolerated by most patients, but rare adverse effects such as inflammatory arthritis have been noted. A review of the literature found that very few cases of inflammatory arthritis due to clopidogrel have been reported [4–13]. We describe 2 cases of acute polyarthritis associated with clopidogrel that resolved with discontinuation of clopidogrel and did not recur after prasugrel initiation.

Case report

Case 1

A 54-year-old white man with history of ST elevation myocardial infarction requiring percutaneous intervention (PCI) and drug-eluting stent placement (DES) presented 2 weeks later to a local emergency room with complaints of bilateral shoulder pain, left hand pain, and swelling. He was started with a loading dose of clopidogrel, and was later continued on clopidogrel and aspirin as dual-antiplatelet therapy in the view of his acute myocardial infarction. The other medications initiated were coumadin, atorvastatin, carvedilol, and furosemide for acute myocardial infarction complicated by left ventricular thrombus. Approximately 2–3 days after initiating the medications, he complained of bilateral shoulder pain and right hand pain with diffuse swelling. The initial impression was statin-induced myalgias; therefore, atorvastatin was discontinued. The furosemide dose was adjusted for acute renal insufficiency. A week later, he was re-evaluated in our emergency room for worsening bilateral shoulder pain associated with tingling and numbness of both hands, new-onset left hand pain, and right hip pain.

On examination, the patient was sitting comfortably; his heart rate was 88 bpm, blood pressure was 156/57 mmHg, and temperature was 100°F (37.8°C). The cardiovascular system, abdomen, lungs, and skin examinations were within normal limits. A neurology examination showed normal sensory examination, normal deep-tendon reflexes, and normal strength in all extremities except for 4/5 power in both proximal and distal muscles of the left upper extremity. On joint examination, Heberden's nodes and Bouchard's nodes on the 2nd through 5th fingers were present bilaterally. He had swelling and tenderness involving the dorsum of the left hand and wrist, associated with decreased range of motion. A bilateral shoulder joint examination showed restricted active and passive range of motion. The right knee had very minimal effusion, no tenderness on palpation, and normal range of motion.

Laboratory testing showed a white blood cell count of 13.5 K/mm^3 (normal 3.7–10.5 K/mm^3) with 78% neutrophils, 8.1% lymphocytes, and 0.9% normal eosinophils. He had elevated blood urea nitrogen (38 mg/dL; normal, 10–20 mg/dL) and serum creatinine (1.3 mg/dL (normal, 0.7–1.3 mg/dL). His erythrocyte sedimentation rate (ESR) was 101 mm/h (normal, 0–15 mm/h) and C-reactive protein (CRP) was 29.7 mg/dL (normal, 0–0.5 mg/dL). The serum uric acid level was 10.9 mg/dl (normal, 2–7.8 mg/dl) with normal liver function tests and normal serum creatine kinase 44 IU/L (normal, 39–308 IU/L).

He was evaluated by neurosurgery and orthopedic surgery for the bilateral upper-extremity tingling and numbness and the left upper-extremity weakness. An MRI of the cervical spine demonstrated severe stenosis at C5–C6. The cervical spine was stabilized with a soft cervical collar as the patient was on coumadin and dual-antiplatelet therapy. Elective surgery was planned once the patient was stable enough to tolerate anticoagulation and dual-antiplatelet agents prior to surgery.

On day 3 of hospitalization, the inflammatory markers were still elevated, with ESR of 116 mm/h and CRP of 26.6 mg/dL. On evaluation, the left hand pain and swelling had resolved, but he had developed similar pain and diffuse swelling involving the soft tissues of the right hand. An infectious disease workup was negative.

On day 4 of hospitalization, clopidogrel was discontinued and the patient was started on prasugrel 10 mg orally daily and continued on aspirin for post-PCI thrombosis prophylaxis. The next day, the right hand pain and swelling had completely resolved and the inflammatory markers were improved, with ESR of 11 mm/h and CRP of 5.1 mg/dL. There was no reoccurrence of symptoms. However, the bilateral upper-extremity tingling and numbness, as well as the left upper-extremity weakness, persisted due to the severe stenosis at C5–C6, and there was no progression of those symptoms.

The diagnosis of clopidogrel-induced acute polyarticular inflammatory arthritis was determined by excluding other causes of this condition, including statin-induced myalgia, infectious, crystal arthropathy, rheumatoid arthritis, and immune-mediated reaction to other medications.

Case 2

A 77-year-old white man with a history of hypertension, lymphoma, and recently-diagnosed crescendo angina requiring PCI 2 weeks prior presented with complaints of left shoulder

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and left hip pain. He was started on a loading dose of clopidogrel, and was later continued on clopidogrel and aspirin as dual-antiplatelet therapy, along with isosorbide nitrate for angina after his PCI. He was continued on his home medications, which included atorvastatin, carvedilol, lisinopril, and multivitamins. Approximately 1 week after starting dual-antiplatelet therapy, he developed acute nocturnal onset of severe left hand pain and swelling extending from his lower forearm to the distal fingers. The pain was associated with erythema, stiffness, and warmth. He was evaluated in his local emergency room and discharged home with hydromorphone. His symptoms resolved gradually. The following week he developed similar symptoms in the right forearm and hand and he was evaluated by his primary care physician. The initial impression was gout, and he was started on colchicine. A week later, these symptoms resolved and he then developed pain and stiffness of the right shoulder despite continuing colchicine therapy. He was evaluated in the rheumatology clinic 6 days later. His right shoulder pain had resolved but he then had severe pain and restriction of mobility of his left shoulder and left hip joints. He also complained of subjective fever, chills, weight loss, and asthenia for the last 3 weeks.

On examination, the patient was sitting comfortably; his heart rate was 62 bpm, blood pressure was 183/78 mmHg, and temperature 98.1°F (36,7°C). The cardiovascular system, abdomen, neurology exam, and skin examination were within normal limits. The lungs exams revealed bilateral basilar crackles. On joint examination, there was tenderness on palpation and restricted range of motion of the left shoulder joint and left hip joint.

On review of labs obtained at the local emergency room, the cell counts, renal function, liver function test, ESR and CRP, and uric acid were reported within normal limits. The rheumatoid factor and anti-cyclic citrullinated were negative. Repeat laboratories at the primary care physician's office showed an ESR of 62 mm/h and CRP of 13.9 mg/dL. Repeat ESR and CRP at the rheumatology clinic were 92 mm/h and 15.3 mg/dL, respectively. An infectious disease work-up was negative. Arthrocentesis was negative for crystals and infection. The radiology images of the bilateral shoulder joints, hip joints, and hand were reported to be within normal limits.

Since common causes of inflammatory polyarthritis were excluded, including rheumatoid arthritis, crystalline arthritis, infectious, and post-infectious etiologies, our impression was clopidogrel-induced polyarthritis. After discussion with his interventional cardiologist, clopidogrel was discontinued and the patient was started on prasugrel 10 mg orally daily and continued on aspirin for post-myocardial infarction thrombosis prophylaxis. The symptoms completely resolved and the inflammatory markers returned to baseline, with ESR of 31 mm/h and CRP of 0.5 mg/dL. There was no recurrence of symptoms.

Discussion

Platelets play an important role in the pathogenesis of atherothrombotic coronary artery disease. Antiplatelet therapy has been an important pharmacotherapy for the management of coronary artery disease for several decades [14]. The known antiplatelet medications are ticlopidine, clopidogrel, ticagrelor, and prasugrel. These medications play an important role in preventing thrombotic vascular events in patients with acute coronary syndrome. The dual-platelet therapy after myocardial infarction reduces the risk of stent thrombosis, myocardial infarction, and, possibly, cardiovascular death [1,2].

Although ticlopidine, ticagrelor, clopidogrel, and prasugrel are in the antiplatelet class of medications, inflammatory arthritis has been noted with clopidogrel [4–13] and ticlopidine [15]. There currently are no reported cases of polyarticular arthritis associated with ticagrelor or prasugrel. The exact mechanism of inflammatory polyarthritis associated with clopidogrel and ticlopidine is unknown. Studies done on rat models suggest that proinflammatory effect of clopidogrel may be due to an unknown effect on cells, rather than on platelets, via an increase in proinflammatory cytokines such as IFN-γ, IL-6, and IL-1β [16]. Further studies are required to elucidate this mechanism and may be the key to understanding how to better treat this condition.

Migratory polyarthritis secondary to clopidogrel is a diagnosis of exclusion. In our first case, the patient presented with migratory polyarthritis approximately 2–3 days after initiating clopidogrel, and the symptoms lasted in each joint for 1–2 days. He had elevated serum uric acid, most likely due to acute renal insufficiency. Polyarticular gout was a possible diagnosis; however, in gouty arthritis, symptoms in each joint typically persist for approximately 3–10 days without any active intervention [17] and the serum uric acid levels are often normal to low during the acute gout attack [18]. In this patient, the elevated serum uric acid levels were most likely due to acute renal insufficiency. After discontinuing clopidogrel, the joints pain and the very minimal left knee effusion completely resolved, so arthrocentesis was deferred. The inflammatory markers returned to baseline, which is typical of an immune-mediated drug reaction. Prasugrel was the selected alternative antiplatelet therapy [19].

In our second case, the migratory polyarthritis started 1 week after initiating clopidogrel, and the symptoms lasted in each joint for approximately 2–3 days. Clinical examination and laboratory findings ruled out other possible causes of acute inflammatory polyarthritis. The symptoms completely resolved after discontinuing clopidogrel.

In both cases, the loading dose of clopidogrel was similar, but in the first case symptoms started after a few days, and in the second case the patient became symptomatic 1 week after

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initiating the clopidogrel therapy. A diagnosis of acute migratory inflammatory polyarthritis related to clopidogrel was determined in both the cases by excluding other causes of this condition, including statin-induced myalgia, infectious or post-infectious process, crystal arthropathy, rheumatoid arthritis, and immune-mediated medication reaction to other medications. In both cases the eosinophil count was within normal limits, thereby differentiating the disease process from an acute allergic reaction [20–22]. The symptoms completely resolved after discontinuing clopidogrel, and the inflammatory markers returned to baseline. There was no reoccurrence of symptoms in either case after starting prasugrel.

A review of the literature showed very few cases of clopidogrel-related inflammatory arthritis [4–13]. All these cases developed symptoms with elevated inflammatory markers within 1–3 weeks after initiating clopidogrel. In all these cases, the inflammatory markers returned to baseline and the symptoms resolved after discontinuing the clopidogrel and changing the therapy to either ticagrelor or prasugrel. Such cases need to be reported in the literature, as early diagnosis and timely intervention can completely resolve the symptoms.

Conclusions

Identifying the etiology of inflammatory arthritis in a patient on clopidogrel needs extensive evaluation. Rare conditions like clopidogrel-related inflammatory arthritis should not be missed in these patients. Clopidogrel-related inflammatory arthritis is challenging to diagnose and requires a high level of suspicion. Early diagnosis and timely intervention are essential, as the symptoms completely resolve after discontinuing clopidogrel, and the inflammatory markers return to baseline. There was no recurrence of symptoms in our 2 cases after starting prasugrel.

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