Migratory Polyarthritis Associated With Clopidogrel: A Case Report

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Abstract- Clopidogrel, a selective thienopyridine, is used for secondary prevention of major adverse cardiovascular events. Some studies have reported inflammatory arthritis as a rare adverse effect of Clopidogrel. A 47-year-old male underwent percutaneous coronary intervention and was subsequently prescribed a 600 mg loading dose of Clopidogrel, followed by a daily dose of 75 mg. After six days of taking Clopidogrel, the patient presented to the emergency department with right knee pain. The knee joint exhibited swelling, warmth, and tenderness, although there was no redness or crusting. After two and six days of hospitalization, despite receiving antibiotics and Indomethacin, he developed arthritis of the metacarpophalangeal and metatarsophalangeal joints, respectively. According to the laboratory investigation, cultures, synovial fluid analysis, and imaging, infectious, rheumatologic, and crystallopathy diseases were ruled out for the patient. Clopidogrel was discontinued, and the patient was switched to ticagrelor 90 mg twice daily. All symptoms and signs of joint inflammation had improved within five days of stopping the Clopidogrel. After one week and one and six months of follow-up, there has been no recurrence of symptoms.

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Keywords: Clopidogrel; Arthritis; Case report

Introduction

Coronary artery disease is currently the most common cause of death from non-communicable diseases globally (1-3). Clopidogrel is a selective thienopyridine used for secondary prevention of major adverse cardiovascular events following revascularization of coronary artery disease (4,5). The incidence of Clopidogrel adverse effects is rare, and patients often exhibit good tolerance. Gastrointestinal bleeding is the most prevalent side effect of Clopidogrel. Other adverse effects include back pain and arthralgia (6). Inflammatory arthritis has been reported in some studies as a rare adverse effect of Clopidogrel (4,7). We documented a male patient with migratory polyarthritis linked to Clopidogrel treatment.

Case Report

A 47-year-old man diagnosed with non-ST segment elevation myocardial infarction underwent percutaneous coronary intervention (PCI) with a drug-eluting stent. He had been on aspirin 81 mg daily, atorvastatin 80 mg daily, and metoprolol succinate 25 mg twice daily for six months due to stable ischemic heart disease. Additionally, he had been taking Amlodipine/Valsartan for hypertension for two years. Following the PCI, he was also started on Clopidogrel with a 600 mg loading dose, followed by 75 mg daily. He reported no other systemic diseases, allergies, or medications.

Two days after being discharged (six days after starting Clopidogrel), the patient was referred to the emergency department due to experiencing pain in his right knee. He reported no fever and chills, diarrhea, dysuria, or cough. On the first examination at hospitalization, he was afebrile (T=36.9° C) with respiratory rate, plus rate, and blood pressure of 16 breaths/Min, 68 beats/Min, and 108/64 mmHg, respectively. Additionally, the knee joint exhibited swelling, warmth, redness, and tenderness without crusting (Figure 1). He was hospitalized with a diagnosis of arthritis. Examination of the skin, cardiovascular, respiratory, gastrointestinal, genitourinary, and nervous

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systems revealed no abnormalities. The patient had not recently traveled, received blood transfusions, or engaged in unsafe sexual activity. Following the necessary laboratory tests to assess the causes of arthritis, he was prescribed empiric antibiotics and Naproxen (500 mg twice daily).

After two days of hospitalization, despite receiving antibiotics, he developed swelling, erythema, and arthralgia of the metacarpophalangeal (MCP) joint of the third finger of the right hand with a significantly limited range of motion (Figure 1). Radiography of the knee and MCP joints showed only soft tissue swelling without erosion, fracture, or deformity (Figure 2).

The initial laboratory investigation revealed a white blood cell count of 15.24×10^9/L (reference range: 4.6-10.2×10^9/L), an erythrocyte sedimentation rate (ESR) of 63 mm/hr (reference range in males < 50 years old: ≤15 mm/hr), a C-reactive protein (CRP) level of 4.60 mg/dL (reference range: 0.3-1.0 mg/dL). A complementary laboratory workup showed a normal range of blood uric acid concentration (4.4 mg/dL), hemoglobin (15.4 g/dL), blood urea nitrogen (23 mg/dL), and serum creatinine levels (1.1 mg/dL). Liver and thyroid function tests were normal, and blood and urine cultures were negative twice. Serum tests for Brucella and Lyme disease, rheumatologic tests, including antinuclear antibodies, antibodies to extractable nuclear antigens, antineutrophilic cytoplasmic antibodies, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, and the HLA-B27 typing were negative. Serum and urine protein electrophoresis and immunofixation were unremarkable. Synovial fluid analysis showed some white blood cells with negative culture and without crystals. Infectious, rheumatologic, and crystallopathy diseases were ruled out for the patient. Therefore, the antibiotic was stopped .

On the sixth day of hospitalization, the patient developed arthralgia and swelling of the left metatarsophalangeal (MTP) joint of the third finger of the left foot with erythema and limited range of motion (Figure 1).

Based on the findings and literature review, it was determined that arthritis was associated with Clopidogrel. Clopidogrel was discontinued, and the patient was switched to Ticagrelor 90 mg twice daily. Within five days of stopping Clopidogrel, all symptoms and signs of joint inflammation had improved, and the patient was discharged. There were no recurring symptoms after one week and then again at six months of follow-up.

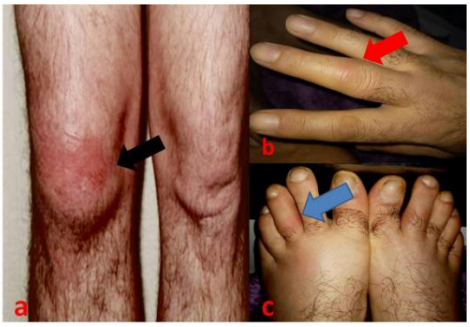

Figure 1. Migratory polyarthritis associated with Clopidogrel. The initial presentation was swollen, warm, erythema, and tender without crusting of the knee joint (1a, Black arrow). Next, swelling and erythema of the MCP joint of the third finger of the right hand with a marked limited range of motion (1b, Red arrow). Eventually, swelling of the left MTP joint of the third finger of the left foot with erythema and limited range of motion (1c, Blue arrow). MCP, metacarpophalangeal; MTP, metatarsophalangeal

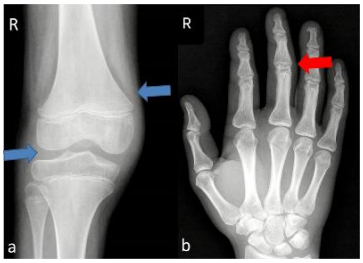

Figure 2. The X-ray showed soft tissue swelling of the right knee joint (1a, Blue arrow) and proximal MCP of the third right finger joint (1b, Red arrow) without erosion, fracture, or deformity

Discussion

In this study, we presented a case of a CAD patient with migratory polyarthritis. Common causes of arthritis include infectious or postinfectious state, crystal arthropathies, rheumatoid arthritis, and immune-mediated adverse drug reactions. In order to diagnose Clopidogrel-related arthritis, other common causes must be ruled out (7). Based on the results of the assessments, the potential diagnoses were ruled out for our patient. Additionally, statin-related arthralgia was not considered due to its use a year prior. Arthritis related to Clopidogrel was confirmed by excluding other potential diagnoses and the resolution of arthritis after stopping the Clopidogrel.

Adverse effects linked to Clopidogrel have been documented in studies, including bursitis, arthralgia, polyarthritis, and migratory polyarthritis (4,6-8). Acute arthritis induced by Clopidogrel can impact both large and small joints. The key features of acute arthritis related to Clopidogrel encompass fever, rash, pruritis, and acute arthritis (8). Consistent with the current study, this complication may manifest within a few days of administration or up to three weeks after starting Clopidogrel (6,7). The mechanisms behind this complication have not been determined, but it appears that arthritis is caused by activating proinflammatory cytokines (9). Arthritis with elevated plasma levels of proinflammatory cytokines, including Interferon-gamma, IL-6, and IL-1b, leukocytosis and neutrophilia, and increased platelet counts have been observed in model rats treated with Clopidogrel compared to untreated model rats. Increases in inflammation markers (ESR and CRP) have also been shown to be Clopidogrel-induced arthritis, similar to the present study (9,10).

Management principles involve discontinuing Clopidogrel and managing symptoms with nonsteroidal anti-inflammatory drugs. Arthritis gradually subsides after stopping Clopidogrel, typically within four days (8,10). In our patients, symptoms resolved within five days after discontinuing Clopidogrel. Other antiplatelet therapies, including Ticagrelor and Prasugrel, should be considered after discontinuing Clopidogrel. Based on previous research, arthritis has been observed with Clopidogrel and Ticlopidine, while patients tolerate Ticagrelor (7,10). Currently, there are no reports of acute arthritis associated with Ticagrelor. In the current study, the patient was switched to Ticagrelor, and there has been no reoccurrence of arthritis. Given the widespread use of Clopidogrel globally, this study may aid in promptly and efficiently diagnosing Clopidogrel-induced arthritis.

Migratory polyarthritis is a rare adverse reaction of Clopidogrel, and it should be considered in patients with arthralgia after the beginning of Clopidogrel.

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