Acute Polyarthritis Associated with Clopidogrel Treatment

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Atherothrombotic coronary artery disease is the most common cause of death worldwide and a growing public health problem. Platelets play a central role in the pathogenesis of atherothrombosis and are therefore commonly targeted by one or more antiplatelet drugs as part of primary and secondary atherosclerosis prevention strategies. The efficacy of long-term antiplatelet therapy with a non-competitive inhibitor of adenosine 5'-diphosphate-induced platelet aggregation, such as clopidogrel, has been demonstrated [1–3]. We report a case of acute polyarthritis associated with the use of this drug.

Patient Description

A 60 year old man presented to the emergency department of the Bnai Zion Medical Center on 1 September 2004 with intense pain and swelling of joints, and said that he was "unable to move." He had a 10 year history of CAD, with angina pectoris and myocardial infarction, as well as hyperlipidemia, and was taking the following medications once a day: bisoprolol fumarate 5 mg, aspirin 100 mg and simvastatin 10 mg. The CAD had been stabile on treatment until 2 months before the emergency room visit when he began to develop new symptoms at rest. Three weeks prior to presentation he underwent percutaneous transluminal coronary angioplasty of the distal left coronary artery with stent insertion. After this procedure he was prescribed clopidogrel 75 mg once daily in addition to his maintenance treatment. Two weeks later he developed widespread pruritus, with appearance of a faint macular rash on his trunk and back. This was associated with a fever of 38°C and myalgias. The next day when his wrists, hands and knees were swollen, painful and red, he presented to the emergency room. The patient was treated with 500 mg hydrocortisone intravenously and hydroxyzine hcl. Clopidogrel was discontinued. After 24 hours he was discharged from the hospital on antihistamine treatment alone. Two days later, the pain and swelling in his joints had worsened and again he had the feeling that he was "unable to move." He returned to the emergency department.

On examination he had a temperature of 37.6°C but no evidence of a macular rash over his trunk or extremities. Cardiovascular, respiratory and gastrointestinal examinations were unremarkable and no lymphadenopathy was noted. Examination of the joints revealed active inflammatory arthritis involving his wrists, right elbow, shoulders and hip joints. The following laboratory tests were normal: electrolytes, liver and renal studies, uric acid, erythrocyte sedimentation rate and complete blood count; but C-reactive protein concentration was increased to 49 mg/L (normal <5 mg/L). His chest X-ray and those of the involved joints were normal. A 99^{m} technetium bone scan demonstrated increased uptake at the wrists. While crystal-induced acute arthritis is not uncommon in the elderly population with CAD treated with multiple drugs, the clinical picture – particularly the accompanying rash – and absent laboratory and X-ray findings refuted this diagnosis. The patient was placed on prednisone 30 mg once daily. After 3 days his condition had improved dramatically, with resumed joint mobility already on the second treatment day. The pain and swelling subsided and he recovered full range of movement in all his joints. C-reactive protein concentration decreased to normal. Hepatitis C and B, rheumatoid factor and antinuclear antibodies were negative. At follow-up 2 weeks later the patient had discontinued the prednisone and 3 months later he felt well and had no further symptoms or signs of arthritis.

This clinical picture was believed to represent a drug reaction with fever, rash, pruritus, arthritis, increased C-reactive protein concentration, and improvement after discontinuation of the drug.

Comment

Antiplatelet therapy plays a pivotal role in the treatment of patients across the entire spectrum of CAD and stroke. Platelets are believed to be integrally involved in acute thrombotic complications. While aspirin remains the traditional antiplatelet agent in patients with CAD, adverse vascular events continue to occur in patients on aspirin therapy. Clopidogrel is a relatively new antiplatelet agent in use for the last 10 years. It is currently one of the more widely prescribed drugs for the treatment of symptomatic CAD [1], stroke [2], antithrombotic therapy after PTCA with stent placement and prevention of vascular death. As a member of the class of drugs known as the thienopyridines, clopidogrel irreversibly prevents platelet activation by blocking one of the three known ADP receptors on the platelets' surface [1].

CAD = coronary artery disease

PTCA = percutaneous transluminal coronary angioplasty

The most common side effect of this drug is gastrointestinal. Others are allergic skin reaction, rash and pruritus, described in 3–4% of those taking the drug, and fever in 1–3%. Musculoskeletal adverse reactions of clopidogrel therapy include arthralgia (6%) and back pain (6%).

A Medline search revealed only three other cases of clopidogrel-associated acute arthritis, reported in the internal medicine literature [3] within the last 10 years. All the patients described were similar to our patient: age 60–76 years, developing acute arthritis 10–14 days after commencement of the drug, typically associated with a rash, with significant elevations in the concentrations of acute phase reactants, and who promptly improved with steroids and cessation of the drug. This clinical picture associated with an urticarial rash suggests that an idiosyncratic reaction is most likely [3].

We would like to call the attention of primary physicians and rheumatologists alike to the possibility of clopidogrel as a potential cause of acute arthritis. While rechallenge with the drug may be necessary to prove this connection, due to the severity and prolonged nature of the idiosyncratic reaction along with availability of alternative medication, rechallenge did not seem feasible, nor was it found necessary in previously described cases. Clopidogrel therapy may be very important in the setting of acute CAD with recent intervention, and the abrupt cessation of this treatment has been associated with complications [4,5]. A change to other antiplatelet agents *a priori* does not seem warranted for this rare complication.

ADP = adenosine 5'-diphosphate

References

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