Mystery of Clopidogrel Associated Inflammatory Arthritis

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Abstract

Clopidogrel is an antiplatelet medication that plays an important role in management and prevention of thrombotic vascular events in patients with ACS and ischemic stroke. Few cases have been reported about Clopidogrel induced inflammatory arthritis after receiving it as part of ACS. Here we report a male patient who received maintenance dose of Clopidogrel as part of stroke treatment, and developed inflammatory arthritis after 5 days of starting the treatment. He underwent extensive evaluation and testing to look for other common causes of inflammatory arthritis including autoimmune etiologies. All of these tests were non-explanatory of his symptoms, and we hypothesized that this arthritis was induced by Clopidogrel. Discontinuing resulted in complete resolution of symptoms. Since it's a diagnosis of exclusion, we recommend patients should undergo complete work up of inflammatory arthritis and discussing with neurology risk *versus* benefits of DAPT in ischemic stroke patients with prior history of RA.

Keywords: Inflammation; Arthritis; Plavix; Clopidogrel; Rheumatology

Introduction

Based on American Heart Association/American Stroke Association (AHA/ASA) guidelines, short-term DAPT with aspirin and clopidogrel after a qualifying Transient Ischemic Attack (TIA) or minor ischemic stroke has become standard of care. Our patient based on these recommendations was started on DAPT (aspirin and Clopidogrel) therapy; however within few days of starting the treatment he developed inflammatory arthritis in multiple joints. We were not able to find this in any other reported patients who received DAPT (aspirin and clopidogrel) as a stroke treatment.

Case Presentation

A 43-year-old male with past medical history of ischemic stroke with no residual neurological deficits (diagnosed two weeks ago) comes in with pain and redness of right shoulder, right knee, left knee and left 3rd and 4th metacarpal for last five days. Patient was recently admitted for ischemic stroke and discharged on aspirin, clopidogrel and atorvastatin. Soon after discharge, he began to develop severe right shoulder pain associated with redness and tenderness, followed by similar symptoms in his right knee, left knee and then right third metacarpal. Denied fever, chills, chest pain, dyspnea, cough, hemoptysis, Nausea, hematochezia, hematemesis, dysphagia, odynophagia, rash, psoriasis, vision or neurologic changes, photosensitivity, inflammatory eye disease, dactylitis, Raynaud's, history of pleuritis or pericarditis, nail pitting or dysmorphia. No unusual outdoor or travel exposures. No known tick bites, fishing accidents, or other atypical infection risks. There was no personal or family history of autoimmune, rheumatic diseases or inflammatory bowel disease.

Physical exam revealed swelling, erythema, tenderness of right shoulder and left knee. The cardiovascular system, abdomen, neurology exam, and skin examination were within normal limits. Initial laboratory showed normal cell counts, renal function and liver function test. Other notable labs included serum uric acid level of 3.5 milligrams per deciliter (mg/dL, and ESR (Erythrocyte Sedimentation rate) at 35 mm. Arthrocentesis of left knee was performed, total

nucleated cell count of 2K, with Polymorphonuclear Neutrophils (PMNs) 72%, with no crystals and negative gram stain and culture. Further laboratory studies showed, negative Rheumatoid Factor (RF), Anti-Cyclic Citrullinated (CCP), ANA (Antinuclear Antibody), ANCA (Antineutrophil Cytoplasmic Antibodies), Lupus anticoagulant, dsDNA (anti-double stranded DNA), complement C3 and C4, protein C & S and normal serum IgE levels. ASO titer value 189 IU/ml. Serum protein electrophoresis and immunofixation were unremarkable. Genetic testing for familial Mediterranean fever was also negative. Dual-Energy CT (DECT) right and left knee was performed showing moderate osteoarthritis with no crystals. Symptomatic pain relief was performed with Tylenol and capsaicin topical. However, swelling and tenderness still persisted. Clopidogrel was discontinued, and he was only continued on aspirin and atorvastatin for his ischemic stroke. In the next three days his symptoms completely resolved, and the inflammatory markers returned to baseline. There was no recurrence of symptoms, on his 6 weeks follow up visit with his primary care physician (Figure 1).

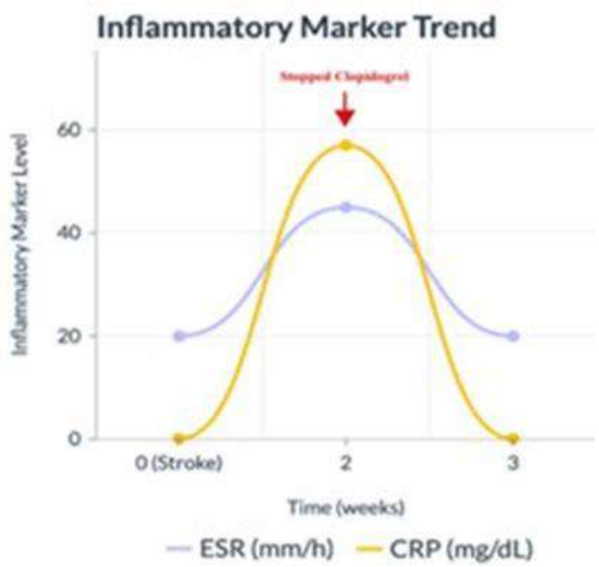

Figure 1: Shows the timeline of events.

Discussion

Polyarthritis refers to a joint disease that involves at least five joints. One or more signs of inflammation, including pain, movement restriction, swelling, warmth, and redness, are seen in the joints involved. If polyarthritis limits itself in less than 6 weeks, it is defined as acute polyarthritis. Our patient had acute polyarthritis given the involvement of above described joints, within 1 week of starting Clopidogrel. Differential diagnosis we considered was autoimmune arthritis, infectious arthritis, reactive arthritis, gout, pseudogout and serum sickness disease or atypical initial presentation for SLE, RA or vasculitis. The work up of acute polyarthritis includes laboratory tests, imaging, and analysis of synovial fluid. Laboratory work up includes Complete Blood Count (CBC), Liver Function Tests (LFT), urinalysis, acute phase reactants including ESR, CRP, serum amyloid A, complement components, alpha-1 antitrypsin, fibrinogen, ferritin, uric acid, creatine kinase, hepatitis panel, and Lactate Dehydrogenase (LDH). Autoantibodies are critical in the diagnosis of Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE) and systemic vasculitis which can contribute to polyarthritis. This includes rheumatoid factor, anti-CCP antibodies and ANA. If any of these are positive, we recommend checking complete autoimmune workup. Synovial fluid analysis is also critical in the differential diagnosis of polyarthritis. Our patient did initially present with the swelling of left knee, necessitating the synovial analysis. Lastly, imaging the joint spaces with plain radiographs may be helpful in visualizing the disease process although in many cases MRI may be ordered as this is more sensitive in differentiating inflammatory arthritis diseases.

Our patient although had asymmetric join involvement, he didn't have any preceding gastrointestinal or genitourinary symptoms with absence of fever or rash. Extra-articular manifestations such as dactylitis, enesthitis or uveitis were also absent. Inflammatory markers were normal to slightly elevated making reactive, viral or bacterial arthritis less likely. Absence of crystals in the synovial analysis doesn't completely rule out the possibility of crystal induced arthropathy, therefore we performed dual-energy CT scan.

Over the last 2 decades, there have been some reported cases of clopidogrel induced migratory inflammatory polyarthritis [1-7]. This was seen in patients receiving both loading and maintenance dose of clopidogrel as a part of treatment of

acute coronary syndrome. Our patient received 75 mg of clopidogrel as a treatment of acute stroke as per American Heart Association/American Stroke Association (AHA/ASA) guidelines. There were number of factors in common in these reported cases, such as developing acute fevers, chills, and rashes followed by severe joint pain and inflammation seen approximately 1 week (on average), after the initiation of clopidogrel (Table 1). Our patient didn't have systemic symptoms such as fever, chills, or rash. We also observed, that just like all other reported cases [1-7], there was resolution of arthritis symptoms upon the discontinuation of clopidogrel. Clopidogrel induced arthropathy is a diagnosis of exclusion. Clopidogrel is an older, safe medication given to patients most commonly for acute coronary syndrome. Clopidogrel induced arthritis is rare [8]. Therefore, a comprehensive work up must be performed first to rule out more common presentations such as lupus associated arthropathy, statin induced myalgias, or other autoimmune processes. The exact pathophysiology of clopidogrel induced arthritis is unknown at this time. However, in a recent rat model study revealed clopidogrel in combination with a chronic arthritis state can exacerbate arthritis type symptoms and increase in inflammatory cytokines such as IFN-y, IL-b, and IL-6 were observed which may have played a role in the cases that were already reported [9]. Our patient didn't have any prior history of autoimmune disease or arthritis. We recommend exercising caution while using this medication in patients with known autoimmune disease or prior arthritis. In some patients with inflammatory arthritis, it is not possible to establish a specific diagnosis during the first several weeks to months following symptom onset. However, resolution of symptoms of in 3 days of discontinuation of clopidogrel raised suspicion of it causing the possible inflammatory response. Patient was therefore followed up in 6 weeks in evaluate any recurrence.

Study	Age (years)	Sex	Symptoms	Treatment indication	Onset following administration	Dosage	Joints involved	Laboratory values	Treatment
Kanadiya M, [1] et al.	52	M	P (hands and feet), R, F, C,	Progressive angina	2 weeks	75 mg qd	Bilknees, hips, shoulders, hands, and elbows	CRP (171.7 mg/L), ESR (68 mm/hr)	Discontinuation, and methylprednisolone
Agrawal S, [2] et al.	64	M	F	Progressive angina, stent procedure	4 days	Not reported	R shoulder, neck, bil wrists	CRP (15 mg/dL), ESR (89 mm/hr),	Discontinuation, prasugrel, colchicine, indomethacin
Coulter CJ, [3] et al.	64	M	C, F	Cardiac catheterization	8 days	75 mg qd	L metacarpophalangeal joint, L talocrural, L ankle	CRP (0.71 mg/dl), ESR (26 mm/hr), WBC (15.2 × 10^3/mm^3)	Discontinuation, prasugrel,

Bedy SC, [4] et al.	65	M	Swelling, redness, F, C	Pacemaker placement	2.5 weeks	75 mg qd	Hands, feet, elbow	CRP (2.60 mg/dL), ESR (35 mm/hr), WBC (17.64 × 10^9 /L)	Discontinuation, prednisone, ticagrelor
Chen KK, [5] et al.	60	F	F, P, rash (trunk, back)	gastroscopy	10 days	75 mg qd	Hips, shoulders, wrists, hands, knees	CRP (408 mg/L), ESR (64 mm/hr), ALT (81 U/L), AST (54 U/L), Alkphos (157 U/L), GGT (49 U/L)	Discontinuation, prednisone, celecoxib
Khan EA [6], et al.	50	M	Rash (limbs, trunk), F	Stent procedure	3 days	600 mg stat dose	Shoulders, R hand	CRP (21 mg/L), urate (mmol/L), GGT (62 U/L), ALT (43 U/L), eosinophils (0.10 × 10^9/L), WBC (107,700 × 10^6/L- L wrist aspiration)	Discontinuation, ticlopidine
Ayesha B, [7]et al. Case 1	54	M		Stent procedure	3 days	75 mg qd	Bil shoulder, bil hands, R hip	WBC (13.5 K/ mm^3), ESR (101-116 mm/hr), CRP (29.7-26.6 mg/dL), uric acid (10.9 mg/dl)	Discontinuation, prasugrel
Ayesha B, [7] et al. Case 2	77	M	F, C, weight loss, asthenia	angina, percutaneous coronary intervention	2 weeks	75 mg qd	L shoulder, L hip, R shoulder, L hand	ESR (62-92 mm/hr), CRP (13.9 15.3 mg/dL)	Discontinuation, prasugrel

Conclusion

Clopidogrel induced arthritis is rare and is diagnosis of exclusion. Therefore, a comprehensive work up of the possible differential diagnosis should be performed. It should also be kept in mind that some patients with inflammatory arthritis, it is not possible to establish a specific diagnosis during the first several weeks to months following symptom onset, therefore all these patients should be closely followed up after discharge.

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