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Case Report

Peripheral artery disease in patient with end-stage renal disease on regular hemodialysis: a case report

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ABSTRACT

Patients with end-stage renal disease (ESRD) had a higher risk of developing cardiovascular disease, including peripheral artery disease (PAD). The presence of PAD in hemodialysis patients leads to an increase in the incidence of amputation and mortality. However, early diagnosis of PAD in hemodialysis patients is still challenging. Clinical manifestation of PAD in ESRD patients is often atypical manifestations and present in severe manifestations. We reported a case of PAD in the right leg of a 54-year-old woman with end-stage renal disease (ESRD) on regular hemodialysis with comorbid diabetes mellitus and hypertension. Ankle-brachial index (ABI) of the right leg was 0.82 and the result of echo-Doppler supported the presence of PAD in the right distal femoral artery. Then, the patient was treated with antiplatelet therapy, cilostazol, and other medication to control comorbidities. The pain was partly relieved after treatment and the patient was referred to a tertiary hospital for further diagnosis and management. Endocrine and biochemical abnormalities lead to a higher prevalence of PAD in ESRD patients on routine hemodialysis. The non-invasive approach on PAD in ESRD patients has an advantage in improving patients' outcomes if the diagnosis is established in the earlier stage.

Keywords: Peripheral artery disease, End-stage renal disease, Hemodialysis, Cilostazol

INTRODUCTION

Peripheral artery disease (PAD) is described as an atherosclerotic lesion of a peripheral artery, causing complete or partial obstruction. A total of 236.62 million people aged 25 years and older had PAD in 2015 worldwide. The incidence of PAD was also higher with increasing age, history of smoking, diabetes hypertension, hypercholesterolemia, and kidney disease.[1] Patients with chronic kidney disease have a higher risk of developing cardiovascular disease, including PAD. The prevalence of PAD was higher in end-stage renal disease (ESRD) and dialysis patients, ranging from 12% to 40%, than normal population.[2,3] Several studies have also revealed the risk of severe PAD, including amputation, is significantly increased in ESRD.[4] The risk of chronic limb-threatening ischemia (CLTI) also increased with the increase in the stage of chronic kidney disease (CKD), about 77.6% in CKD stage 1 or 2 to 100% in CKD stage 5.[5]

Clinical manifestation of PAD in ESRD patients is often atypical, making the diagnosis is still challenging.[6] Most patients come with more severe symptoms such as the presence of CLTI and gangrene which was limited the option and delayed the administration of treatment. Endocrine and biochemical abnormality in ESRD on hemodialysis patients play a critical role in the atherogenic process and progression of PAD. These patients often have other comorbidities, which also contribute to the pathogenesis of PAD, such as other cardiovascular diseases, hyperlipidemia, and diabetes mellitus.[7,8] The combination of PAD with ESRD increases the incidence of amputation, hospitalization, and mortality from the cardiovascular event or generalized conditions.[2,9,10]

It is important to recognize and diagnose PAD as early as possible in ESRD patients, who are a population at risk of having a poor outcome. In this article, we reported a case of PAD in a woman with CKD on regular hemodialysis who was successfully detected in the early stage and experienced partly symptomatic relief following medical therapy.

CASE REPORT

A 54-year-old woman, Balinese, a housewife, was consulted by internist with complained of pain in her right leg while doing hemodialysis in hospital. The pain had been felt since a month ago and worsen in the last 3 days. Pain appeared suddenly on the calf, in the form of a burning sensation and discomfort. The pain worsened when the patient walks and lessen when resting. The pain became more severe and was felt even when the patient only walks a few steps and did not immediately disappear after resting. The pain was slightly relieved with analgesics. The patient also complained of tingling sensation and sometimes feeling cold in the right toes, but could relieve spontaneously.

The patient had a history of diabetes mellitus for five years and chronic renal failure for two years. The patient underwent routine hemodialysis once a week. Patients routinely use basal and postprandial insulin to control their blood glucose. The patient also had a history of hypertension and was taking antihypertensive agents routinely.

On physical examination, blood pressure was 150/90 mmHg and body mass index (BMI) was 27.68 kg/m^2. Examination of both extremities revealed weaker pulses in the dorsalis pedis and popliteal arteries of the right leg than in the left leg. The ankle-brachial index (ABI) on the right leg was 0.84 and on the left leg, it was 0.92, while the ABI on the left leg was calculated using the right arm systolic pressure because of the inability to examine the left arm due to access to an arteriovenous fistula. Laboratory examinations showed an increase in serum creatinine levels of 3.8 mg/dl and blood sugar at 240 mg/dl. Echo-Doppler ultrasound examination revealed a biphasic (+) flow and no thrombus on the right distal femoral artery and there was reflux in the right femoral vein.

The patient was diagnosed with right lower extremity peripheral artery disease, Fontaine IIB and Rutherford 3, ESRD on HD, and diabetes mellitus type 2. The patient then received additional therapy in the form of antiplatelet, aspirin 80 mg every 24 hours orally, clopidogrel 75 mg every 24 hours orally, cilostazol every 12 hours orally, paracetamol 500 mg every 8 hours orally. The previous therapy was continued and the patient underwent hemodialysis as scheduled. Three days later, the patient returned for hemodialysis and her pain was partly relieved. Then, the patient was referred to a tertiary hospital with angiographic facilities for further diagnosis and management.

DISCUSSION

PAD is a spectrum of atherosclerosis associated with coronary and carotid artery disease. The prevalence of PAD was found to be higher in patients undergoing long-term hemodialysis (HD) than in the general population. Some predictors of PAD in ESRD on HD patients are old age, male, history of diabetes, smoking, coronary artery disease, duration of dialysis, malnutrition, blood pressure before dialysis, and parathyroid hormone levels.[7,11,12] Patients with ESRD with diabetes mellitus increase the risk of developing PAD by 4-times. Hypertension and hyperlipidemia are also risk factors for PAD.[8,13] The patient, in this case, had a history of diabetes mellitus for five years, chronic renal failure for two years, and hypertension which made the patient more susceptible to PAD.

Chronic kidney disease patients on dialysis have biochemical and endocrine abnormalities known to be associated with PAD. The condition of chronic uremia is associated with systemic inflammation. The presence of comorbid diabetes and hypertension also has an important role in the pathophysiology of PAD in CKD. Those also trigger vascular calcification, inflammation, oxidative stress, uremic toxins, and microvascular disease which also increase the risk of PAD in CKD patients. Inflammation contributes to the progression of cardiovascular disease by inducing the release of cytokines, such as interleukin (IL)-1, IL-6, IL-1β, IL-8, tumor necrosis factor (TNF)-α, TGF-β, high-sensitivity C-reactive protein, and fibrinogen, all of which induce pro-fibrotic and atherothrombotic processes. This condition triggers exacerbation of vascular calcification and endothelial dysfunction in PAD. Uremia in CKD patients is also a potent prothrombotic agent that induces post-intervention thrombosis by upregulating tissue factors in the vessel wall to trigger the extrinsic coagulation cascade and by increasing platelet reactivity. This toxin increases oxidative stress and inflammation and inhibits angiogenesis, together with pro-atherothrombotic effects contributing to the development of PAD and poor outcome after vascular intervention in CKD patients.[4,5] Secondary hyperparathyroidism was an abnormality in CKD which accelerate the atherosclerosis process by targeting endothelial cells and inducing an increase in serum calcium and phosphorus.[14]

Detection and diagnosis of PAD in CKD patients are still challenging because most patients present with atypical symptoms, or are asymptomatic. Moreover, PAD patients with CKD on dialysis present on the first visit with more severe symptoms such as ischemic ulcers or gangrene compared to pain at rest.[7,11] The patient in this report presented with intermittent claudication that improved with rest. Complaints were also accompanied by tingling, probably due to peripheral neuropathy on diabetes and sometimes cold sensation in the feet, due to inadequate blood flow to distal of feet. Intermittent claudication is the most common symptom in PAD. Most patients complain

of stabbing pain, cramping, or tightness in the leg or calf muscles that appear with activity and improve with rest. The pain usually disappears within a few minutes by resting or stopping the activity. Approximately, 70% of PAD patients did not experience this complaint. Some of the reasons that cause this condition are the presence of diabetic neuropathy which can mask symptoms, or not reporting symptoms due to avoiding activities that trigger pain.[13,15]

Physical examination should focus on palpation of lower extremity pulses and auscultation for vascular murmurs.[11,15] Physical examination may reveal paresthesia, ulceration, numbness, and gangrene at an advanced stage with multiple lesions or redness with swelling, shiny skin, hair loss, and muscle atrophy on the lower extremity. Pulse examination should be performed on several arteries, including the femoral, popliteal, dorsalis pedis, and posterior tibial arteries.[13,15] This patient had weaker pulses in the dorsalis pedis and popliteal arteries of the right leg than in the left leg, based on palpation.

ABI at rest is the first-line test for PAD with varied sensitivity between 94-97% compared to the gold standard for vascular angiography imaging, while specificity varies considerably based on patient comorbidities. Several guidelines recommended resting ABI testing for patients with history or examination findings suggestive for PAD.[15] The ABI can also be measured immediately after activity and is usually equal to or slightly higher than the resting value. The normal value of ABI is equal to or more than 1.0. The ABI examination is performed by measuring the systolic blood pressure in each ankle and dividing it with the greater value of systolic blood pressure between the left and right arm (brachial artery).[13] The resting ABI assessment in this patient's right leg was 0.84, so the patient could be diagnosed with PAD clinically. Despite, ABI on the left leg slightly decrease (0.92), the patient did not complain of pain or any abnormality on the left leg.

This clinical diagnosis was supported by the results of ultrasound echo-doppler examination which showed that in the right distal femoral artery there was abnormal blood flow with no thrombus, and there was reflux in the right femoral vein. Duplex ultrasound examination is an inexpensive, safe, and accurate diagnostic modality in PAD.[16,17] More advanced modalities, such as computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) may help plan revascularization procedures in some patients.[4,17] However, there is a risk of contrast-induced nephropathy (CIN) so the use of iodinating contrast and gadolinium is quite limited, especially in ESRD patients. Non-invasive tests such as CTA and MRA as well as invasive conventional angiography with iodinated contrast should be performed in patients with severe claudication or CLI who do not respond to non-invasive therapy.[6,9] PAD can be classified according to Fontaine and Rutherford classification system. The Fontaine classification is divided into five stages while the Rutherford criteria are classified into seven stages.[9] This patient has severe claudication, even when walking a few steps (<200 m) but the complaint improves with rest so it is classified into Fontaine IIB and Rutherford 3.

In general, the therapeutic approach in CKD patients with PAD includes: treating local lesion symptoms and preventing an increased risk of cardiovascular events.[14] Symptoms of local lesions are improved by revascularization, including open surgical or endovascular procedures. Several parameters including type of lesions and comorbidity affect the choice of intervention. Several studies have shown that CKD patients may be offered fewer revascularization procedures than patients without CKD despite comparable severity of PAD. It could be affected by various factors, such as the high rate of complications in CKD patients, poor nutritional and functional status, and more severe injuries in the renal. Another thing to note is the concern for contrast-induced nephropathy.[5] Several previous studies have revealed that patients with CKD have worse outcomes after revascularization, such as failure of limb salvage and increased risk of amputation, despite similar or better graft patency.[5,18]

The patient in this case was referred to a tertiary care facility for further diagnosis and therapy. Meanwhile, the patient was given cilostazol and was partly relieved in pain. Cilostazol is a phosphodiesterase-3 inhibitor that has been shown to be effective in the treatment of intermittent claudication. Cilostazol therapy has been shown to improve walking time and reduce claudication compared to placebo. Cilostazol is also recommended as first-line therapy for CKD but should be administered with caution in severe CKD and on dialysis patients due to high protein binding and impaired excretion in significant low creatinine clearance.[19] Therefore, the initial administration of cilostazol in CKD patients should be starting at lower doses.[6] To prevent an increased risk of CV events, several lifestyle modifications, such as smoking cessation, weight loss, healthy diet, and supervised exercise programs, have been shown to be effective in the management of PAD patients and should be administered, including in CKD patients.[20] Other therapies that need to be given are antihypertensive, lipid-lowering, and antithrombotic drugs. Statins improve amputation-free survival in patients with PAD and are recommended in patients with CKD over 50 years of age.[18,20]

Endocrine and biochemical abnormalities lead to a higher prevalence of PAD in CKD patients on dialysis. The patient was successfully diagnosed at early stage due to her complained of intermittent claudication. The patient reported partly clinical improvement after receiving medical therapy with antiplatelet and cilostazol and other comorbid conditions. The patient was still referred to a tertiary care unit for further diagnosis and therapy. Non-invasive therapy in PAD has the potential to provide

promising outcomes if the diagnosis is established in an earlier stage in ESRD on hemodialysis patients.

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