ACUTE LIMB ISCHEMIA IN ANTITHROMBIN III DEFICIENCY WITH PATIENTS NEPHROTIC SYNDROME

Sari Harahap, Naomi Dalimunthe, Rahmad Isnanta, Zainal Safri, Refli Hasan, Herlina M. Sitorus

Division Of Cardiology, Department Of Internal Medicine, University Of North Sumatra Medical Faculty / Hospital Center H. Adam Malik

INTRODUCTION

Arterial thrombosis is rarely in Nephrotic syndrome is frequently causes venous thromboembolic complications as these patients have a hypercoagulable state. Plasma concentration of antithrombin III is decreased in patients with nephrotic syndrome as a result of increased filtration through the glomerular basement membrane. The outcome in these cases was unsatisfactory because of the high rates of limb loss and recurrence of thrombosis.

We report of a 75-year-old man who suffered from left upper extremity acute limb ischemia. He was admitted to our hospital with pain and fingertips blackened left hand was suffered 5 days before admitted to hospital Adam Malik. The physical examination found the fingers of the left hand end of the fingertips swollen and blackened and painful especially when driven encountered no pulse was palpable in his left radialis. High blood pressure of 180 / 90 mmHg pulse, respiratory rate and body temperature within normal limits. Examination of laboratory: Hb: 11.7 mg / dl, leukocytes: 5,880 / mm3, platelets: 401,000 / mm3, albumin: 1.4 g / dl, physiology of hemostasis time protrombin: 0.93, INR: 0.94 APTT: 0.85, thrombin time: 1.92, fibrinogen: 633 mg / dl, D-dimer: 450 ng / mL, antithrombin III 18.9%, lipid profile Total Cholesterol: 371 mg / dL; triglycerides 148 mg / etc; Cholesterol HDL 34 mg / dL; LDL cholesterol 377 mg / dL. 24 hour urine protein 5000 mg / 24h, electrocardiogram sinus rhythm, arteriography results palmar artery stenosis in the left digit I, II, III, and V and occlusion a. Intraosseuss posterior sinistra

Patients diagnosed with Acute Ischemic Limb (PAD) and Hypertension stage II and Nephrotic Syndrome with antithrombin III deficiency. During hospitalization patients treated with albumin, fresh frozen plasma, egg white diet, heparin 10,000 iu/day, simvastatin 40 mg, ramipril 5 mg, aspilet 100 mg, ketorolac injection 30 mg and metilprednisolon. Pasien hospitalized for 17 days and the patient's condition improved after the outpatient discharge.

Key words: acute limb ischemia, nephrotic syndrome, antithrombin III deficiency
Although venous thromboembolism caused by nephrotic syndrome is a well-recognized complication of a hypercoagulable state, arterial thrombosis has rarely been reported. As such, nephrotic syndrome may be associated with a reduction in circulating antithrombin III and free protein S levels. Associated spontaneous thrombotic complications are generally venous in comparison, with arterial thrombosis occurring less frequently. Even more unusual are reports of upper extremity arterial thrombosis with nephrotic syndrome.\textsuperscript{1,2}

Acute limb ischemia is related to a sudden decrease in arterial perfusion in the limb. Thrombotic or embolic causes can be involved. The viability of the limb is mostly threatened in this context. Quick and proper management is needed for limb salvage. Once the clinical diagnosis is established, treatment with unfractionated heparin should be given. Analgesic treatment is often necessary. The level of emergency and the choice of therapeutic strategy depend on the clinical presentation.\textsuperscript{3}

**CASE REPORT**

A 75-year-old man admitted to our hospital on the 17th of February 2016 with pain and fingertips blackening on the left hand. It was suffered 5 days before admitted to hospital Adam Malik. History of hypertension and diabetes were not found. He was smoked for 20 years and had stopped since 2 years ago and no history of Diabetes Melitus type II.

The physical examination found the fingers swollen dan painfull especially when driven no pulse was palpable in his left radialis and of the fingertips swollen blackened. We found acites and swollen both in lower extremities. We found high blood pressure of 180/90mmHg pulse, respiratory rate and body temperature within normal limits.

Laboratory data revealed Hb: 11.7 mg/dL, leukocytes: 5.880/mm\(^3\), platelets: 401,000/mm\(^3\), albumin: 1.4 g/dl physiology of hemostasis time prothrombin: 0.93, INR: 0.94 APTT: 0.85, thrombin time: 1.92, fibrinogen: 633 mg/dl, D-dimer: 450 ng/mL and level of antithrombin III 18.9 % (normal 75-125%) , HBsAg : negatif Anti HCV : negatif lipid profile Total Cholesterol: 371mg/dL; triglycerides 148 mg/ etc; Cholesterol HDL 34 mg/dL; LDL cholesterol 377 mg/dL. Arteriography results palmar artery stenosis in the left digiti I, II, III, and V and occlusion a. Intraosseuss posterior sinistra
Patients performed for the management of acute limb ischemia with administration of heparin 10,000 IU/day subcutan and aspilet 100mg once daily, simvastatin 40 mg and ketorolac injection 30 mg three times a day. One day after the administration of heparin was found urinating blood and heparin discontinued. Then urinalysis examination found four positive protein, erythrocyte sediment epithelial cells: 30-40 / field view. Sediment leukocytes: 1-3 / field view, Cylinders: 2-3, Epithelium: 2-5 resume 24-hour urine examination found urine protein 5000mg / 24 hours. In laboratory tests for kidney function is not found abnormalities followed by renal sonography within normal limits. Later examination of antithrombin III found 18.9%.

For treatment of nephrotic syndrome in patients with albumin substitution therapy administration and continued by dietary protein per body weight of 0.8 and supplemented with protein urine for 24 hours and the provision of methylprednisolone 4 mg 5 tablet morning night 5 tablets 5 tablets daily lunch given at 6 to 8 weeks, and do administration of ramipril 5 mg in patients. For the management of the deficiency of antithrombin III should be given antithrombin III concentrate, but because of the unavailability regimen is then given the provision of fresh frozen plasma as much as 900cc and after the administration found an increase in antithrombin III to 67% then the heparin therapy is continued for 5 days after it was followed by warfarin 2 mg once daily. After 15 days of treatment found improvement in patients where the left hand fingers and the pain was not blackened, swollen leg was not found ascites no longer exist and blood pressure during treatment uncontrolled systolic 130-140 mmHg and diastolic 70-90 mmHg. Patient discharge at 17th day.

DISCUSSION

Acute limb ischemia (ALI) is a serious medical condition characterized by a rapid decrease in limb perfusion. It usually produces new or worsening symptoms or signs, and often threatens limb viability. ALI is a sequela of peripheral artery disease (PAD). There are diverse etiologies for ALI, with the two most common being embolus and thrombosis in situ secondary to underlying disease such as atherosclerosis. The 30-day mortality and amputation rates are 15% and up to 25–30%, respectively. Outcomes and prognosis of ALI largely depend on the rapid diagnosis and initiation of appropriate and effective therapy. Patients should also be asked about serious concurrent disease or atherosclerotic risk factors, including: Hypertension Diabetes Smoking Hyperlipidemia. In this case report we found onset in 5 days, had hypertension, smoking and dyslipidemia.
Patients with ALI may initially present with the following five symptoms, known as the “5 Ps”: Pain: variables include time of onset, change over time, location and intensity. Pulselessness: the absence of pedal pulses suggests that the patient has ALI. An absent Doppler flow signal in the arteries of the feet is indicative of ALI. Pallor: patients with ALI commonly experience changes in color and temperature. Paresthesia: approximately half of patients experience some form of numbness. Paralysis: this is a very significant indicator that the patient has a poor overall prognosis. In this case report we found pain, pulselessness.

The viability of the limb is mostly threatened in this context. Quick and proper management is needed for limb salvage. Once the clinical diagnosis is established, treatment with unfractionated heparin should be given. Current recommendations include administration of 325 mg aspirin, unless there is a contraindication. Analgesic treatment is often necessary. The level of emergency and the choice of therapeutic strategy depend on the clinical presentation, mainly the presence of neurological deficiencies, and the thrombotic vs. embolic cause. The clinical categories are presented in Table 1.3,4

Tabel 1: Clinical categories of acute limb ischaemia

<table>
<thead>
<tr>
<th>Grade</th>
<th>Category</th>
<th>Sensory loss</th>
<th>Motor deficit</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Viable</td>
<td>None</td>
<td>None</td>
<td>No immediate threat</td>
</tr>
<tr>
<td>II A</td>
<td>Marginally threatened</td>
<td>None or minimal (toes)</td>
<td>None</td>
<td>Salvageable if promptly treated</td>
</tr>
<tr>
<td>II B</td>
<td>Immediately threatened</td>
<td>More than toes</td>
<td>Mild/ moderate</td>
<td>Salvageable if promptly revascularized</td>
</tr>
<tr>
<td>III</td>
<td>Irreversible</td>
<td>Profound, anaesthetic</td>
<td>Profound, paralysis (rigor)</td>
<td>Major tissue loss Amputation. Permanent nerve damage inevitable</td>
</tr>
</tbody>
</table>

Quoted from peripheral artery disease guideline ESC 2011
In this case report from clinically manifestation we found none sensory of loss and motor deficit and marginally threatened and management by medical treatment.

Nephrotic syndrome is characterized by heavy proteinuria of greater than 3.5 gm over a 24-hour period, hypoalbuminemia, edema, hyperlipidemia. Hypercoagulability is a recognized complication of nephritic syndrome, which commonly affects the venous system. Thrombosis involving the arterial system is rare, and has mainly reported in nephritic children. Multiple factors are responsible for the hypercoagulable state and vascular thrombosis in nephrotic syndrome. Alterations in blood levels of various factors involved in coagulation and fibrinolytic systems, endothelial cell dysfunction, alterations in platelet functions, hyperviscosity.
of blood, hemoconcentration due to diuretics use, and possibly long-term steroid use are contributory factors. Venous thromboembolism is much more frequent than arterial thrombosis. 1,6,7

The propensity of patients with nephrotic syndrome to have venous and arterial thrombosis has been attributed to a hypercoaguable state, the pathogenesis of which is multifactorial. Deficiencies in the coagulation inhibitors antithrombin III and protein S play a major role in generating the increased risk of thrombosis in patients with nephrotic syndrome. Increased blood and plasma viscosity caused by hemoconcentration and elevated fibrinogen levels aggravated by the use of diuretics contributes to a hypercoagulability. Steroids often used to treat this condition can increase the concentration of clotting factor VIII and shorten prothrombin and partial thromboplastin times. 1

Thrombocytosis, increased platelet aggregation, and adhesiveness associated with nephrotic syndrome may also contribute to the generation of thromboembolic complications. Decreased fibrinolytic activity associated with hypertriglyceridemia and decreased plasma plasminogen correlating with the magnitude of proteinuria has been observed as well. In addition, nephrotic syndrome is characterized by a profound change in the turnover and concentration of many plasma proteins including those involved in the coagulation cascade. Factors IX, XI, and XII are decreased through urinary loss, whereas procoagulant factors II, V, VII, VIII, X, and XIII are increased, both correlating with the degree of reduction in serum albumin. The coagulation cascade consists of a highly regulated system of enzymes and cofactors that interact to eventually produce thrombin. The procoagulant effects of thrombin include activation of factors V and VIII in a positive feedback reaction, proteolytic conversion of soluble fibrinogen to insoluble fibrin, activation of factor XIII causing cross-linking of insoluble fibrin, and activation and aggregation of platelets. Pathologic thrombin generation leading thrombus formation is counteracted by several physiologic anticoagulants including antithrombin III, the vitamin-K dependent cofactors protein S and protein C, and by the newly described tissue factor pathway inhibitor. 1

In 1965 Egeberg first noted an association between antithrombin III deficiency and thromboembolic complications. Antithrombin III is a serine protease
inhibitor synthesized by the liver and endothelial cells that interacts with thrombin and other serine proteases in a progressive irreversible manner. Although with less efficiency, antithrombin III also inactivates factors Xa, IXa, XIa, XIIa, and kallikrein. Antithrombin III can also function as a heparin cofactor necessary for heparin anticoagulant activity. Heparin markedly enhances the antifactor Xa activity of antithrombin III.¹

Inactivation of thrombin and factor Xa by antithrombin III occurs through the interaction of heparin with antithrombin or by the interaction of heparin with a specific protease. In the presence of heparin the preferential target of antithrombin III is thrombin, followed by factor Xa. Plasma concentration of antithrombin III is decreased in patients with nephrotic syndrome as a result of increased filtration through the glomerular basement membrane. Increased urinary concentrations of antithrombin III have been measured in patients with nephrotic syndrome along with decreased serum levels, both of which correlated with decreased serum albumin levels.¹

Nishimura et al. reviewed lower extremity arterial thrombosis with adult nephritic syndrome. In nephrotic patients, arterial thrombosis, though rare, has been reported in aorta, mesenteric, axillary, subclavian, brachial, femoral, ophthalmic, carotid, cerebral, renal, pulmonary, and coronary arteries. Three of seven cases resulted in amputation of the leg, and two of these three also sustained recurrent thrombosis.⁶,⁷

Arterial thrombosis can be diagnosed with the use of duplex scanning, CT, or magnetic resonance imaging. MDCT angiography has replaced conventional arteriography in almost all centers. Once the diagnosis of vascular thrombosis is established, anticoagulation therapy should be started. Patient can be treated with conventional or low molecular weight heparin, followed by oral Warfarin and antiplatelet agents. Thromboembolectomy or thrombolytic therapy is indicated in patients with ischemic limbs due to arterial thromboembolism. Attempts to reduce the degree of proteinuria, hyperlipidemia, and hypertension should be made in all nephrotics. Prophylactic anticoagulation may be considered in high-risk patients such as steroid resistant nephrotic syndrome, persistent hypoalbuminemia (serum albumin <2 gm/dl), and membranous nephropathy.¹,³
In this case report our patient had heavy proteinuria of greater than 3.5 gm over a 24-hour period, hypoalbumemia, edema, hyperlipidemia. Plasma concentration of antithrombin III was decreased was treated anticoagulation therapy, aspirin, substitution of albumin with fresh plasma frozen, antidyslipidemia, steroid. As he had a thrombus involving many arteries, he was continued on oral anticoagulation.

CONCLUSION

Vascular thrombosis is a rare but a serious complication of nephrotic syndrome which can also be found a deficiency of antithrombin III. Assessment of various risk factors like duration and severity of hypoalbuminemia may be useful for identifying high-risk patients in whom possibility of vascular thrombosis needs to be expected.1,7

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