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# Skin Biopsy as Alternative for Renal Biopsy in Acute Renal Failure and Suspected Cholesterol Emboli Syndrome

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## 1. Introduction

A 74-year old man with complaints of malaise was diagnosed with acute renal failure of unknown cause and was referred to our outpatient clinic because of bluish-red maculae in a reticular pattern on his forefeet and toes of unclear duration. Six weeks prior to the onset of his general symptoms he had undergone an endovascular aorta repair (EVAR) procedure. A lesional skin biopsy was taken and revealed multiple cholesterol emboli. The cholesterol emboli syndrome is a complication of atherosclerosis caused by cholesterol crystal embolization. These cholesterol crystals originate from atherosclerotic plaques of the large arteries and can migrate to various organs like the kidneys and the skin where they occlude small arteries causing ischemia and tissue damage. Often precipitating factors like vascular procedures, cardiac or aorta surgery, or treatment with anticoagulant or thrombolytic drugs can be identified. With our cutaneous findings an invasive renal biopsy could be avoided.

## 2. Case

A 74-year old man was referred to our Dermatology outpatient clinic by a nephrologist because of non-painful bluish-red discoloration of his feet and toes of unclear duration. He had been suffering from general malaise for some days and the laboratory results in the emergency department had revealed acute renal insufficiency of unknown cause. Six weeks prior to the emergence of symptoms he was treated for an aneurysm of the infrarenal aorta with a so-called EVAR (Endovascular Aneurysm Repair or Endovascular Aortic Repair) procedure.

On physical examination we observed livid-erythematous maculae in a reticular pattern on the distal end of both feet and toes (figure 1). The pulsations of the tibialis posterior and dorsalis pedis arteries were present, and there was a normal capillary refill.

Laboratory results showed a creatinine of 601  $\mu\text{mol/L}$ , urea of 359  $\text{mmol/L}$ , an erythrocyte sedimentation rate (ESR) of 70  $\text{mm/hour}$ , a white blood cell (WBC) count of  $8.4 \times 10^9/\text{L}$ , with eosinophils of  $0.59 \times 10^9/\text{L}$ , and thrombocytes of  $161 \times 10^9/\text{L}$ .

We performed a 3 mm lesional skin biopsy (from a blanched area) which showed compact hyperkeratosis and a normally structured epidermis and dermis. However, in the dermis we observed a small artery with some intimal hyperplasia containing a number of needle-shaped



Fig. 1. Livid-erythematous maculae in a reticular pattern on the plantar surface of the distal forefoot and toes.

spaces which occluded the lumen (figure 2). Herewith a histological diagnosis of cholesterol emboli syndrome was made.

### 3. Discussion

The cholesterol emboli syndrome (or cholesterol embolization syndrome) is a complication of atherosclerosis as a result of cholesterol crystal embolization. These cholesterol crystals originate from atherosclerotic plaques in the larger arteries and can migrate to various organs like the skin, the kidneys, gastro-intestinal system and central nervous system. Because these small crystals are hydrophobic and low in weight they can travel swiftly through the blood vessels until they strand in the arterial bifurcations or when the calibre of the arterial lumen decreases. This means that they will usually occlude small peripheral arteries leading to localized ischaemia which can result in (sometimes severe) end-organ damage. The cholesterol emboli syndrome primarily affects patients above 60 years of age with two or more risk factors for atherosclerosis.(1, 2)

The incidence of the syndrome in the general population, is low. For example, in the Dutch population, an average rate of 6.2 cases per million people per year has been reported.(3) However, in high risk patients, such as those undergoing cardiac catheterization, incidence rates up to 1.4% have been reported.(4)

In post-mortem studies, cholesterol emboli were observed in up to 20% of patients older than 60 years of age with a history of atherosclerotic disease.(5) Considering the relatively low rate of the clinical diagnosis of cholesterol emboli (even in high risk patients groups), it thus appears that the diagnosis is frequently missed.

Since the disintegration of (ulcerated) atherosclerotic plaques in the arterial vessel wall is the cause of cholesterol embolization, affected patients generally have severe (but sometimes subclinical) atherosclerotic disease. Although the syndrome may appear spontaneously without any clearly established predisposing etiological factor, there are three distinctive clinical settings that are known to increase the risk for cholesterol embolization. The first is prior arterial or coronary catheterisation (as for our patient) and cardiac or aorta surgery, which may disrupt an atherosclerotic plaque, leading to emboli within hours to several weeks of the procedure. The second is prolonged treatment with anticoagulant drugs, which slowly dissolves the clot that strengthens the brittle atherosclerotic plaque exposing eroded areas of the plaque to the shear stress of the arterial blood flow. The anticoagulant drug-induced syndrome of cholesterol emboli usually occurs within 1 to 2 months of initiating therapy. This 'warfarin blue toe syndrome' is not limited to anticoagulation with warfarin and can occur after treatment with other (classes of) anticoagulant drugs. The third setting in which cholesterol embolization can occur is when thrombolytic therapy is initiated for acute myocardial infarction or stroke. In this case, the embolization process may occur within hours to days of thrombolytic therapy.(6) A summary of the most common predisposing factors for cholesterol emboli syndrome is presented in table 1.(1, 7-10)

In our case the referring nephrologist made a provisional diagnosis of acute renal insufficiency due to cholesterol embolization related to the prior EVAR procedure after excluding all other possible causes. When performing an EVAR procedure of the infra-renal aorta, the catheters usually reach above the renal artery branches.

Manipulation with the endovascular catheter and stent in this area can cause small fragments (emboli) to detach from a friable atherosclerotic plaque in the arterial wall. The nephrologist sought support for his provisional diagnosis in the accompanying skin symptoms since the emboli can also migrate to the peripheral small arteries in the skin resulting in the typical reticular vascular pattern. With the demonstration of cholesterol emboli in a skin biopsy a more invasive ('gold standard') renal biopsy could be avoided.

In the cholesterol emboli syndrome the clinical symptoms may include fever, weight loss, myalgias, altered mental status and a rapid onset of arterial hypertension. Transient ischemic attacks, strokes, renal failure, gastrointestinal ulcerations and hemorrhagic pancreatitis may also occur. Patients with extensive organ involvement can have significant morbidity, and may even die from complications of the embolization process.(6) Generally, the primary site of cholesterol embolization is the kidney, followed by the skin and gastrointestinal tract.(3) Skin manifestations are present in 35 to 100% of patients and are often the first clinical symptom of the cholesterol emboli syndrome. Their clinical presentation is variable ranging from the symmetrical livedo reticularis, acrocyanosis, ulcerations, and purpura to severe leg and/or foot pain and focal digital ischaemia ("blue toe syndrome")(11). Findings of a relatively large English case study included: livedo reticularis (49%), multiple sites of peripheral gangrene (35%), cyanosis (28%), ulceration (17%), nodules (10%) and (retiform) purpura (9%).(5) Because these figures originate from a review article that also included patients in whom the diagnosis was made post-mortem (41%), it probably underestimated the true incidence of cutaneous findings in patients suffering from the cholesterol emboli syndrome.(6) This point is corroborated by a study of eight patients with acute renal insufficiency of unknown cause, whose history suggested cholesterol emboli. On careful examination, all eight were found to have prior unrecognized livedo reticularis, which on histological sections confirmed the diagnosis of cholesterol emboli.(12) In two of these patients, the livedo reticularis was visible in the standing position, but disappeared when the patients were placed in the supine position. Retiform purpura are usually a purpuric accentuation of the livedo reticularis pattern, and therefore may have been included as livedo reticularis in some reports. This may explain the relatively low observation rate of retiform purpura in the study by Falanga et al. Livedo reticularis is usually found in the lower extremities but upper extremity lesions may also occur if the atherosclerotic plaque is located in the aortic arch.(6)

The skin manifestations are often (but not always) painful and peripheral pulsations are generally intact. Elevations in the ESR, serum creatinine, BUN and amylase and transient elevations of creatine kinase, leukocytosis, thrombocytopenia as well as decreased complement levels are frequent associated findings, but are not always present.(5, 13) Peripheral blood eosinophilia is common, occurring in up to 80% of confirmed cases, and may be related to generation of the complement component C5.(13) Other reported laboratory findings include heme-positive urine and/or stool.

The acute onset of peripheral livedo reticularis (and even more so if retiform purpura are also present) should raise the suspicion of cholesterol or oxalate embolization. The occurrence of oxalate emboli is rare and recognized histologically as birefringent yellow-brown crystal depositions in and around arteries of deep reticular dermis and subcutis. Oxalate crystal embolization is an uncommon event, usually occurring in association with



primary hyperoxaluria. Primary hyperoxaluria is caused by a rare metabolic disorders of increased oxalic acid production or increased intestinal absorption. Hyperoxalemia will eventually lead to calcium oxalate deposition in various tissues.(14, 15) The history of kidney stones in a patient with sudden-onset livedo reticularis or retiform purpura should point in the direction of hyperoxaluria as a key diagnostic possibility. In addition to emboli from acute bacterial or fungal endocarditis (which are generally inflammatory in nature), cutaneous emboli or thrombi have been occasionally reported in patients with atrial myxomas, marantic endocarditis, crystal globulins and hypereosinophilic syndrome. Emboli resulting from these disorders may produce retiform purpura, but cutaneous manifestations may vary.(6) Other differential diagnoses one should consider include (small vessel) vasculitis (kidney and skin involvement) and perniones ("chilblains").(16)

A lesional (large) skin biopsy or elliptical excision of a blanched area of the livedo reticularis is diagnostic in 92% of cases, provided the sample includes tissue from the mid- to deep reticular dermis.(1) Areas of retiform purpura usually provide excellent diagnostic findings in punch biopsy specimens and should be the first choice for biopsy when present.(6) Frozen sections show birefringent cholesterol crystals and with the Schulz staining blue-green coloured crystals can be observed.(17) However, in fixated material the cholesterol crystals are dissolved during the laboratory workup and the negative image remains in the form of needle-shaped optical empty spaces (figure 2), often in association with thrombi.(18) Neutrophils, eosinophils and mononuclear cells may be present in the arterial wall within 24-48 hours in an experimentally produced cholesterol embolus. This is followed by the invasion of multinucleated histiocytes within 3 to 6 days, and sometimes intimal fibrosis. Lesions of different ages can be observed in the same patient, which is consistent with repeated showers of emboli.(6)

The cholesterol emboli syndrome is associated with a very high mortality rate (up to 80%).(1, 2) The prognosis depends on the degree of organ damage and severity of the underlying vascular condition. Treatment with aspirin appears to have a beneficial effect and in patients suffering from aortal atherosclerosis regression of the atherosclerotic plaque size was observed upon treatment with statins.(19) Furthermore, discontinuation of anticoagulation, initiation of anticoagulation in patients with severe renal damage, corticosteroid therapy, and infusion of the prostacyclin analogue iloprost have all been proposed as being effective in sporadic patients, but no therapeutic gold standard exists.(13, 18, 20) Additional measures include supportive treatment like hydration, antihypertensive therapy and haemodialysis.(21) Our patient needed long term haemodialysis; after approximately one and half year spontaneous recovery of renal function occurred, allowing discontinuation of haemodialysis.

#### 4. Conclusion

In summary, we believe that in all patients presenting with the classical triad of peripheral livedo reticularis, acute renal failure, and eosinophilia, the cholesterol emboli syndrome should be suspected. An invasive vascular procedure or recent initiation of anticoagulant or thrombolytic treatment in the months preceding onset of symptoms is an important diagnostic clue. A proper (large) lesional skin biopsy can confirm the diagnosis and therewith a more invasive renal biopsy can be avoided.

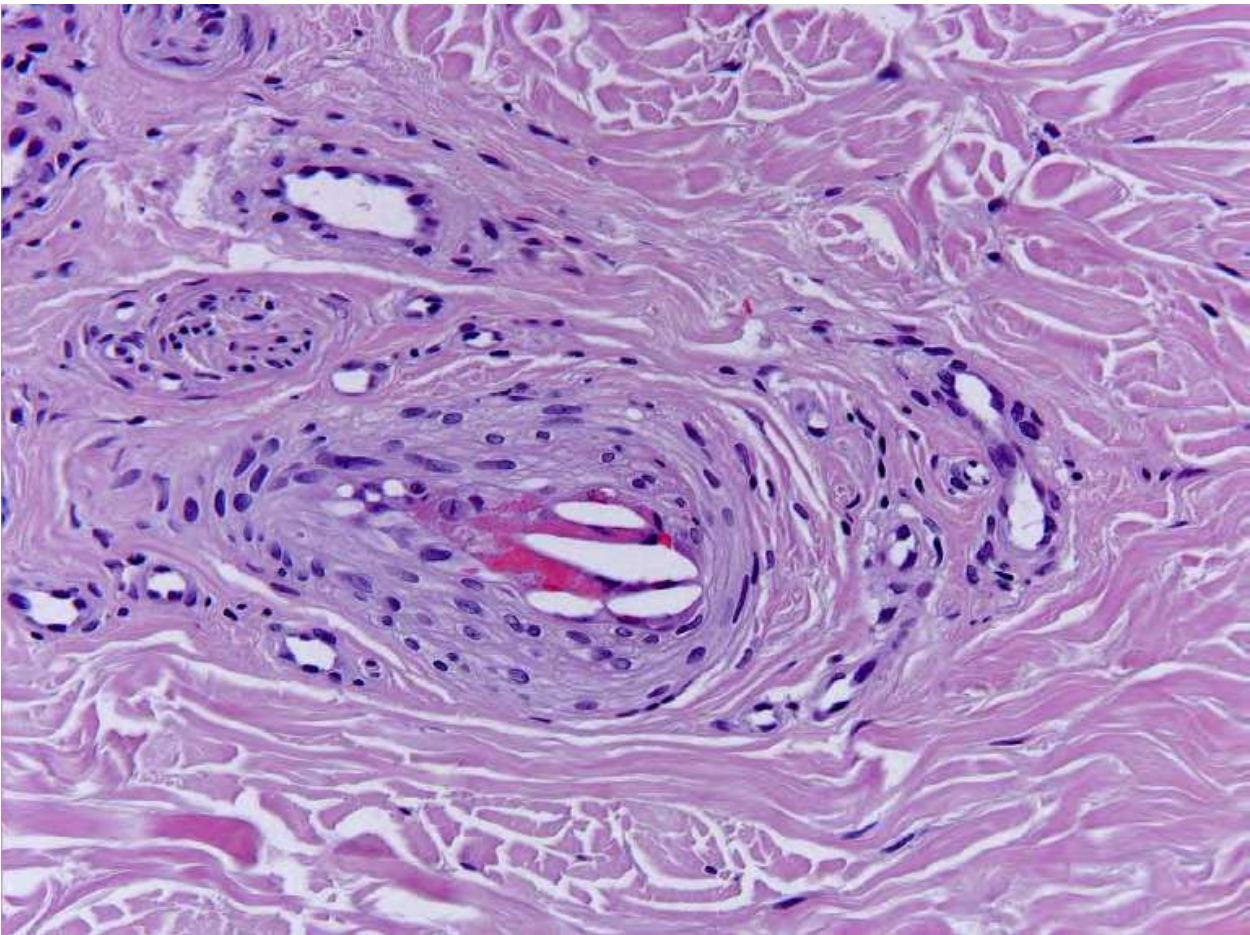


Fig. 2. Histological slide showing a small dermal artery branch with needle-shaped optical empty spaces as a result of the cholesterol crystals that dissolved during tissue processing (HE 20x).

<p>The cholesterol emboli syndrome should be suspected if the following items apply:</p> <ul style="list-style-type: none"><li>• confirmed atherosclerotic lesions in large vessels</li><li>• history of potential triggering predisposing factors (see below)</li><li>• typical clinical presentation, including renal failure, livedo reticularis or ulceration of the toes with intact peripheral arterial pulsations</li><li>• exclusion of small vessel vasculitis</li><li>• exclusion of diseases causing infective emboli (e.g. endocarditis)</li><li>• typical histopathological findings; evidence of cholesterol crystals (optical empty spaces) in the lumen of small arteries accompanied by an inflammatory cell infiltrate</li></ul> <p>Potential predisposing factors for the cholesterol emboli syndrome:</p> <ul style="list-style-type: none"><li>• angioplasty</li><li>• vascular surgery</li><li>• any invasive vascular procedure (including angiography)</li><li>• prolonged anticoagulant therapy</li><li>• fibrinolytic therapy</li></ul>
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Table 1. Diagnosis of the cholesterol emboli syndrome

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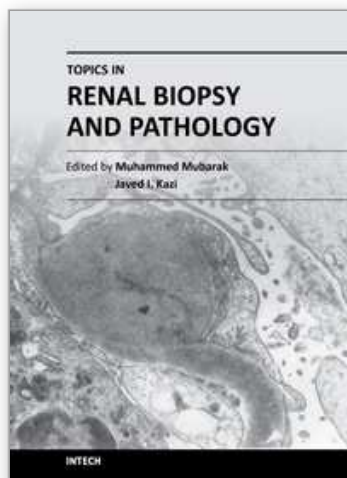
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