CASES

Cholesterol microembolization syndrome: a complication of anticoagulant therapy

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An elderly man with a history of hypertension and atrial flutter was referred to an internal medicine outpatient clinic because of purple-tinged and painful toes for over a year. His medications were candesartan, lercanidipine and warfarin. One and a half years earlier he had been given warfarin for paroxysmal atrial flutter. After six months on warfarin, the patient had been examined for the same symptoms in his toes by a vascular surgeon. At that time, computed tomography (CT) of the aorta, Doppler ultrasonography of the arteries of the legs and ankle pressure measurements had been performed, but no substantial abnormalities had been found. Only slightly elevated serum creatinine levels of 130–140 (normal 60–100) μmol/L had been observed.

At his visit to the outpatient clinic, the patient reported that the pain in his toes occurred with walking or putting socks on. On examination, his toes were purple with plaques (Figure 1) and tender on palpation. Distal pulses were present. No discoloration of fingers or skin elsewhere was detected. Except for the presence of atrial flutter, the rest of his physical examination was normal. Conventional and transesophageal echocardiographic examinations were performed, along with CT of the aorta and ultrasonography of the abdomen. Echocardiography showed minor mitral and aortic valve insufficiencies, but no signs of bacterial vegetations were evident. Computed tomographic investigation showed small plaques in the aortic wall. Ultrasonography of the abdomen showed no abnormalities. As found previously, the patient's serum creatinine level was slightly elevated (134 μmol/L), but no kidney abnormalities were observed on the CT scan. Results of laboratory tests, including urinalysis, were normal, except for an international normalized ratio that was above 2.0 because of the warfarin therapy.

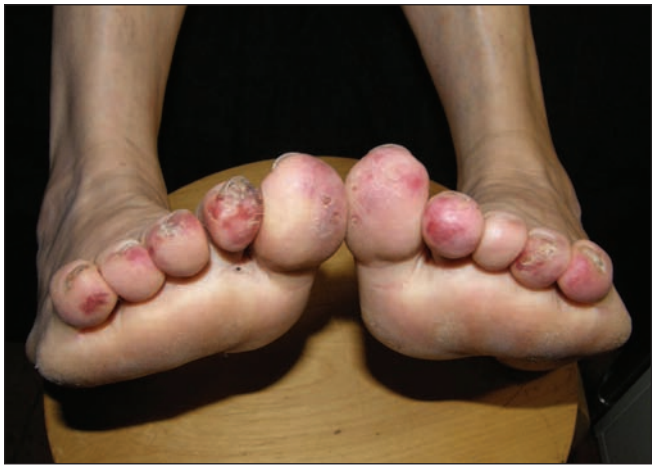

Figure 1: Purple discoloration and plaques on the toes of an elderly man treated with warfarin.

Key points

- Although hemorrhagic complications of anticoagulant therapy are well known, nonhemorrhagic complications, such as cholesterol microembolization syndrome, can also occur.
- The clinical presentation of cholesterol microembolization syndrome ranges from typical cutaneous manifestations, such as blue or purple toes, livedo reticularis and cyanosis, to multiorgan systemic failure.
- No specific laboratory test exists for cholesterol microembolization syndrome. If the diagnosis is uncertain, biopsy of the affected organ or the involved skin area is justified.
- No specific therapy exists for the syndrome. Prevention is critical. If anticoagulants are a cause, the use of these medications should be avoided.

Based on these findings, ischemia of the large vessels could be excluded as a cause of the patient's discoloured and painful toes. Vasculitis was also unlikely, because typical clinical findings and a suggestive pattern of laboratory parameters were lacking. The findings of echocardiographic examinations and laboratory tests excluded the possibility of infective endocarditis and bacterial emboli. Instead, the presence of atherosclerotic plaques in the aortic wall and continuous warfarin therapy launched the suspicion of cholesterol

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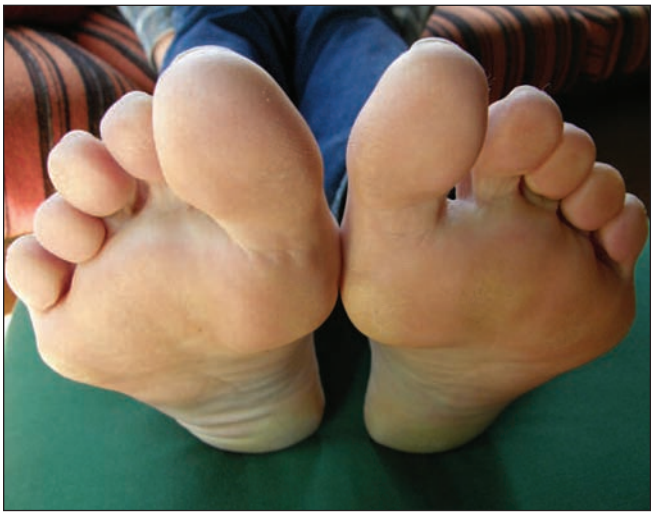

Figure 2: Resolution of the discoloration three months after warfarin was discontinued.

microembolization syndrome.[1–4] Interestingly, the patient had also started to wonder whether his toe problems were caused by warfarin, because they had appeared for the first time after warfarin therapy had been started.

A biopsy was scheduled, but the patient reported that he had stopped taking warfarin a couple of days before his visit to the outpatient clinic and found that his toe problems had diminished. The biopsy was cancelled. Warfarin was discontinued permanently and replaced by acetylsalicylic acid (ASA). Although warfarin is known to be more effective than ASA in decreasing the risk of thromboembolic stroke in patients with atrial flutter,[5] the patient was unable to tolerate warfarin and thus another treatment strategy had to be employed. Furthermore, the risk of thromboembolic complications in this patient was considered moderate rather than high.[5]

About one month after the patient stopped taking warfarin, the symptoms in his toes disappeared completely, and the patient could walk and wear socks without difficulty. Three months later, his toes were normal (Figure 2). A year after his presentation to the outpatient clinic, the patient received a permanent pacemaker for syncope related to sick sinus syndrome. After installation of the pacemaker, he developed atrial flutter again. The cardiologist replaced ASA therapy with phenindione therapy. A month later, the purple and sore plaques on the patient's toes reappeared. Phenindione was stopped and ASA was reintroduced. The patient's toes became normal again within a month. His cardiac rhythm remained in flutter.

Discussion

Cholesterol microembolization syndrome is a multiorgan ischemic disorder resulting from occlusion of small vessels by cholesterol crystals that originate from atherosclerotic plaques of large arteries.[1] In a general population, the incidence of the syndrome is low. For example, in the Dutch population, an average frequency of 6.2 cases per million inhabitants per year has been reported.[6] However, in selected patients, such as patients undergoing cardiac catheterization, the incidence of cholesterol microembolization syndrome has been reported to be as high as 1.4%.[7] This is also true for fibrinolytic and long-term anticoagulant therapies.[2,4] Any vascular intervention that scratches the luminal surface of the vascular wall makes the release of cholesterol crystals from atherosclerotic plaques possible and markedly increases the risk for cholesterol microembolization syndrome.[4] The syndrome may also appear spontaneously without any clearly established predisposing etiological factor. A summary of the most common predisposing factors of the syndrome is presented in Box 1.[3,4,8,9]

Clinical presentation

The clinical presentation of cholesterol microembolization syndrome is highly variable and depends on the flow distribution of cholesterol crystals.[4] The syndrome is said to be a great mimic, which makes its diagnosis challenging. There are no specific laboratory tests for cholesterol microembolization syndrome. On laboratory testing, azotemia, proteinuria, normocytic anemia and eosinophilia are often found.[8,9] Cholesterol crystals that are carried to lower extremities cause a typical appearance of blue or purple toes,[2,4] as with our patient. Other cutaneous signs that can occur in cholesterol microembolization syndrome include livedo reticularis, cyanosis, ulceration and even gangrene.[3,4] In the central nervous system, cholesterol microembolization syndrome may cause strokes with paresthesia, but may also reduce cognition.[10] Nausea, abdominal pain or discomfort, and melena may occur with gastrointestinal involvement because of ischemia or infarction of the alimentary tract.[3,9] Renal artery occlusion develops frequently and can lead to end-stage renal failure.

Box 1: Diagnosis of cholesterol microembolization syndrome[3,4,8,9]

Cholesterol microembolization syndrome should be considered if the following factors are present:*

- established atherosclerotic lesions in large vessels
- history of possible triggering factors (see below)
- typical clinical presentation, including renal failure, livedo reticularis or gangrene of the toes with intact pulses
- exclusion of small vessel vasculitis
- exclusion of disease states causing microbial emboli
- typical histopathological findings, in particular, evidence of cholesterol crystals (dissolved by the tissue processing) in the lumen of small arteries and inflammatory cell infiltration including eosinophilic infiltration around the occluded vessels

Potential triggers for cholesterol microembolization syndrome:

- angioplasty
- vascular surgery
- any invasive vascular procedure including angiography
- long-term anticoagulant therapy
- fibrinolytic therapy

*Of the above factors, typical histopathology is most reliable for the diagnosis of cholesterol microembolization syndrome. However, biopsy is commonly limited to cases in which diagnosis is uncertain or progressive renal or other life-threatening organ failure develops.

Most deaths that occur as a consequence of cholesterol microembolization syndrome are a result of end-stage renal failure combined with multi-organ failure.[4,9] If acute renal failure occurs, it typically develops within a week of the initiation of warfarin therapy, but subacute and chronic renal failures tend not to manifest until several weeks or months after initiation of treatment.[4] Evidence suggests that cholesterol crystals derived from erythrocyte fragments of intraplaque hemorrhage may also contribute to the progression and destabilization of atherosclerotic plaques of coronary arteries.[11]

The differential diagnosis includes vasculitis and infective endocarditis. In our patient, we excluded these conditions before the diagnosis of cholesterol microembolization syndrome was finally made on the basis of clinical features. After our patient was started on phenindione therapy, he developed relapsing purple toe syndrome. Similarly to warfarin, phenindione is a vitamin K–dependent anticoagulant and the reappearance of purple toes consistent with a diagnosis of cholesterol microembolization syndrome confirmed the diagnosis. However, if the diagnosis based on clinical presentation and investigations remains uncertain, a biopsy of the affected organ or the involved skin area may be considered.[4,9] Biopsy results in cholesterol microembolization syndrome typically show cholesterol crystals in the lumen of arteries, where they appear as elongated, biconvex, needle-shaped transparent clefts, since the crystals themselves are dissolved by the tissue processing. Varying degrees of inflammatory cell infiltration including eosinophilic infiltration may also be seen around the occluded vessels.

Management

There is no specific and curative treatment for cholesterol microembolization syndrome. Therefore, prevention is critical.[4,9] If a patient develops the syndrome, long-term anticoagulation should be withdrawn if possible.[4] Interestingly, it has been reported that it is possible to become asymptomatic even if oral anticoagulation is continued.[2] Any new invasive vascular procedure should also be avoided if possible.[4,8] Various therapies have been used to treat cholesterol microembolization syndrome, such as glucocorticoids, antiplatelet agents and heparin, but they have been found to have little or no effect.[9] Because kidney failure is the most common life-threatening condition in the syndrome, hypertension should be treated aggressively and renal function monitored regularly.[4,12] Statins may be beneficial, because they can stabilize and may cause regression of atherosclerotic plaques.[4]

Considering the large number of patients on warfarin, it is important to recognize the syndrome in its early stages before more serious complications develop. Patients on anticoagulant therapy complaining of even minor toe symptoms should be examined for possible cholesterol microembolization syndrome.

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