Blue toe syndrome caused by cholesterol crystal embolisation in a patient with warfarin use

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DESCRIPTION
A man in his early 90s presented with purple discoloration and pain in his toes of uncertain onset. He had multiple, cardiovascular diseases for which he was receiving atorvastatin, low-dose aspirin and warfarin. He had had no invasive medical intervention after receiving a percutaneous, coronary intervention 6 years previously. Physical examination revealed purple discoloration of the toes with tenderness (Figure 1). Laboratory tests demonstrated prolonged prothrombin time with an international normalised ratio (INR) of 3.32 (normal: 0.90–1.10). A skin biopsy of the right great toe revealed cleft-like spaces in the arteries with perivascular, lymphocytic inflammation and endothelial cell swelling (Figure 2) consistent with cholesterol crystal embolisation (CCE). Transthoracic echocardiography found no cause of embolism. His warfarin dose was titrated. By his 2-month follow-up visit, the toe discoloration had improved.

Blue toe syndrome (BTS), first described in 1976 in patients receiving oral anticoagulants,1 is characterised by the acute development of blue or violaceous discoloration in one or more toes which often become painful and tender to the touch.2 3 The cardinal mechanism of BTS is the embolism of small vessels and subsequent, sluggish blood flow or vascular damage.2 3 The rash blanches with pressure in the beginning, but later the discolouration becomes non-blanchable, indicating red cell extravasation.2 The most common cause of BTS is an atheroembolism, including CCE, but cardiac embolism (eg, infective endocarditis, cardiac myxoma), hyperviscosity syndromes (eg, cryoglobulinaemia, cold agglutinins), hypercoagulability states (eg, malignancy, antiphospholipid syndrome), vasculitis and other conditions (eg, calciphylaxis) may also lead to its development.2 3

Figure 1 Painful, purple discoloration of the toes.

Figure 2 Skin biopsy of the right great toe showing cleft-like spaces in an artery with perivascular lymphocytic inflammation and endothelial cell swelling.
CCE is a rare manifestation of atherosclerosis stemming from the embolisation of the contents of an atherosclerotic plaque (small cholesterol crystals and atheroma debris) from a proximal, large artery to distal, small-sized or medium-sized arteries. CCE causes end-organ ischaemia in the skin, kidney, gut, eye, brain and heart. Skin ischemia in CCE typically manifests as BTS or livedo reticularis, which are key to diagnosing CCE, as in the present case. The pathophysiology of CCE is thought to be a plaque rupture, which can occur spontaneously, traumatically or iatrogenically (especially via cardiovascular manipulation) and subsequently induces mechanical plugging and an inflammatory response. Furthermore, it is hypothesised that anticoagulation is a risk factor of plaque haemorrhage, plaque rupture and subsequent CCE although a causal relationship between anticoagulant use and CCE has not been established. Further study is needed to determine whether or not INR exceeding the therapeutic range increases the CCE risk.

Learning points

- Blue toe syndrome (BTS) is characterised by the acute development of blue or violaceous discolouration in one or more toes, which are often painful and tender to the touch.
- Cholesterol crystal embolisation (CCE) is the most common cause of BTS, and the pathophysiology of CCE is thought to be plaque rupture, which may be induced by anticoagulants.
- A causal relationship between anticoagulant use and CCE has not been established, and further study is needed to determine whether or not international normalised ratio exceeding the therapeutic range increases the CCE risk.

REFERENCES