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section 16 Cardiovascular disorders 3688 Filardo G, et al. (2012). Surgery for small asymptomatic abdominal aortic aneurysms. Cochrane Database Syst Rev, 14(3), CD001835. NICE (2012). Peripheral arterial disease: diagnosis and management. Clinical guideline. https://www.nice.org.uk/guidance/cg147 Patel R, Sweeting MJ, Powell JT, Greenhalgh RM; EVAR trial investi- gators (2016). Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial. Lancet, 388, 2366–74. Setacci C, Ricco JB; European Society for Vascular Surgery (2011). Guidelines for critical limb ischaemia and diabetic foot—introduction. Eur J Vasc Endovasc Surg, 42(Suppl 2), S1–3. Thompson PD, et al. (2002). Meta-analysis of results from eight ran- domized, placebo-controlled trials on the effect of cilostazol on pa- tients with intermittent claudication. Am J Cardiol, 90, 1314–19. Wanhainen A, et al. (2019). European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Aneurysms. Eur J Vasc Endovasc Surg, 57, 8–93. 16.14.3 Cholesterol embolism Christopher Dudley ESSENTIALS Cholesterol embolism occurring after vascular surgery or intraarterial angiographic procedures is not uncommon, but is often unrecog- nized. The clinical features mimic several conditions, including con- trast nephropathy and systemic vasculitis, and—if misdiagnosed—can result in the inappropriate use of powerful immunosuppressive drugs. A high index of suspicion is required when an elderly patient with widespread vascular disease develops a nonspecific systemic illness with progressive renal impairment, particularly after vascular surgery or arteriography. Biopsy of affected tissue, especially skin or kidney, is diagnostic—showing biconvex, needle-shaped cholesterol clefts within the lumen of arteries or arterioles. Treatment is sup- portive and the

prognosis is often poor. Introduction When atheromatous plaques ulcerate and become denuded of their endothelial covering, the underlying cholesterol-rich extracellular matrix can become detached and embolize. If the dislodged plaque and superimposed thrombus is sufficiently large, occlusion of a major systemic artery results in infarction of the organ or ischaemia of the limb supplied. This has been termed ‘thromboembolism’. By con- trast, ‘atheroembolism’ or cholesterol-crystal embolism occurs when much smaller and more numerous particles, composed principally of cholesterol crystals, lodge in a number of small arteries or arteri- oles simultaneously. The presence of a collateral circulation usually prevents infarction, and the event frequently passes unrecognized by the patient or their physician. However, tissue damage in certain organs can result from multiple showers of emboli. Because severe ulcerative atherosclerosis is most frequently present in the abdom- inal aorta, cholesterol embolism commonly affects the legs, gastro- intestinal tract, and kidneys. The condition usually presents as a complication of vascular surgery or angiographic procedures, when mechanical dislodgement of crystals from ulcerated plaques occurs. Anticoagulant and thrombolytic use has also been implicated as a predisposing factor. The clinical features are those of a systemic dis- order with renal failure that can mimic vasculitis, although more in- dolent cases with stable renal failure have been observed. Epidemiology The incidence of cholesterol-crystal embolism found at post- mortem is high: 77% after aortic surgery, 30% after aortography, and 25.5% after cardiac catheterization. By contrast, the clinical syndrome of cholesterol-crystal embolism is rare, complicating less than 2% of cardiac catheterizations. In two large renal biopsy series, an incidence of 1% was reported, and it has been suggested that cholesterol-crystal embolism could account for 5–10% of cases of acute kidney injury, although most nephrologists would regard this as an overestimate. Since the condition occurs in patients with severe atheromatous disease, it is most often seen in older male patients with obvious risk factors (e.g. hypertension, diabetes mellitus, smoking) and overt vascular disease (e.g. ischaemic heart disease, abdominal aortic an- eurysm, cerebrovascular disease). Although spontaneous cholesterol embolism can occur, it is much more common after vascular sur- gery or invasive radiology including aortography, angiography, and angioplasty. Under these circumstances, direct trauma to the vessel may result in detachment of atheromatous material from a ruptured plaque, or denude the endothelial lining of the vessel exposing the underlying atheroma for subsequent embolization. Angiography is the most common cause of cholesterol-crystal embolization, ac- counting for approximately 80% of cases in some series. Anticoagulant use has been associated with cholesterol embolism, and it has been proposed that by preventing thrombosis of ulcerating atheromatous plaques, anticoagulants favour the dissemination of atheromatous material. However, a causal relationship is unproven and many patients with widespread atherosclerosis coincidentally receive anticoagulants for a variety of reasons. Cholesterol embolism following the use of thrombolytic agents and novel oral anticoagu- lants (NOACs) has been reported. Prevention Prevention is important, particularly with the increasing number of older patients submitted to invasive angiography. Noninvasive methods of arterial imaging such as CT or magnetic resonance angi- ography are to be preferred in patients with diffuse atherosclerosis. When invasive angiography is unavoidable, careful attention must be paid to the angiographic technique, including the arterial ap- proach (brachial, or radial instead of femoral, for cardiac catheter- ization), use of softer, more flexible catheters, and reduced catheter manipulation.

16.14.3 Cholesterol embolism 3689 Clinical features Symptoms are often nonspecific with fever, weight loss, and my- algia. The clinical features are, otherwise, determined by the pattern of organ

involvement and are usually referable to the gastrointes- tinal tract, kidneys, and legs. Bilateral skin changes over the lower extremities are the commonest physical finding and include livedo reticularis, a purpuric rash, ‘trash feet’, blue toes (acral cyanosis), and focal digital necrosis (Figs. 16.14.3.1 and 16.14.3.2). Ulceration, nodules, and petechiae have also been described. Despite these skin changes and the presence of calf claudication (or frank myositis), pedal pulses may be felt easily, emphasizing that small vessels are occluded in this disorder. Carotid and femoral bruits are frequently heard, reflecting widespread and generalized atherosclerosis. Abdominal pain, gastrointestinal bleeding, and pancreatitis may occur, and embolism to the stomach, small bowel, colon, gallbladder, and spleen have all been reported. The most frequently involved of these sites is the colon. Because of their large blood supply and proximity to the abdominal aorta, the kidneys are commonly affected. This usually manifests as a subacute stepwise deterioration in renal function over 2 to 6 weeks, invariably accompanied by a worsening of pre-existing hypertension that can be labile and difficult to control. Cardiac failure with pul- monary oedema is a common accompaniment. Thus, a typical case is an elderly man presenting after angiography with progressive renal failure accompanied by a low-grade fever, abdominal pain, livedo reticularis of the lower body, and purpura over the feet with focal digital ischaemia of the toes. Acute kidney injury with necrotizing glomerulonephritis and crescent formation on renal biopsy has been described, but is rare. A further presentation is with slowly pro- gressive chronic kidney disease, which is underdiagnosed because extrarenal manifestations are absent and renal biopsy rarely under- taken. Cholesterol embolism has been reported in renal transplants. Transient ischaemic attacks, amaurosis fugax, and strokes can occur when embolism is from the carotid arteries or aortic arch. Retinal cholesterol-crystal emboli may be observed on ophthalmoscopy as bright refractile plaques within the retinal arterioles, especially at their bifurcation. Spinal cord infarction has also been reported. Differential diagnosis The diagnosis is frequently missed during life, or confused with that of acute renal failure induced by radiocontrast media (contrast neph- ropathy) when renal failure occurs after arteriography. A high index of clinical suspicion is therefore required, particularly in elderly pa- tients with evidence of atherosclerotic disease who develop renal failure after arteriography or following aortic or cardiac surgery; cholesterol embolism should also be considered in the differential diagnosis of a multisystem disease in elderly patients. Spontaneous cholesterol-crystal embolism associated with renal failure, fever, rash, and eosinophilia may, not surprisingly, be misdiagnosed as a vasculitic illness such as granulomatosis with polyangiitis (Wegener’s granulomatosis), microscopic polyangiitis, eosino- philic granulomatosis with polyangiitis (Churg–Strauss syndrome), polyarteritis nodosa, or bacterial endocarditis (see Chapters 19.11.7, 19.11.9, and 16.9.2). A false-positive antineutrophil cytoplasmic antibody (ANCA) test (not uncommonly by immunofluorescence, rarely to specific antigen) may further compound the diagnostic difficulty. Under these circumstances, renal biopsy is mandatory to make the correct diagnosis. Clinical investigation Laboratory findings are nonspecific, but frequently include a raised erythrocyte sedimentation rate, plasma viscosity, and C-reactive protein. Leucocytosis and a transient eosinophilia are common and may be pronounced. Depending on the tissue involvement, an elevation in creatine phosphokinase, amylase, lactate dehydro- genase (LDH), serum aspartate aminotransferase (AST), and al- kaline phosphatase may all be seen. Hypocomplementaemia is rare and usually mild. As stated earlier, ANCA have been re- ported, and their presence may further confuse the diagnosis with a multisystem vasculitic process. Mild proteinuria is generally pre- sent, and nephrotic-range proteinuria has been reported. Urine microscopy may be bland or reveal red cells, white cells (particu- larly eosinophils), and hyaline and granular casts. Renal failure is frequently nonoliguric. Fig. 16.14.3.1 Livedo reticularis

and vasculitic-like erythematous nodules on the leg of a patient in whom cholesterol-crystal embolization occurred after coronary angiography. Fig. 16.14.3.2 Purpuric spots and acral cyanosis of the toes from cholesterol embolism after aortic aneurysm repair.

section 16 Cardiovascular disorders 3690 Histology The definitive histological diagnosis of cholesterol-crystal embolism can usually be made from biopsies of kidney, skin, or muscle (including clinically uninvolved areas), although sampling error may miss the lesion due to its patchy distribution. Ante-mortem histological diag- noses have also been made from other tissues, including a gastric biopsy, prostatic currettings, and a bone marrow biopsy. The diag- nostic feature is of biconvex, needle-shaped cholesterol clefts within the lumen of arteries or arterioles that remain after the crystals have dissolved during routine histological preparation (Fig. 16.14.3.3). In fresh samples, the crystals can be identified by birefringence under po- larized light or by specific histochemical staining of cholesterol. In the kidneys, the typical finding is occlusion of small arteries and arterioles of between 150 and 200 μm in diameter, such as the arcuate and inter- lobular arteries, resulting in patchy areas of ischaemia and small areas of infarction. Crystals can also be seen within the glomeruli. In chronic cases, ischaemia produces a wedge-shaped lesion involving all compo- nents of the renal cortex radiating towards the capsule. The glomeruli appear ischaemic and sclerosed and the tubules become atrophic and separated by interstitial fibrosis. Grossly, the kidneys may be reduced in size with a rough granular surface and wedge-shaped scars. Based on animal studies involving the injection of atheromatous material, the presence of cholesterol crystals in the vascular lumen is thought to trigger a localized inflammatory and endothelial vascular reaction. Inflammatory cells (mainly macrophages and eosinophils) infiltrate, and multinucleated giant cells engulf the cholesterol crys- tals, but these are resistant to the scavenger effects of macrophages and may persist for many months. The inflammatory phase is fol- lowed by marked intimal thickening with concentric fibrosis and occlusion of the vessel. Depending on the extent of organ involve- ment, these pathological changes result in ischaemia, infarction, or—rarely—necrosis of the distal tissue. Management There is no effective therapy and no clinical trials of treatment in this condition have been performed. Steroids, aspirin, dipyridamole, and low molecular weight dextran have all been tried, but without any clear effect. There are anecdotal reports of a response to hydroxyl methyl glutaryl coenzyme A (HMG CoA) reductase inhibitors (statins), theoretically inducing plaque stabilization, but recovery may have been spontaneous. Nevertheless, statin use is recom- mended, even when started after the condition has been diagnosed. Anticoagulants are of no proven benefit and should be avoided given their potential role in the pathogenesis of the disorder. Encouraging results with iloprost and low-density lipoprotein apheresis have been reported, but these observations require replication. CT scanning of the aorta has been used to identify the precise source (e.g. aortic aneurysm, localized aortic plaque) of cholesterol emboli, and surgical replacement of the diseased vessel with a graft has been advocated. However, major surgery in elderly patients with widespread vascular disease and renal impairment carries signifi- cant risks and is generally avoided. Supportive therapy is directed at stopping anticoagulation unless essential, avoiding further angiographic or vascular surgical pro- cedures, controlling hypertension, and appropriate management of renal failure. Use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers has been advocated, but careful moni- toring of renal function is required. Prognosis Mortality is high due to the coexistence of cardiac and vascular dis- ease with renal failure in elderly patients. Renal impairment may re- main stable, but frequently progresses such that dialysis is required, although partial recovery has been reported, even after several months of dialysis. The mechanism of this recovery is uncertain. FURTHER READING Elinav E, Chajek-Shaul T, Stern M (2002). Improvement in cholesterol emboli

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Revision #1
Created 2026-01-22 16:39:23 UTC by Omar Ayman
Updated 2026-01-22 16:39:23 UTC by Omar Ayman