

Case Report

The Role of Statins on the Outcomes on the Cholesterol Embolism Syndrome with Secondary Vasculitis - A Case Report and Review of the Literature

Miko Bajič¹, Alojzija Hočvar¹, Žiga Rotar^{1*}, Sonja Praprotnik¹, Vesna Jurčič², and Matija Tomšič^{1,2}

¹Department of Rheumatology, University Medical Centre Ljubljana, Slovenia

²Department of Medicine, University of Ljubljana, Slovenia

***Corresponding author**

Žiga Rotar, University Medical Centre Ljubljana, Department of Rheumatology, Vodnikovacesta 62, 1000 Ljubljana, SLOVENIA, Tel: 38615225533; Fax: 38615225598; Email: ziga.rotar@gmail.com

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Abstract

The cholesterol embolization syndrome (CES) is a potentially severe complication of atherosclerosis, caused by embolization of atherosclerotic plaques, most frequently after vascular surgery or endovascular procedures. The clinical presentation closely mimics that of systemic vasculitides hence it should be considered in the differential diagnosis in patients with suspected vasculitis. Skin lesions (e.g. acrocyanosis, blue toe syndrome, livedo reticularis, purpura, nodules, ulcerations, gangrene) are almost invariably present and usually an early sign of CES. Rare reports of CES presenting as secondary necrotizing vasculitis emphasize the need for careful pathohistological examination of affected tissue to obtain the correct diagnosis, and choose the optimal treatment strategy. We report a case of a patient with spontaneous CES with clinical features of necrotizing small vessel vasculitis suggestive of polyarteritis nodosa, and present a thorough literature review of the nine cases of CES with secondary necrotizing vasculitis reported thus far. Based on the available data, bearing in mind their paucity, we suggest co-medication with statins may be organ- or even life-saving in this setting.

ABBREVIATIONS

CES: Cholesterol Embolization Syndrome; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; SAA: Serum Amyloid A; cANCA: Cytoplasmic Anti-Neutrophil Cytoplasmic Antibody; PR3: Proteinase-3; MPO: Myeloperoxidase; CT: Computed Tomography; PAN: Polyarteritis Nodosa

CASE PRESENTATION

A 67-year-old Caucasian male was admitted to the Department of Rheumatology at the University Medical Centre Ljubljana in February 2014 with a four week history of malaise; a weight loss of 5 kg; acrocyanosis, painful erythematous, necrotizing nodular skin lesions of the lower extremities; pain in his right testis, as well as aching shoulders and pitting ankle oedema. His prior medical history was notable for arterial hypertension which was controlled by lisinopril, and palmoplantar psoriasis.

He was a current smoker with a 20 pack-year history of smoking. He denied any recent endovascular procedures or vascular surgery. On admission he was in distress due to painful skin lesions. He had a body mass index of 26.2, was a febrile, with a pulse rate of 86 beats per minute, and a blood pressure of 167/80 mm Hg. The physical examination was notable for the multiple necrotizing maculae, erythematous infiltrated plaques, and nodules on his lower extremities (Figure 1). The left big toe was blue. The peripheral arterial pulses were normally palpable and symmetrical. Bruits were heard over the right carotid, and left renal arteries.

The erythrocyte sedimentation rate (ESR) was 39 (ref. < 15) mm/h, C-reactive protein (CRP) 56 (ref. < 5) mg/L, and serum amyloid A (SAA) 308 (ref. < 6.4) mg/L. A complete blood count revealed a mild normocytic anaemia with haemoglobin of 127 (ref. 140–180) g/L; a mildly elevated white blood cell count

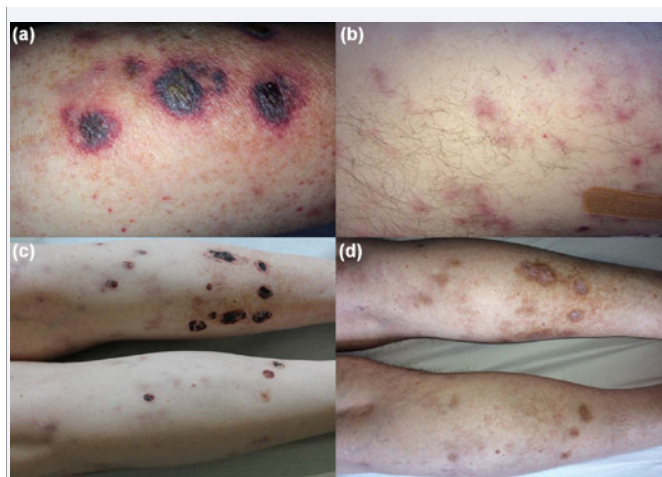


Figure 1 At presentation the patient had an annular necrotic maculae up to 2 cm in diameter with surrounding hyperpigmentation (a); erythematous maculae, plaques and nodules (b) on the lower limbs. At follow up, three months after presentation, the necrotic maculae showed signs of healing and were covered by crusts. There were several residual livedoid maculae (c). At follow up after six months, a month after the discontinuation of glucocorticoids, scars were seen in place of the previously necrotic maculae, and a few scattered hyperpigmented maculae (d).

of $10.7 \times 10^9/L$ (ref. $4.0-10.0 \times 10^9/L$) with a normal differential and a normal platelet count. Unexpectedly for a patient with advanced atherosclerosis not treated with lipid lowering agents, the lipid panel was mostly unremarkable with a total cholesterol of 4.1 (ref. 4.0–5.2) mmol/L, high-density lipoprotein 1.3 (ref. 1.4–2.8) mmol/L, low-density lipoprotein 2.4 (ref. 2.0–3.5) mmol/L, triglyceride 0.9 (ref. 0.6–1.7) mmol/L. Creatinine, serum urea, electrolytes, liver function tests, muscle enzymes, serum electrophoresis, and tumor markers were within normal limits. The cytoplasmic anti-neutrophil cytoplasmic antibody pattern (cANCA) was detected on immunofluorescence. The antigen specificity could not be determined after ELISA testing for proteinase-3 (PR3), myeloperoxidase (MPO), azurocidine, lactoferrin, neutrophil elastase, cathepsin G and bactericidal/permeability increasing protein, and lysozyme. A low lupus anticoagulant activity was detected. Hep-2 test, antibodies against double stranded DNA (Farr method), antibodies against extractable nuclear antigens (Sm, U1RNP, Ro, La, Scl-70, Jo-1, PCNA, PM/Scl, SL, Ku); rheumatoid factor; anti-pyruvate dehydrogenase antibodies; cryoglobulin; anti-glomerular basement membrane antibodies; IgG, IgM anticardiolipin antibodies; IgG, IgM, and IgA anti-beta-2-glycoprotein I antibodies were all negative. C3c and C4 complement levels showed no abnormalities.

Doppler ultrasonography of the carotid and vertebral arteries revealed a hemodynamically insignificant atheromatous plaque in the left carotid artery. A computed tomography (CT) angiogram of the aorta and its major branches showed circumferential aortic plaque with predominantly lipid-enriched cores up to 9 mm wide. No (micro-) aneurysms of the visceral arteries were observed. Ultrasonography of the right testicle showed hypoechoic areas without a clear demarcation in the heterogeneous testicular parenchyma. No significant pathology was revealed on EKG, chest X-ray, transthoracic

echocardiography, contrast enhanced abdominal CT scan, and electromyography. Antibodies against hepatitis C virus and hepatitis B virus surface antigen as well as antibodies against hepatitis B virus core protein were all negative.

A bright field and direct immunofluorescence microscopy examination of a nodular skin lesion revealed mixed-cell perivascular infiltrates; panniculitis involving the deep dermis and the subcutaneous fat, and cholesterol crystals' clefts in the lumen of the small-diameter arteries; fibrinoid necrosis of the medium and small arteries consistent with cholesterol embolization syndrome with secondary vasculitis (Figure 2).

Due to the necrotic skin lesions and vasculitis, treatment with methyl-prednisolone 0.8 mg/kg qd was started. Glucocorticoids were stopped after a five month taper. Rosuvastatin 10 mg qd was also prescribed. At a follow up, six months after presentation, the skin lesions as well as the other symptoms were resolved (Figure 1).

DISCUSSION

Cholesterol embolization syndrome (CES) was first described over 150 years ago, but still frequently remains unrecognized. CES occurs predominately in elderly patients with severe atherosclerosis. It may develop spontaneously as

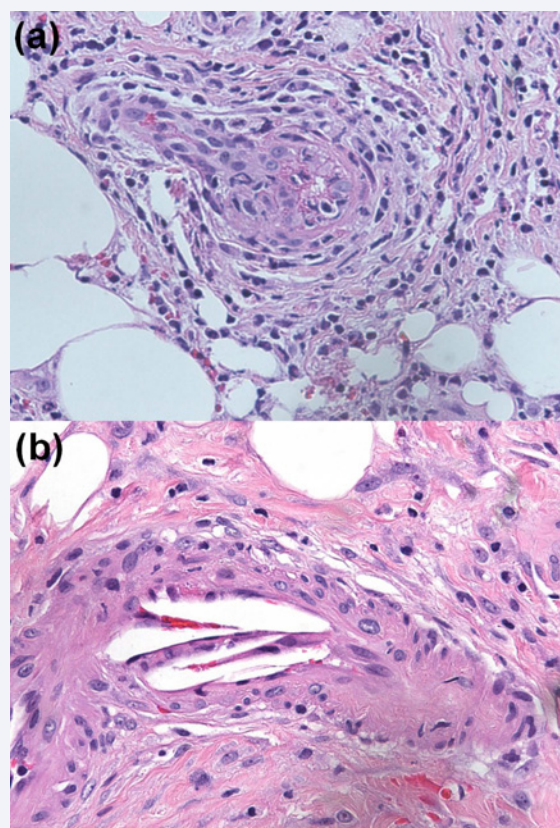


Figure 2 In the same skin sample one small artery shows transmural inflammatory cell infiltration (a), and another one (in the subcutaneous fat) empty clefts characteristic of cholesterol emboli within its obliterated lumen and only a few inflammatory cells within its wall (b). (both haematoxylin and eosin stain; original magnification $\times 400$).

Table 1: Literature review of cholesterol crystal embolization syndrome cases associated with secondary vasculitis.

Reference	Sex, age	Biopsy specimen/ autopsy	Organ involvement	ANCA	Recent vascular surgery or endovascular procedures?	Therapy	Outcome
Goldman M et al., 1985 [2]	M, 75	Kidney	Kidney, eye	N/S	Aortic catheterization for carotid angiography	HD	ESRD
Peat DS et al., 1996 [3]	M, 73	Skin, kidney Autopsy	Skin, kidney, lung	+	No	GC; CYC; HD	Death due to CHF
Kaplan Pavlovic S et al., 1996 [4]	¹ M, 63 ² F, 69	¹ Skin, kidney ² Skin, kidney	¹ Skin, kidney ² Skin, kidney	¹ pANCA/ MPO ² pANCA/ MPO	¹ No ² No	¹ GC; HD ² N/S	¹ N/S ² N/S
Sijkens Y et al., 1997 [5]	M, 62	Skin, pleura, muscle Autopsy	Skin, pleura, muscle, brain	Neg.	No	GC; CYC	Death
Ballesteros AL et al., 1999 [6]	M, 69	Skin, kidney, Autopsy	Skin, kidney, GIT	Neg.	Resection of an abdominal aortic aneurysm with aortic-bi-femoral graft	GC; CYC	Death due to MOF
Sugimoto T et al., 2006 [7]	M, 75	Skin	Skin, kidney	MPO	Coronary angiography, CABG	GC; HD; Atorvastatin	Cutaneous lesions and renal function improved
Yücel AE et al., 2006 [8]	M, 53	Skin, amputated digit	Skin, kidney, blue toe	Neg.	Coronary angiography, CABG	GC; HD; Simvastatin	Cutaneous lesions and renal function improved
Maejima et al., 2010 [9]	M, 76	Skin	Skin, lung	MPO	No	GC	Skin eruptions resolved
Our patient	M, 67	Skin	Skin, testis, blue toe	cANCA/ neg.*	No	GC; Rosuvastatin	Skin lesions and other symptoms regressed

* ELISA for proteinase 3 (PR3), myeloperoxidase (MPO), azurocidine, lactoferrin, neutrophil elastase, cathepsin G and bactericidal/permeability increasing protein, lysozyme;
Abbreviations: CABG: Coronary Artery Bypass Grafting; CHF: Congestive Heart Failure; CYC: Cyclophosphamide; ESRD: End Stage Renal Disease; F: Female; GC: Glucocorticoids; GIT: Gastrointestinal Tract; HD: Hemodialysis; M: Male; MOF: Multiple Organ Failure; N/S: Not Specified

in our patient, although the likelihood markedly increases after invasive vascular procedures and with the use of thrombolytic agents or anticoagulants. The cholesterol crystals detach from the atherosclerotic plaques in the large arteries and lodge downstream in small and medium sized arteries. The classical features of CES include a variety of skin lesions (e. g. acrocyanosis, *bluetoes syndrome*, livedoreticularis, purpura, nodules, ulcerations, gangrene) and progressive renal failure. The involvement of the gastrointestinal tract, central nervous system, and coronary arteries has also been reported [1]. CES may present with a variety of symptoms and laboratory findings mimicking systemic vasculitis as demonstrated in our case. Namely, CES may provoke an inflammatory reaction with a fever, weight loss, myalgia, leucocytosis and elevated acute phase reactants as well as eosinophilia and hypocomplementemia. The cholesterol crystals are birefringent and can be directly visualized under polarized light in snap frozen biopsy specimens. They are washed away during processing of formalin fixed paraffin embedded biopsy specimens, however, the characteristic clefts within the lumen of the affected arterioles or small arteries can be observed on bright field microscopy. In the tissues the cholesterol crystals may induce an obliterative arteritis, also known as *pseudovasculitis* due to CES, which further obfuscates the distinction between CES and systemic vasculitides. Thus far, nine cases (89% male) of CES

with secondary vasculitis have been described in the available literature (Table 1) [2-9].

Severe vasculitis, secondary to CES was histologically found in our patient. Without a histopathological examination and the detection of the distinctive empty clefts in the lumens of the small and middle sized arteries we could not have diagnosed CES. At admission, polyarteritis nodosa (PAN) was considered the most likely diagnosis, especially due to the extent and localization of the skin lesions, and the testicular pain. Although the testicular involvement is one of the characteristics of PAN, we found a report of a patient with histologically confirmed segmental testicular infarction due to CES [10]. ANCA of an unknown specificity was detected by immunofluorescence in our patient's serum but he lacked the other clinical, laboratory and histopathological features of ANCA-associated vasculitis. MPO-ANCA was rather commonly observed in CES [4,7,9]. It has recently been suggested that the cholesterol crystals within the vascular lumen trigger and potentiate an inflammatory response within the vascular wall by activating the innate immunity through the NLRP3 inflammasome which leads to the recruitment of the neutrophils and macrophages [11]. The activated neutrophils also release MPO, against which the immune system could produce the ANCA-MPO antibodies as described in drug induced lupus [12].

No recommendations based on evidence for the treatment of CES exist. Primary and secondary prevention of atherosclerosis including changes to life style, statins and anti-aggregation therapy are advised. Although the causality might be questionable due to the small sample size, the thus far published case reports of patients with CES with secondary vasculitis suggest that the statins may reduce CES related mortality (Table 1). Recently it has been shown that a reduction of low-density lipoproteins by apheresis, and rosuvastatin improved renal prognosis, and stabilized aortic atherosclerotic plaques in patients with cholesterol embolism, respectively [13-15]. In addition to the lipid lowering effects the statins also possess anti-inflammatory properties. Their immune modulatory effect is exerted through a variety of molecular pathways of both the innate and adaptive immunity [16]. Innate immunity has a central role in the pathogenesis and progression on an atherosclerotic plaque rupture, and according to recent findings also in CES induced inflammation [11].

Glucocorticoids were reported successful in some cases with pseudovasculitis (Table 1) [17]. We believe that treatment with both glucocorticoids, controlling the acute inflammation, and statins, which primarily reduced the frequency of spontaneous cholesterol emboli, hastened our patient's recovery and feel that combination therapy might have a role in CES cases with secondary vasculitis. The initial dosing and tapering schemes of glucocorticoids are lacking at present.

In conclusion, CES is a great imitator. Not only does it clinically mimic systemic vasculitides, the cholesterol crystals may even induce secondary vasculitis. A high level of clinical suspicion and histopathological examination of affected tissues especially in older patients with atherosclerosis are required to avoid missing this condition. The limited data on the management of CES as well as our clinical experience suggest the co-medication with statins may be organ- or even life-saving in this setting.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Informed consent was obtained from the patient for whom identifying information is included in this case report.

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