

# Vasospastic angina pectoris associated with Churg–Strauss syndrome

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## SUMMARY

**Background** A 50-year-old woman presented with recurrent episodes of unstable angina pectoris refractory to vasodilator treatment. Relevant coronary stenoses were excluded by coronary angiography and intravascular ultrasonography. Intracoronary infusion of acetylcholine revealed diffuse coronary vasospasms associated with clinical signs of myocardial ischemia and ST-segment elevation. Symptoms of bronchial asthma, polyneuropathy, nasal polyps, allergic rhinitis, gastritis and eosinophilia led to a diagnosis of Churg–Strauss syndrome.

**Investigations** Serum chemistry, coronary angiography, left-heart catheterization, intravascular ultrasonography and coronary vasospasm provocation with acetylcholine.

**Diagnosis** Vasospastic angina pectoris associated with Churg–Strauss syndrome.

**Management** Treatment with systemic corticosteroids and cyclophosphamide.

**KEYWORDS** Churg–Strauss syndrome, corticosteroids, cyclophosphamide, eosinophils, vasospastic angina pectoris

## CME

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Received 1 April 2005 Accepted 13 July 2005

www.nature.com/clinicalpractice  
doi:10.1038/ncpcardio0299

## THE CASE

In October 2001, a 50-year-old woman presented at hospital with severe chest pain and underwent cardiac catheterization. Coronary angiography revealed a 75% stenosis of the left anterior descending artery and percutaneous coronary angioplasty was performed. In June 2003, the patient had another attack of severe chest pain and was admitted to the same hospital. ST-segment elevation was seen in electrocardiography leads II, III and aVF. A severe thrombotic alteration of the proximal right coronary artery (RCA) was visualized by coronary angiography, which was treated with coronary angioplasty and stent implantation.

We first saw the patient in September 2003, after admission for recurrent chest pain at rest. She had a history of moderate bronchial asthma, polyposis nasi, sinusitis, gastritis and allergy to paracetamol and nonsteroidal anti-inflammatory drugs such as ibuprofen, diclofenac and aspirin. Chest-pain episodes lasted a few minutes and were unrelated to bronchial asthma attacks. Previous treatment with a combination of nifedipine 40 mg daily and diltiazem 180 mg daily had not relieved symptoms. Nitrates administered sublingually partly relieved symptoms, but use of the calcium-channel blocker diltiazem at 180 mg daily, the angiotensin-converting-enzyme inhibitor quinapril at 5 mg daily, clopidogrel at 75 mg daily and the coronary vasodilator trapidil at 600 mg daily did not stop the angina episodes.

The patient underwent cardiac CT, which showed normal parenchyma perfusion and no indication of atherosclerotic lesions or previous myocardial infarction. On the first day of admission and subsequent hospital visits, the patient's total white blood cell count was normal, but her erythrocyte sedimentation rate was 47 mm/h (normal range <20 mm/h). A differential blood count revealed an eosinophil count of  $0.812 \times 10^9$  cells/l (normal range  $0.08\text{--}0.36 \times 10^9$  cells/l), corresponding to 20% of total leukocytes. Histology carried out after

**Box 1** American College of Rheumatology criteria for Churg–Strauss syndrome.

Asthma  
 Eosinophilia >10% of total leukocytes  
 Neuropathy, mononeuropathy or polyneuropathy  
 Pulmonary infiltrates  
 Paranasal sinus abnormality  
 Extravascular eosinophil infiltration on biopsy findings

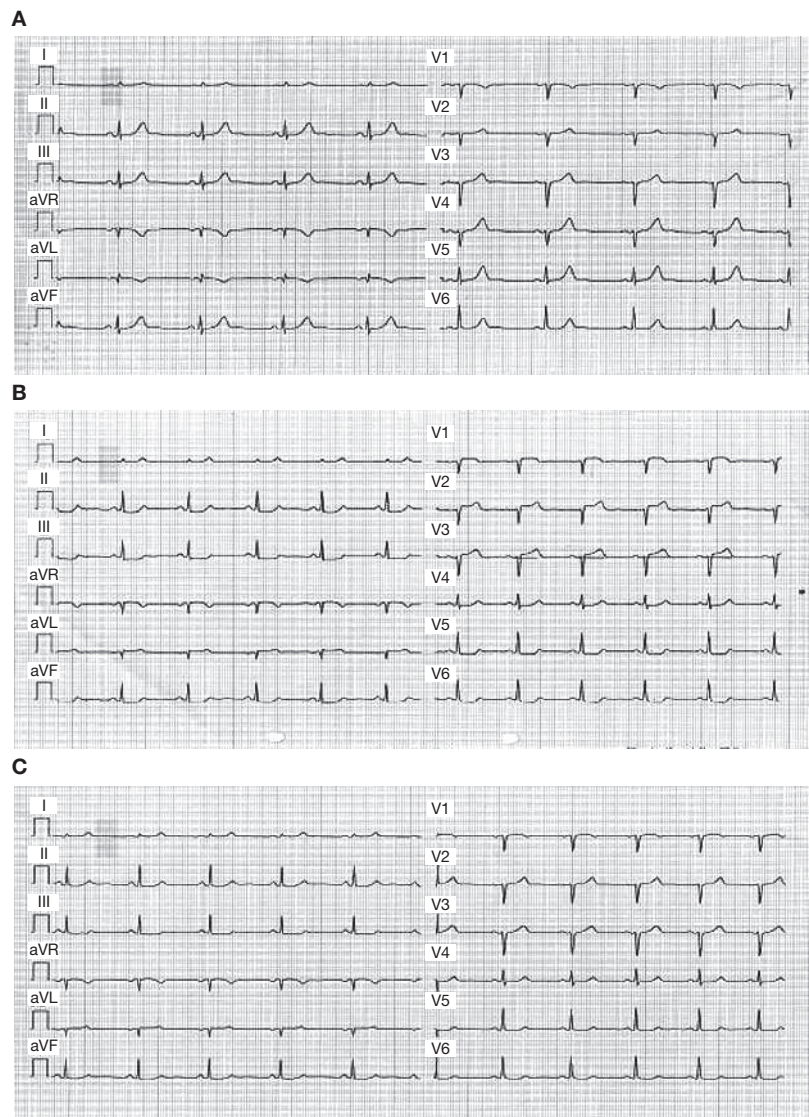
Clinical findings qualify with or without pathologic material; a diagnosis can be made when at least four of the six criteria are present.

bone-marrow aspiration confirmed reactive eosinophilia, but no pulmonary infiltrates were observed. A neurologist diagnosed a peripheral neuropathy, expressed as symptoms of foot extensor paresis, numbness and tingling sensations in the left foot. The patient was also diagnosed with mild gastritis. Symptoms of asthma, paranasal sinus abnormality, mononeuropathy, mild gastritis and eosinophilia led to a diagnosis of CHURG–STRAUSS SYNDROME (CSS), according to the classification criteria of the American College of Rheumatology (Box 1).<sup>1</sup> Inhaled corticosteroid therapy with 400 µg budesonide daily failed to suppress the patient's eosinophilia.

Circulating blood levels of proinflammatory cytokines were measured to assess levels of systemic inflammation. The concentration of interleukin-6 was 4.2 pg/ml (normal values <9.0 pg/ml), of interleukin-2 receptor was 1.47 ng/ml (normal values <0.94 ng/ml) and of tumor necrosis factor-α was 31.6 pg/ml (normal values <27.0 pg/ml), indicating moderate systemic inflammation. Several electrocardiography controls revealed typical ST-segment depression as well as a monomorphic nonsustained ventricular tachycardia during typical angina pectoris episodes at rest (Figure 1).

Coronary stenosis was excluded by coronary angiography. Alternative causes of coronary vasospasm such as smoking, potassium or magnesium electrolyte disturbances, cocaine use, cold exposure, hyperventilation, and insulin resistance were also excluded.

The refractory nature of the patient's unstable angina including nonsustained ST-segment elevations, and exclusion of coronary stenoses led us to prescribe daily treatment with 50 mg systemic corticosteroids. This dose was gradually reduced by 10 mg every 5 days until a maintenance dose of 5 mg daily was reached.



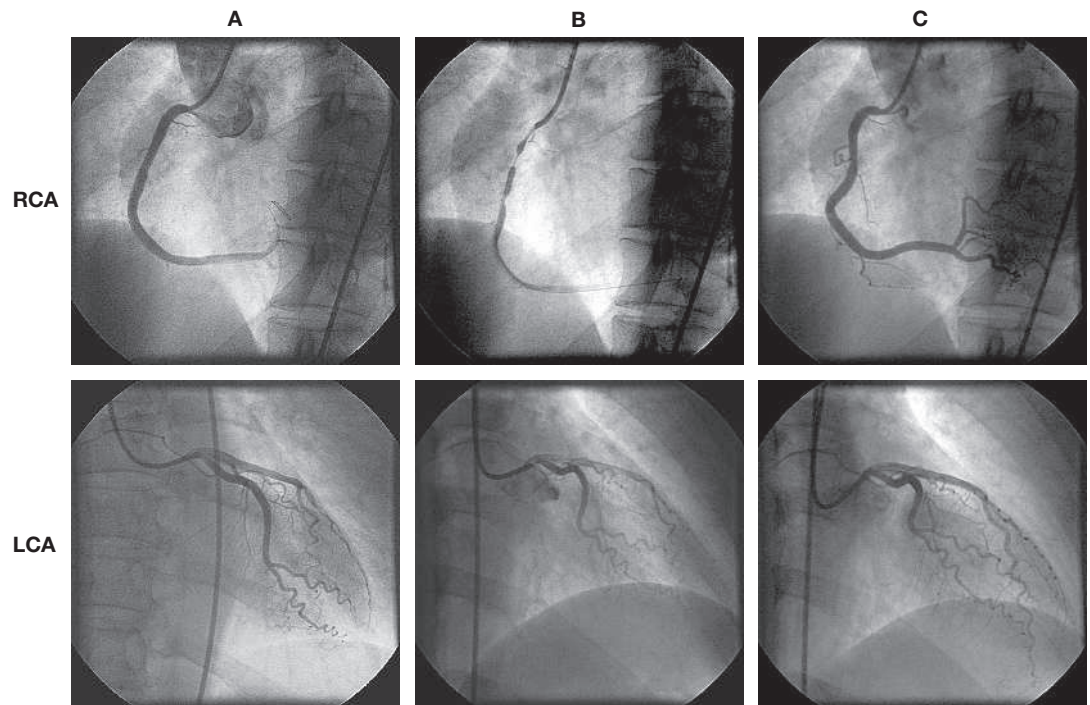
**Figure 1** Representative examples of electrocardiograms taken at rest, during an episode of vasospastic angina and after relief of symptoms with nitrates. **(A)** Native electrocardiogram with no clinical symptoms of chest pain. **(B)** Severe chest pain attack with typical ST-segment depression in leads II, III, aVF, V5 and V6, and ST-segment elevation in leads V1, V2 and V3. **(C)** Symptoms were relieved and the ST-segment normalized within 1 min of administration of sublingual nitrates.

No further angina attacks occurred during the patient's stay in hospital. Ten days after initiation of corticosteroid therapy, her eosinophil levels had decreased to  $0.4 \times 10^9$  cells/l and proinflammatory cytokine levels were also lower (interleukin-2 receptor 1.19 ng/ml, tumor necrosis factor-α 21 pg/ml).

In December 2003, while still taking 5 mg corticosteroids daily, the patient was readmitted with angina pectoris symptoms. Electrocardiography showed intermittent ST-segment depressions

**GLOSSARY****CHURG–STRAUSS SYNDROME**

A widespread allergic granulomatosis and angiitis that affects various organs



**Figure 2** Coronary arteriogram showing epicardial vasomotor response before after infusion with intracoronary acetylcholine, and after administration of intracoronary bolus nitroglycerin. **(A)** Coronary arteriogram taken before infusion of intracoronary acetylcholine. **(B)** Severe coronary artery spasms were observed in both proximal and distal segments of the right coronary artery after intracoronary infusion with 15  $\mu\text{g}/\text{min}$  acetylcholine. Moderate vasospasm occurred in the proximal and distal segments of the left coronary artery. These changes were associated with chest pain and ST-segment depression in leads II, III and aVF. **(C)** Intracoronary bolus administration of 0.2 mg nitroglycerin immediately reversed the acetylcholine-induced spasm and led to dilatation of epicardial vessels. LCA, left coronary artery; RCA, right coronary artery.

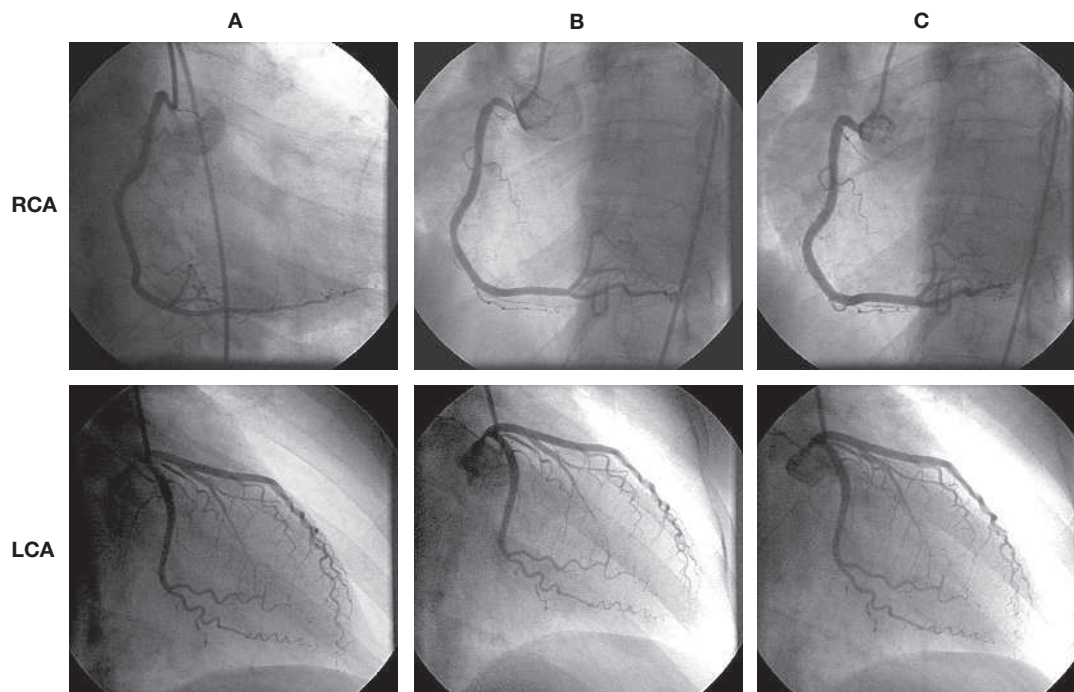
in leads II, III and aVF. Blood analysis revealed slightly raised troponin I levels at 0.23 ng/ml (normal values  $<0.1$  ng/ml) and her eosinophil count had increased to  $1.2 \times 10^9$  cells/l.

Cardiac catheterization was performed. Coronary angiography of the RCA and left coronary artery (LCA) were normal. Acetylcholine infusion to the RCA provoked a significant spasm, resulting in 99% occlusion at proximal and distal segments. Severe chest pain and ST-segment depression in leads II, III and aVF were elicited. Vasodilatation was achieved by subsequent intracoronary bolus administration of nitroglycerin and electrocardiographic alterations and angina symptoms resolved. Infusion of acetylcholine in the LCA led to diffuse vasoconstriction and vasospasm mainly in the distal vessel segments (Figure 2). Clinical signs of myocardial ischemia were visible, but without ST-segment abnormalities. No atherosclerotic plaques were revealed in the coronary arteries by

intravascular ultrasonography, although slight intima-media thickening ( $<0.3$  mm) was found in the area of the RCA stent.

The corticosteroid dose was raised to 50 mg daily and daily treatment with 100 mg cyclophosphamide was initiated. The patient's angina pectoris symptoms abated rapidly with cyclophosphamide treatment and her eosinophil count returned to normal ( $0.1 \times 10^9$  cells/l). Since no further electrocardiographic alterations were documented, the patient was discharged. After 8 weeks, the daily cyclophosphamide dose was reduced to 50 mg. Corticosteroid treatment was tapered back to 5 mg daily during this 8-week period.

At 3-month follow-up, the patient had had no further angina pectoris. On the day of the visit, she presented with acute sinusitis, elevated levels of circulating tumor necrosis factor- $\alpha$  (71 pg/ml) and an eosinophil count of  $0.32 \times 10^9$  cells/l. During acetylcholine infusion into the RCA, slight



**Figure 3** Coronary arteriogram showing normal vasomotor responses taken at 3 month follow-up, after combination therapy with steroids and cyclophosphamide. No chest pain or electrocardiogram alterations were noted. **(A)** Coronary arteriogram taken before infusion of intracoronary acetylcholine. **(B)** Normal vasomotor responses were seen at 3-month follow-up. No coronary artery spasms were induced in either the right or left coronary artery after intracoronary infusion with 15 µg/min acetylcholine. **(C)** Coronary arteriogram after intracoronary bolus administration of 0.2 mg nitroglycerin. LCA, left coronary artery; RCA, right coronary artery.

spasm was provoked at proximal segments but no significant stenosis was seen. Infusion in the LCA led to a slight vasoconstriction in the distal vessel segments (Figure 3). No abnormalities on electrocardiography or typical symptoms of angina pectoris were documented. After 6 months of daily treatment with 5 mg corticosteroids and 50 mg cyclophosphamide, followed by a further 6 months of daily treatment with 2.5 mg corticosteroids and 25 mg cyclophosphamide, the patient remained free from angina pectoris and neuropathic symptoms. Cardiac catheterization revealed a normal coronary angiogram. Intracoronary infusion of acetylcholine led to vasodilatation of both the RCA and LCA, indicating normal epicardial endothelial function. No electrocardiographic alterations or signs of angina pectoris were observed, and her eosinophil count was lower than  $0.04 \times 10^9$  cells/l. No significant side effects have arisen from the treatment. The patient's level of C-reactive protein was slightly elevated during each hospital visit (8–17 mg/l, normal values <5 mg/l).

#### DISCUSSION OF DIAGNOSIS

Vasospastic angina is caused by sudden occlusive vasoconstriction of an epicardial artery segment, resulting in transmural myocardial ischemia. ST-segment elevations are typical and occur either alone or with ventricular tachyarrhythmias that can result in syncope or even cardiac arrest. The actual incidence of vasospastic angina is unknown because of its refractory character and because provocation tests are rarely performed in Western countries. Spasms can occur in either normal or atherosclerotic vessels and in the absence of any preceding increase in myocardial oxygen demand. Nitroglycerin or calcium-channel blockers can usually reverse the spasm.<sup>2</sup>

Several stimuli are used to induce coronary vasospasm in provocation tests, but ergonovine and acetylcholine are considered to have the highest sensitivity and specificity.<sup>3</sup> Cigarette smoking can be a predisposing factor for coronary vasospasm,<sup>4</sup> but it can also be caused by endothelial-cell dysfunction; elevated levels of

**Box 2** Clinical manifestations of Churg–Strauss syndrome.

**Cardiovascular**

Eosinophilic endomyocarditis  
Coronary vasculitis  
Valvular heart disease  
Cardiac arrest or myocardial infarction  
Acute or constrictive pericarditis or cardiac tamponade  
Congestive heart failure or cardiomyopathy

**Gastrointestinal**

Eosinophilic gastroenteritis

**Dermatologic**

Cutaneous eruptions (nodules, papules, vesicles)

**Pulmonary**

Asthma  
Rhinitis, sinusitis, nasal polyposis  
Pulmonary infiltrates  
Pleural effusion

**Neurologic**

Mononeuritis multiplex  
Diffuse symmetrical neuropathy  
Cerebral infarction

**Renal**

Focal segmental glomerulonephritis  
Microscopic hematuria  
Proteinuria  
Mild or moderate renal failure

serotonin, histamine, thromboxane and endothelin have been described as biochemical markers.<sup>5</sup> Evidence shows that local inflammation of endothelial cells is a causative factor, and that inflammatory cytokines, such as tumor necrosis factor- $\alpha$ , can promote functional reprogramming of endothelial cells in patients with chronic vascular inflammation.<sup>6,7</sup> Microscopic analysis of pathologic tissue from a patient with coronary vasospasm revealed more mast cells in the adventitia of an artery involved in a previous vasospasm, compared with levels of mast cells found in arteries from patients with atherosclerotic coronary artery disease, or sudden death without documented vasospasm, and normal controls.<sup>8</sup> In addition, Kohchi *et al.*<sup>9</sup> reported focal infiltration of inflammatory cells in the adventitia of the involved coronary artery in patients with vasospastic angina pectoris. Local inflammation of the coronary arterial wall is, therefore, likely to play an important role in the pathogenesis of coronary spasm.

According to the American College of Rheumatology, a patient can be diagnosed with

CSS if at least four of six criteria are met, with a classification sensitivity of 85% and specificity of 99.7% (Boxes 1 and 2).<sup>1</sup> Although asthma is typically associated with eosinophilia, CSS should be considered in the diagnostic work-up if the proportion of eosinophils is greater than 10% of total leukocytes. A biopsy to confirm eosinophilic tissue infiltration or vasculitis is desirable, but is not always possible because of its unpredictable and often incomplete manifestation in various organs.<sup>10</sup> Coronary angiography has revealed vasculopathy consistent with vasculitis in CSS in previous case reports.<sup>11,12</sup>

The major differentiating factor of CSS from other vasculitides such as Wegener's granulomatosis or polyarteriitis nodosa, is its association with bronchial asthma. The typical CSS patient is middle-aged with incident or newly worsened asthma, which might arise long before CSS is diagnosed. Other early symptoms include nasal polyps and allergic rhinitis. The next phase of the disease is often marked by peripheral and tissue eosinophilia, which is frequently associated with pulmonary infiltrates. Normally, eosinophils comprise 5% or less of the total white blood cell count. In CSS, eosinophils levels can reach 60% of leukocytes ( $6.6 \times 10^9$  cells/l). Cardiac disease is the most frequent complication of sustained eosinophilia. Eosinophils play various roles in inflammatory responses and might cause hypercontraction of smooth musculature. Once stimulated, eosinophils can induce the release of vasoactive substances, including histamine, prostaglandin D<sub>2</sub>, and leukotrienes C<sub>4</sub> and D<sub>4</sub>, from mast cells and basophils.

The third phase of CSS is a vasculitis affecting organs including the heart, skin, lungs, kidney and nervous system. Vasculitic lesions in the heart can lead to congestive heart failure or heart attacks, due to sudden occlusive vasoconstriction in a segment of an epicardial artery. Although vasospastic angina is an unusual clinical manifestation of CSS, the case we report suggests that it should be suspected in CSS cases and included in differential diagnostic work.

**TREATMENT AND MANAGEMENT**

Corticosteroids have anti-inflammatory and immunosuppressive effects and are used to treat vasculitis rapidly in CSS patients. High doses of oral steroids (e.g. 40–80 mg) are initially prescribed in an attempt to get the disease into remission as quickly as possible. Once the patient's

condition improves, steroid treatment is gradually tapered down to a maintenance dose range of 2.5–7.5 mg, as achieved in our case. Most CSS patients require steroid treatment indefinitely.

Treatment with a second-line immunosuppressant drug, such as cyclophosphamide, azathioprine, mycophenolate mofetil or ciclosporin, can allow steroid doses to be reduced, thereby minimising side effects.<sup>13</sup> Cyclophosphamide is an effective treatment for immunologically mediated diseases, including some forms of vasculitis. Kubota *et al.*<sup>14</sup> describe a case of cardiogenic shock following acute myocardial infarction in a patient with CSS. The patient recovered after treatment with a combination of prednisolone and cyclophosphamide, and follow-up angiography showed recanalization of the infarct-related arteries.

Tagaki *et al.*<sup>15</sup> suggested that coronary spasms might be induced by arterial hyper-reactivity caused by local inflammation in the coronary arterial wall, and that this can be suppressed by the anti-inflammatory action of corticosteroids. Whether or not corticosteroids have an effect on vasospasms independent of their cause is unclear. Relapse can, however, occur in 25% of CSS patients, so future studies to assess the long-term effects of immunosuppressive therapy are desirable.

## CONCLUSION

In this case of CSS-associated vasospastic angina, coronary stenting did not relieve refractory coronary vasospastic angina. Treatment with immunosuppressive corticosteroid and cyclophosphamide therapy and vasodilators did, however, reduce angina symptoms and restore normal coronary endothelial function.

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## Competing interests

The authors declared they have no competing interests.