

Coronary Arteries Involvement in Churg-Strauss Syndrome Simulating an Acute Coronary Syndrome: An Emblematic Case and Literature Review

Buccheri D^{2,3*}, Chirco PR¹, Piraino D^{2,3}, Carella M², Franca EL¹, Cortese B³ and Andolina G²

¹Cardiac department, Paolo Giaccone Hospital, University of Palermo, Palermo, Italy

²Interventional Cardiology, Paolo Giaccone Hospital, University of Palermo, Palermo, Italy

³Interventional Cardiology, Fatebenefratelli Hospital, Milan, Italy

Abstract

Churg-Strauss syndrome is a rare vasculitis, affecting small to medium vessels, recently renamed Eosinophilic Granulomatosis with Polyangiitis. The American College of Rheumatology proposed the following diagnostic criteria: asthma, eosinophils on the leukocyte count greater than 10%, mononeuropathy or polyneuropathy, migratory or transient pulmonary opacities detected radiographically, paranasal sinus abnormality and evidence of eosinophilic infiltration in extravascular tissues. At least, four out of previous six criteria are needed for the diagnosis. Cardiac involvement has been documented in 16-50% of cases and it often takes the form of acute coronary syndrome or mimic it. Furthermore, it can cause about half of the deaths. The eosinophil-mediated heart damage can evolve through three stages: the acute necrotic, intermediate thrombotic and, finally, fibrotic one. It is known that infiltrating eosinophils can damage the endocardium and vascular endothelium. Rarer but equally important are the vasculitis affecting small myocardial vessels and coronary arteries, which can lead to myocardial ischemia, and ectasia and aneurysms of the coronary arteries due to the eosinophil infiltration and to a direct cytotoxic damage mediated by eosinophilic proteins. Furthermore, an uncommon manifestation of Churg-Strauss syndrome is coronary artery vasospasm that can lead to angina pectoris, acute coronary syndromes or even to cardiogenic shock. Corticosteroids (prednisone or its equivalents) remain the cornerstone of treatment of Churg-Strauss syndrome and the addition of azathioprine or cyclophosphamide is indicated for the treatment of patients with adverse prognostic factors or otherwise prone to relapse. The prognosis of Churg-Strauss syndrome is good, with an overall 10-year survival of 81-92% of patients. Coronary involvement in this disease may however be diffuse and a life-threatening condition. In this light, antiplatelet drugs (aspirin at first) may be evaluated in the field of coronary primary prevention. Here, we are describing a case report and literature review from cardiology point of view, highlighting coronary involvement.

Keywords: Churg-Strauss syndrome; Eosinophilic granulomatosis with polyangiitis (EGPA); Cardiac involvement; Coronary involvement; Acute coronaric syndrome; Percutaneous coronary intervention

Text

Churg-Strauss syndrome (CSS) is a rare vasculitis with multiorgan implications, described for the first time in 1951 [1] and recently renamed Eosinophilic Granulomatosis with Polyangiitis (EGPA) [2] given that essential features of this disease are the prominence of eosinophils in the blood with tissues infiltration. Its incidence is between 0.5 and 6.8 cases/1.000.000 patients per year with a higher prevalence in certain areas of France and Norway and a mean age at diagnosis of 48 years, affecting both sexes equally [3]. EGPA is characterized by the presence of an eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels [4]. Although EGPA belongs to the spectrum of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV), it differs from granulomatosis with polyangiitis (Wegener syndrome) and microscopic polyangiitis because of its association with severe asthma and nasal polyps, and blood and tissue eosinophilia [5]. ANCA-positivity ranges from 30-70% of EGPA patients [5] and it is more frequent when glomerulonephritis, mononeuritis and purpura are present [4]. Furthermore, differential diagnosis includes hypereosinophilic syndrome where asthma presence is unlikely and allergic bronchopulmonary aspergillosis and chronic eosinophilic pneumonia where extrapulmonary involvement is absent [4] (Table 1). Corticosteroids (prednisone or its equivalents) remain the cornerstone of treatment of EGPA and the addition of azathioprine or cyclophosphamide is indicated for the treatment of patients with adverse prognostic factors or otherwise prone to relapse [4].

The American College of Rheumatology (ACR) proposed the following diagnostic criteria with a sensitivity of 85% and a specificity of 99.7%: asthma, eosinophils on the leukocyte count greater than 10%, mononeuropathy or polyneuropathy, migratory or transient pulmonary opacities detected radiographically, paranasal sinus abnormality and evidence of eosinophilic infiltration in extravascular tissues. At least, four out of previous six criteria are needed for the diagnosis [6] (Table 2). It is yet important that these criteria are not used in the absence of histological confirmation of vasculitis because, in this situation, they are insensitive and poorly specific [7].

EGPA follows typically three phases. The first consists in bronchial asthma, allergic rhinitis and/or nasal polyposis. This phase may precede by months or years the development of the second phase that consists in peripheral and tissue eosinophilia, commonly associated with pulmonary infiltrates. Finally, the third phase is characterized by a systemic vasculitis that can be life threatening [4]. Vasculitis commonly affects skin, peripheral nerves, gastrointestinal tract and heart [4].

***Corresponding author:** Dario Buccheri, M.D., U.O.C. di cardiologia, Via Del Vespro, 129, CAP 90127. Palermo, Italy, Tel: 0916554303; Fax: 0916554304; E-mail: dariobuccheri@gmail.com

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| | EGPA | Microscopic Polyangiitis | Wegener Granulomatosis | Chronic Eosinophilic Pneumonia | Allergic Bronchopulmonary Aspergillosis | Hypereosinophilic Syndrome |
|---|----------|--------------------------|------------------------|--------------------------------|---|----------------------------|
| Pulmonary involvement | | | | | | |
| Asthma | Yes | No | No | Yes | Yes | No |
| Lung involvement | Yes | Yes | Yes | Yes | Yes | Yes |
| Rhinosinusitis | Yes | No | Yes | Yes | Yes | No |
| Skin involvement | Yes | Yes | Yes | No | No | Yes |
| Heart involvement | Yes | Rare | Rare | No | No | Yes |
| Gastrointestinal involvement | Yes | Yes | Yes | No | No | Yes |
| Nervous System | | | | | | |
| Central NS | Yes | Yes | Yes | No | No | Yes |
| Peripheral Neuropathy | Yes | Yes | Yes | No | No | Yes |
| Renal involvement | Yes | Yes | Yes | No | No | Rare |
| Hematologic involvement | | | | | | |
| Eosinophilia > 1,500 cells/mm³ | Yes | No | No | Yes | Yes | Yes |
| ANCA positivity | | | | | | |
| | Yes | Yes | Yes | No | No | No |
| | (30-70%) | -80% | -90% | | | |
| Tissue involvement | | | | | | |
| Vasculitis | Yes | Yes | Yes | No | No | No |
| Eosinophil-rich infiltrate | Yes | No | No | Yes | Yes | Yes |
| Granuloma | | | | | | |
| | Yes | No | Yes | Rare | Yes | No |

Table 1: The table shows various differential diagnosis of Churg-Strauss syndrome or Eosinophilic granulomatosis with Polyangiitis. It is distinguished from microscopic polyangiitis and Wegener granulomatosis (the other antineutrophil cytoplasm antibody (ANCA)-associated vasculitis) for the presence of asthma and eosinophilia in blood and tissues. Also cardiac involvement is rare in these former two vasculitis. The presence of a great number of eosinophils in blood and tissues, however, make Churg-Strauss syndrome similar to the hypereosinophilic syndrome, in which, however, asthma is unlikely but the cardiac involvement is also frequent. Finally, the Churg-Strauss syndrome is different from allergic bronchopulmonary aspergillosis and chronic eosinophilic pneumonia due to the multi-organ involvement, including the cardiac involvement, which is typical in EGPA. Moreover, in these respiratory diseases antineutrophil cytoplasm antibody (ANCA) are not present and vasculitis is absent.

| | |
|---|--------------------------------|
| 1 | Asthma |
| 2 | Eosinophilia > 10% |
| 3 | Neuropathy |
| 4 | Nonfixed pulmonary infiltrates |
| 5 | Paranasal sinus abnormality |
| 6 | Extravascular eosinophil |

Table 2: The table shows the most common diagnostic criteria for Churg-Strauss syndrome. The presence of at least four of these criteria is essential for the diagnosis following ACR.

Cardiac involvement has been documented in 16-50% of cases [4] and it often takes the form of acute coronary syndrome (ACS) or mimic it. Other clinical presentations may consist in heart failure, valvulopathy, pericarditis, arrhythmias and coronary vasculitis, above all in negative-ANCA patients, and can cause about half of the deaths [8]. Guillemin et al. identified five factors in EGPA associated with poor prognosis (“five factor score”) with myocardial involvement being one of them [9].

The eosinophil-mediated heart damage can evolve through three stages: the acute necrotic, intermediate thrombotic and, finally, fibrotic one [10]. It is known that infiltrating eosinophils can damage the endocardium and vascular endothelium. This can promote the development of endomyocardial fibrosis with subsequent congestive heart failure [11]. Rarer but equally important are the vasculitis affecting small myocardial vessels and coronary arteries, which can lead to myocardial ischemia, and ectasia and aneurysms of the coronary arteries due to the eosinophil infiltration and to a direct cytotoxic damage mediated by eosinophilic proteins [11]. Furthermore, an

uncommon manifestation of CSS is coronary artery vasospasm that can lead to angina pectoris (commonly refractory to vasodilators but sensitive to immunosuppressive therapy), acute coronary syndromes or even to cardiogenic shock. This event occurs especially in the active phase of the disease, characterized by marked eosinophilia, bronchial asthma, paranasitis, peripheral neuropathy, pulmonary infiltration and gastrointestinal lesions [12].

Several cases of cardiac involvement and, in particular, of the coronary arteries have already been described. One of these [10] relates to an elderly patient admitted to the emergency room for atypical chest pain and fatigue lasting ten days. A 12-lead electrocardiogram (ECG) showed sinus rhythm with a heart rate of 86 beats per minute, a borderline 0.1 mV horizontal ST-segment depression in V4-V5 and minor ST abnormalities in V6, II, III, and aVF. Troponin-I, creatine phosphokinase MB isoenzyme and lactate dehydrogenase were elevated and transthoracic echocardiography (TTE) showed a hyperkinetic left ventricle with thickened interventricular septum and minimal pericardial effusion. After the diagnosis of non-ST segment elevation myocardial infarction (NSTEMI) the patient underwent coronary angiography that was normal. Meanwhile, blood tests showed persistent leukocytosis with eosinophilia. Cardiac magnetic resonance (CMR) was not diagnostic and endomyocardial biopsy was negative, showing an important sub-endocardial eosinophilic infiltrate with multiple aggregates of eosinophils also in the interstitium. The patient's clinical history reported recurrent sinusitis, pollen allergy and asthma. Excluding the major causes for secondary eosinophilia, Churg-Strauss syndrome was diagnosed according to the ACR criteria. Corticosteroid therapy was successful for the healing of the disease [10].

Another emblematic case [13] concerned a 62-year-old lady

admitted with a diagnosis of NSTEMI and worsening dyspnea. In her clinical history, she reported asthma under intermittent steroid treatment. Blood tests showed a marked increase of eosinophils in leukocyte count (25%) and also an increase of troponin. Resting 12-lead ECG showed poor progression of the R wave from V1 to V3; finally, echocardiography showed a reduced left ventricular ejection fraction (35%) and an apical akinesia. Twenty-four hours later the patient suffered an ischemic stroke (diagnosed with brain CT scan) and the level of consciousness and dyspnea worsened leading to intubation. Chest CT scan detected mild pleural effusion with bilateral ground-glass opacities suggestive of pulmonary infiltrates. In view of these clinical informations, a diagnosis of EGPA was made and the patient was treated with a combination of prednisone and cyclophosphamide. Later, coronary angiography showed normal coronary arteries, so antiplatelet therapy was interrupted. The patient was discharged 7 days later on good clinical conditions with immunosuppressive therapy [13].

Another case [12] concerns a woman with previous diagnosis of EGPA who presented to the hospital with typical chest pain. The ECG detected an antero-lateral ST-segment elevation myocardial infarction (STEMI) and emergency coronary angiography revealed a stenosis of the first diagonal branch which was treated with angioplasty and bare-metal stent implantation. A few hours after the procedure, the patient had another episode of chest pain with electrocardiographic signs of an inferior STEMI. A new angiography showed multiple stenosis of the right coronary artery that were related to vasospasm and regressed with the administration of intracoronary vasodilators. The absence of eosinophilia and the mild elevation of C-reactive protein ruled out an active coronary vasculitis, so the addition of immunosuppressive agents was not deemed necessary. Although unusual, vasospasm of coronary arteries is a possible manifestation of the CSS being inactive and this is the first case in the literature that confirms this hypothesis [12].

An another case on the involvement of coronary arteries in CSS [11] a 69-year-old male underwent coronary CT angiography (CCTA) that showed diffuse signs of coronary vasculitis. The CCTA was performed during a regular check on the third year from diagnosis and, although asymptomatic, the patient was smoker, hypertensive and hypercholesterolemic. The scan showed a severe circumferential stenosis followed by a saccular aneurysm (6 mm x 10 mm) of the proximal RCA and a stenosis of the proximal segment of the left anterior descending artery (LAD). A fusiform aneurysm of descending thoracic aorta and abdominal aorta was detected as well. The 3-year CCTA follow-up demonstrated that these findings appeared to be unchanged but an increase in the extent of soft-tissue wall thickening and infiltration. Also the aortic aneurysms resulted increased in size. The patient was still asymptomatic. Coronary angiography was consistent with these findings and the patient was discharged with oral steroids and aspirin [11].

A final important example of organ involvement of CSS is represented by a 58-year-old patient recently treated at our Institution. He arrived at our hospital for worsening asthenia, a few months after a hospitalization for an ischemic and hemorrhagic stroke from which weakness and numbness of both lower limbs persisted. During this hospitalization the diagnosis of CCS was made, based on the history of the various interventions of nasal polypectomy associated with asthma and based on the detection of a marked eosinophilia in the blood tests. The patient had also several cardiovascular risk factors and illnesses: family history for cardiac disease, hypertension, smoking, hypercholesterolemia, a first grade atrio-ventricular block, a mildly reduced EF (50%) and mitral valve prolapsed, with mild mitral

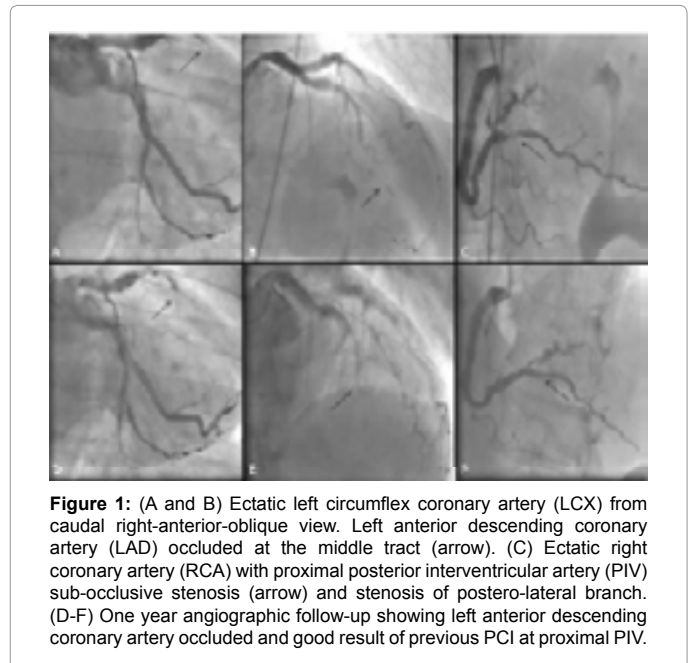


Figure 1: (A and B) Ectatic left circumflex coronary artery (LCX) from caudal right-anterior-oblique view. Left anterior descending coronary artery (LAD) occluded at the middle tract (arrow). (C) Ectatic right coronary artery (RCA) with proximal posterior interventricular artery (PIV) sub-occlusive stenosis (arrow) and stenosis of postero-lateral branch. (D-F) One year angiographic follow-up showing left anterior descending coronary artery occluded and good result of previous PCI at proximal PIV.

regurgitation, diagnosed earlier. Moreover chest CT scan showed multiple bilateral pulmonary ground-glass opacity caused by multiple infiltrates of eosinophils. The scan also had shown severely calcified coronary arteries and coronary angiography showed dilated and diffusely calcified coronary arteries, the occlusion of LAD with good collateral circulation, a critical stenosis of the third segment of RCA with the sub-occlusion of posterior interventricular artery and critical stenosis of postero-lateral branch (Figure 1A-1C). We thus carried out successful coronary angioplasty with the implantation of a bare metal stent (BMS) on the posterior interventricular artery (PIV) with good final angiographic result. The patient was discharged with improved clinical conditions, left ventricular EF (60%) and on steroid therapy. One year later, the patient was in good clinical condition and coronary angiography follow-up showed persisting good results (Figure 1D-1F).

In conclusion, the prognosis of CSS is good, with an overall 10-year survival of 81-92% of patients [14,15]. Coronary involvement in this disease may however be diffuse and a life-threatening condition. In this light, antiplatelet drugs (aspirin at first) may be evaluated in the field of coronary primary prevention. Furthermore, ACS by both coronary disease or coronary vasospasm may be different manifestations of CSS and should be treated as complications caused by other diseases.

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