View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Serveur académique lausannois

Serveur Académique Lausannois SERVAL serval.unil.ch

Author Manuscript

Faculty of Biology and Medicine Publication

This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Published in final edited form as:

Title: Churg-Strauss syndrome with cardiac involvement: case illustration and contribution of CMR in the diagnosis and clinical follow-up.

Authors: d'Ersu E, Ribi C, Monney P, Vincenti G, Schwitter J, Rotman S, Hullin R, Regamey J

Journal: International journal of cardiology

Year: 2018 May 1

Issue: 258

Pages: 321-324

DOI: 10.1016/j.ijcard.2018.02.011

In the absence of a copyright statement, users should assume that standard copyright protection applies, unless the article contains an explicit statement to the contrary. In case of doubt, contact the journal publisher to verify the copyright status of an article.

serval serveur académique lausannois

UNIL | Université de Lausanne Faculty of Biology and Medicine

CHUV

Churg-Strauss Syndrome with cardiac involvement: case illustration and contribution of CMR in the diagnosis and clinical follow-up.

d'Ersu E[a], Ribi C[b], Monney P[a], Vincenti G[a], Schwitter J[a], Rotman S[c], Hullin R[a], Regamey J[a].

[a]Service de cardiologie, Centre Hospitalier Universitaire Vaudois, Switzerland
[b]Service d'immunologie et allergie, Centre Hospitalier Universitaire Vaudois, Switzerland.
[c]Service de pathologie clinique, Centre Hospitalier Universitaire Vaudois, Switzerland.

This report resumes three cases of Churg-Strauss Syndrome (CSS) illustrating the challenges associated with cardiac manifestation of this disease. Here, we exemplify the role of cardiac magnetic resonance (CMR) for diagnosis and follow-up of CSS with a focus on new non-contrast T_2-weighted imaging sequences for quantification of myocardial scar tissue and quantitative T_2 mapping techniques, which allow the detection of myocardial edema.

Churg-Strauss Syndrome (CSS) or "eosinophilic granulomatosis with polyangiitis" (EGPA) is a very rare systemic disease affecting people between 40-60 years old. Typical lesions of CSS are histologically characterized by eosinophilia, necrotizing or granulomatous vascular lesions, and extravascular granulomas. Since distinct diagnostic criteria are missing, CSS syndrome is diagnosed on the basis of the presence of different clinical signs, which in their entity separate CSS from other forms of vasculitis (Lahnam's criteria, 1990 ACR classification, Chapel Hill's classification)[1,2]. CSS is known for 3 clinical phases: the "prodromic" phase with eosinophilic upper airway involvement, the "eosinophilic" phase with peripheral eosinophilia and peripheral organ involvement, and the "vasculitic" phase. These 3 phases may overlap or appear in a variable sequence. Serological markers of CSS are ANCA (essentially pANCA), which are prevalent in 40% of EGPA cases but less in patients with cardiac involvement. Serum IgE levels are usually elevated, and IgG4 occur in 75% of all cases[3,4]. Usually, C-reactive protein (CRP) and erythrocyte sedimentation rate are increased only in the acute phase. Furthermore, eosinophilic cationic protein (ECP) may be elevated in EGPA, and, if so, ECP is useful for monitoring of disease activity[5,6].

Cardiac manifestation of CSS has been reported with a prevalence of 66%[7], however, post-mortem studies suggest a prevalence up to 92%[4]. In 50% of all CSS cases, mortality is associated with cardiac manifestation of the disease presenting as progressive perimyocarditis, myocardial infarction or heart failure. Corticosteroids and long-term immunosuppression may improve event-free and disease-free survival rates in patients with cardiac manifestations of CSS[4].

In the last years, CMR has emerged as a highly valuable tool for diagnosis of cardiac involvement in CSS and for monitoring of treatment[7-11]. CMR enables not only functional characterization but also pathomorphological assessment such as detection of myocardial edema in CSS myocarditis, or quantification of myocardial fibrosis or scar tissue secondary to coronaritis or coronary occlusion. The following three cases will illustrate application of CMR for detection of cardiac manifestation of CSS at our institution.

The first case is a 40-year-old male known for longstanding severe non-reversible obstructive lung disease with epistaxis and hemoptysis and a history of hypereosinophilia. The initial

echocardiogram showed a severely reduced left ventricular ejection fraction (LVEF) with lateral/posterior akinesia and severe functional mitral regurgitation. The CMR study demonstrated widespread, predominantly subendocardial, late gadolinium enhancement (LGE), the coronary angiogram was without significant pathology. The chest-CT revealed fibro-emphysema and some ground glass infiltrates. The bronchoalveolar lavage demonstrated eosinophilia, neutrophilia and hemosiderosis consistent with chronic inflammation and low grade bronchoalveolar hemorrhage. An extensive laboratory work-up revealed elevation of IgE (175 U/L; N<100U/L) and ECP (ECP: 19.8 µg/l; N<16 µg/l). A right ventricular endomyocardial biopsy (EMB) demonstrated lymphocytic and eosinophilic infiltrates and signs of subacute myocarditis while granuloma or vasculitis were absent. CSS with cardiac involvement was suspected and treated with prednisone 1 mg/kg (with progressive tapering) and mycophenolate mofetil (MMF) in addition to optimal medical treatment for LV systolic dysfunction. Subsequently, ECP normalized rapidly. Serial CMR studies demonstrated stable LGE lesions in concordance with the histologic regression of the lymphocytic and eosinophilic infiltrates on the EBM procured after 6 months of immunosuppression. Because of a persistent severe LV dysfunction with left bundle branch block and non-sustained VT episodes, a CRT-D was implanted. Long term stabilization in NHYA functional class II-III was obtained, with mixed cardiac and respiratory limitations.

The second case is a 41-year-old woman treated for hypothyroidism, known for fatigue and palpitations of a few weeks duration in 2009, and high incidence of polymorphic ventricular extrasystoles. The echocardiogram showed a LVEF of 50% with thinning of the basal interventricular septum. CMR demonstrated thinning and akinesia of the basal segments of the anterior/antero-septal walls, with transmural LGE. The patient presented a borderline hypereosinophilia (6% N ≤ 5) and increase of ECP (20.3 µg/l; N<16 µg/l); ANCA were negative. Pulmonary function tests showed mild obstructive syndrome without reversibility. The bronchoalveolar lavage showed a discrete eosinophilia. A right ventricular EBM was without inflammatory lesions. CSS was suspected and the patient was treated with prednisone (starting 1mg/kg) and MMF with rapid normalization of ECP and stability of the cardiac function and LGE distribution on repeated CMR studies. An ICD was implanted after arrival of an exertion-induced syncope and a positive electrophysiology study.

The third case is a 53-year-old obese female with a history of gastric bypass in 2004, presenting with acute chest pain and dyspnea in January 2016. The ECG showed lateral ST segment depression with elevated high sensitive troponins T (peak: 814 ng/L; N< 14), creatine kinase (peak: 224 U/L), NT-proBNP (20’593 pg/ml) and CRP (62 mg/l); the coronary angiogram was normal. CMR imaging showed a non-dilated hypertrophic left ventricle with LVEF of 37%, mimicking hypertrophic cardiomyopathy (HCM). However, T_1 mapping did not reveal fibrosis while T_2-mapping showed diffuse edema of the LV myocardium suggesting acute myocarditis (**fig. 1**). Furthermore, a small pericardial effusion was noted. The patient was treated with ACE-inhibitors, beta-blockers, and initially high dose acetylic salicyl acid. Subsequently, LVEF normalized and myocardial edema as well as hypertrophy decreased in the control CMR at 10 days (**fig. 1**). The clinical evolution was remarkable for the appearance of a papulo-vesicular rash conjoint with peripheral hypereosinophilia (2.6 G/L), which was also present in the bone marrow examination (18%). Neoplasia or parasitic infection were excluded; the immunologic workup showed positive pANCA (1/80) and elevation of anti-MPO titers (26 CU) and ECP (44 µg/l). The skin biopsies showed neutrophilic infiltrates with

leukocytoclasia and an eosinophilic perivascular infiltrate. A right ventricular EMB showed a predominantly lymphocytic infiltrate with rare eosinophils without granuloma or signs of vasculitis. Chest CT and pulmonary function testing were unremarkable. CSS was suspected and the patient was started on prednisone 1 mg/kg with good clinical response. Serial CMR studies showed progressive reduction of the LV hypertrophy and normalization of T_2 measurements (**fig. 1**). After progressive tapering of the prednisone to 30 mg/d, the patient was rehospitalized for dyspnea. A chest CT revealed ground glass in the left upper lobe with eosinophilia in the bronchoalveolar lavage. The prednisone was increased to 50 mg/d and methotrexate 12.5 mg/week was added, with progressive resolution of the lung infiltrate.

The diagnosis of CSS remains challenging because most patients with cardiac involvement are ANCA-negative and initial clinical presentation may vary considerably. In any case, association of peripheral blood eosinophilia, evidence of past or present myocarditis and obstructive lung disease or lung infiltrates should raise the suspicion of CCS. But, peripheral eosinophilia may be absent or mild at the time of the diagnosis[3,4].

Altogether, the first two cases represent later stage CSS disease as indicated by the presence of myocardial scars tissue while the third case illustrates acute CSS. Vasculitis and granuloma were not present in myocardial or skin tissue in neither case, instead we observed lymphocytic and eosinophilic infiltration. This observation is compatible with the absence of renal and/or neurologic disease, which is usually related with typical small-vessel vasculitis. Therefore, we found that the term “Churg-Strauss syndrome” seems to resume these cases more adequately while EGPA is associated with vasculitis and granuloma. In fact, this discordance might reflect that CSS and EGPA are distinct nosologic entities with different clinical presentations.

In summary, the approach for the diagnosis and follow-up of CSS at our institution is based on laboratory markers (eosinophil count, ESR, CRP, ANCA, ECP), echocardiography and CMR, which has been proven as valuable tool in CCS patients[7,8,11,12]. However, EMB procurement is used exclusively for the initial work-up since the new techniques for tissue-characterization have become available at our institution (**fig. 2)**. More recently, these techniques have also been applied for detection of cardiac manifestation of connective tissue diseases[13]. Inflammatory heart disease typically demonstrates subepicardial LGE-positive lesions[14].

The evaluation of CMR in CSS has to consider that LGE is observed at mid-wall, transmural, epicardial, and often subendocardial localisation[15,16], which may reflect coronaritis or coronay spasm related with CSS[17]. Since subendocardial LGE is a hallmark of ischemic heart disease, coronary disease should always be ruled out, particularly when LGE distribution matches to a specific coronary territory. T_2-weighted images for edema detection allow for discrimination of acute from chronic lesions, thus, should always be included in the follow-up of cardiac CSS[15,17,18,19]. Quantitative T_2 mapping can even improve sensitivity for edema detection[20]. At our center, we always include T_1 mapping in CMR based assessment of CSS because extracellular volume fraction (ECV) correlates well with histological indices of interstitial myocardial fibrosis, which is often increased in EGPA patients with decreased LVEF[11]. In case of contra-indications to MRI, FDG-PET may constitute an interesting alternative[10].

CMR has become a useful diagnostic tool for detection and follow-up of cardiac manifestation of CCS. It remains to be shown whether CMR-guided follow-up of cardiac CSS translates in improvement of treatment and prognosis.

References:

1. Mouthon L, Dunogue B, Guillevin L. Diagnosis and classification of eosinophilic granulomatosis with polangiitis (formerly named Churg-Strauss syndrome). J Autoimmun. 2014 Feb-Mar;48-49:99-103.
2. Noth I, Strek ME, Leff AR. Churg-Strauss syndrome. Lancet. 2003; 361:587-594
3. Vaglio A, Buzio C, Zwerina J. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): state of the art. Allergy. 2013 Mar;68(3):261-73.
4. Dennert RM et al. Cardiac Involvement in Churg-Strauss Syndrome. Arthritis Rheum. 2010 Feb;62(2):627-34.
5. Hara T et al. Eosinophilic myocarditis due to Churg-Strauss syndrome with markedly elevated eosinophil cationic protein. Int Heart J. 2013;54(1):51-3.
6. Xia GL, Wang YK, Huang ZQ. The Correlation of Serum Myeloid-Related Protein-8/14 and Eosinophil Cationic Protein in Patients with Coronary Artery Disease. Biomed Res Int. 2016;2016:4980251.
7. Hazebroek MR. Prevalence and prognostic relevance of cardiac involvement in ANCA-associated vasculitis: Eosinophilic granulomatosis with polyangiitis and granulomatosis with polyangiitis. Int J Cardiol. 2015 Nov 15;199:170-9.
8. Fijolek et al. The significance of cardiac magnetic resonance imaging in detection and monitoring of the treatment efficacy of heart involvement in eosinophilic granulomatosis with polyangiitis patients. Sarcoidosis Vasc Diffuse Lung Dis. 2016 Mar 29;33(1):51-8.
9. Yune et al. Detecting cardiac involvement with magnetic resonance in patients with active eosinophilic granulomatosis with polyangiitis. Int J Cardiovasc Imaging. 2016 Jun;32 Suppl 1:155-62.
10. Marmursztejn J et al. Churg-Strauss syndrome cardiac involvement evaluated by cardiac magnetic resonance imaging and positron-emission tomography: a prospective study on 20 patients. Rheumatology 2013 Apr;52(4):642-50.
11. Cereda AF et al. Comprehensive evaluation of cardiac involvement in eosinophilic granulomatosis with polyangiitis (EGPA) with cardiac magnetic resonance. Eur J Intern Med. 2017 Apr;39:51-56.
12. Baccouche H et al. Images in cardiovascular medicine: Magnetic resonance assessment and therapy monitoring of cardiac involvement in Churg-Strauss syndrome. Circulation. 2008 Apr 1;117(13):1745-9
13. Mavrogeni S et al. Cardiovascular magnetic resonance imaging pattern at the time of diagnosis of treatment naïve patients with connective tissue diseases. Int J Cardiol. 2017 Jun 1;236:151-156.
14. Mahrholdt H et al. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. Eur Heart J. 2005 Aug;26(15):1461-74.
15. Giri S et al. T2 quantification for improved detection of myocardial edema. J Cardiovasc Magn Reson. 2009 Dec 30;11:56.
16. Wassmuth R, Schulz-Menger J. Cardiovascular magnetic resonance imaging of myocardial inflammation. Expert Rev Cardiovasc Ther. 2011 Sep;9(9):1193-201
17. Montant P et al. MR imaging assessment of myocardial edema with T2 mapping. Diagn Interv Imaging. 2015 Sep;96(9):885-90.
18. Wassmuth R et al. Variability and homogeneity of cardiovascular magnetic resonance myocardial T2-mapping in volunteers compared to patients with edema. J Cardiovasc Magn Reson. 2013 Mar 27;15:27.
19. Thavendiranathan P et al. Improved detection of myocardial involvement in acute inflammatory cardiomyopathies using T2 mapping. Circ Cardiovasc Imaging. 2012 Jan;5(1):102-10.
20. Lurz P et al. Comprehensive Cardiac Magnetic Resonance Imaging in Patients With Suspected Myocarditis: The MyoRacer-Trial. J Am Coll Cardiol. 2016 Apr 19;67(15):1800-11.

Figures:

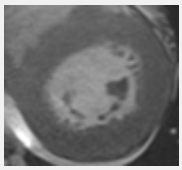
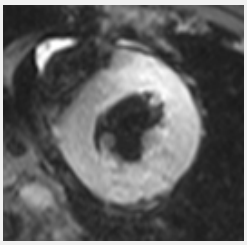
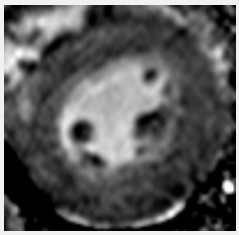
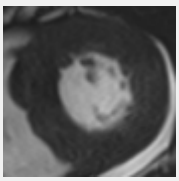
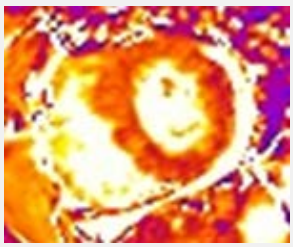
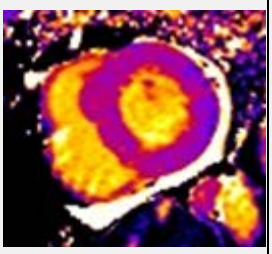
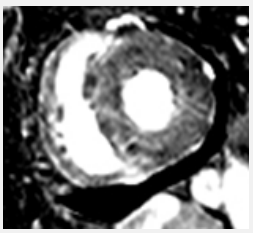
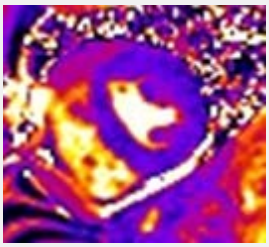
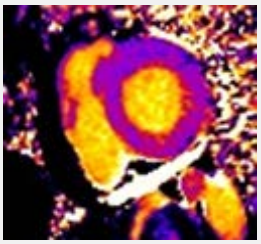
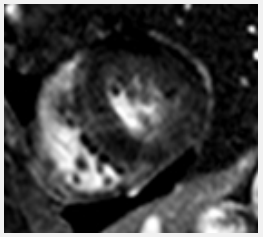
	Cine images (LV mass)	T2	T1	*LGE*
1st day	 (120 g/m2)	 T2 signal elevation (T2 mapping not available)	(not available)	 Diffuse contrast enhancement
10 days	 (86 g/m2)	 T2: 58-65ms	 ECV 32 %	 Diffuse contrast enhancement
2 months	 (58 g/m2)	 T2: 46-50ms	 ECV 24 %	 No LGE

Fig. 1 CMR imaging of **case 3** at diagnosis (first raw), after 10 days (second raw) and 2 months (third raw) follow-up.

- *First column:* Pictures extracted from the cine views demonstrating the left ventricular hypertrophy and initially edematous appearance of the myocardium (upper picture). The progressive reduction of the measured LV mass is also shown below.
- *Second column:* The upper picture is extracted from T2-weighted images. This first study was performed on a machine not allowing T2 mapping. Nevertheless, a higher T2 signal can be demonstrated in the myocardium. In the next two MRI studies, quantitative T2 mapping was performed, demonstrating progressive normalization of the T2 values (N≤ 50ms) in favor of the resolution of the edema.
- *Third column:* T1 mapping with quantification of the extracellular volume (ECV).
- *Fourth columns:* LGE sequence demonstrating an abnormal grey and edematous appearance of the myocardium, without diffuse contrast enhancement.

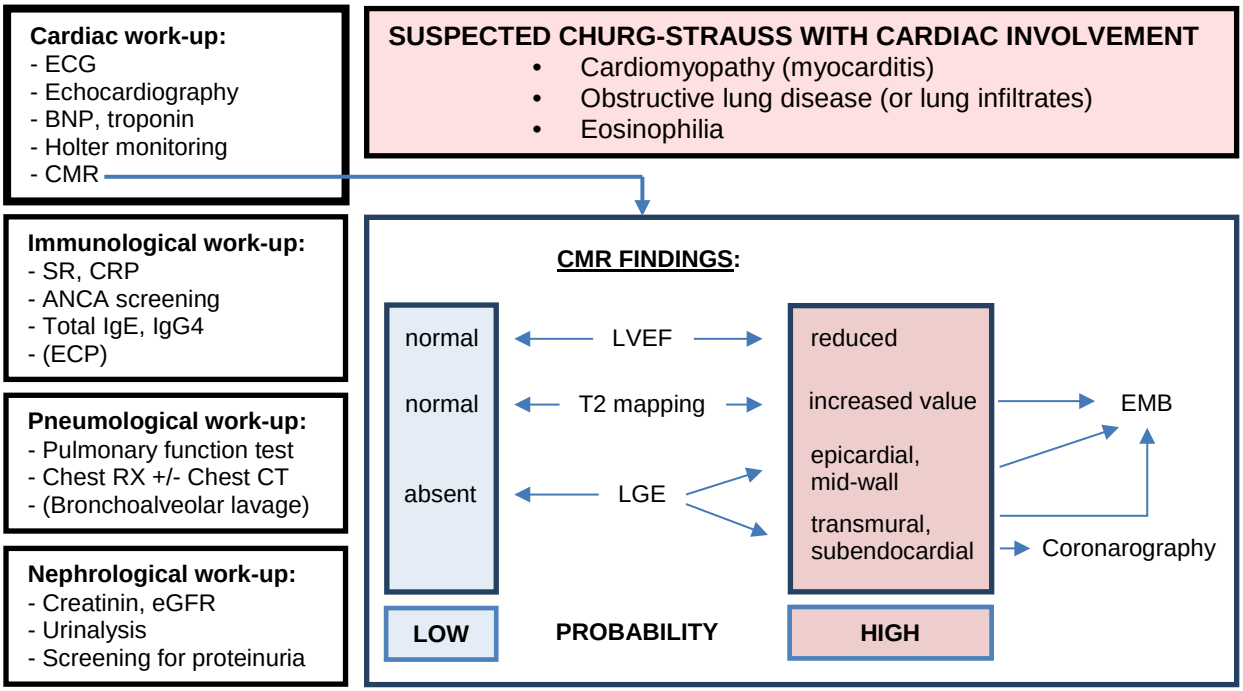


Fig. 2 Suggested initial diagnostic work-up in case of a suspected Churg-Strauss syndrome with cardiac involvement:

- The suggested initial multi-systemic evaluation is illustrated (four boxes of the left raw). A CMR is included in the cardiological assessment. CMR findings (LVEF, LGE, T2 mapping) are then integrated to stratify the probability of a cardiac involvement and guide further investigations and therapy.
- If myocardial edema (T2 mapping) or LGE lesions are detected, endomyocardial biopsies of these lesions should be considered (if feasible with an acceptable peri-procedural risk). If their distribution is transmural of subendocardial, a coronary angiogram should also be performed to rule out coronary artery disease.

(**CMR**: Cardiac Magnetic Resonance, **SR**: Sedimentation rate, **ECP**: Eosinophil Cationic Protein, **LGE**: Late Gadolinium Enhancement)