Clinical Rheumatology (2019) 38:2275–2280
https://doi.org/10.1007/s10067-019-04527-z

CASE BASED REVIEW

A misdiagnosed case of antisynthetase syndrome complicated by myocarditis: when the cardiologist deals with rheumatology

Paolo Diego L'Angiocola[1] · Luisa Mattei[1] · Gerardina Lardieri[1,2]

Received: 26 February 2019 / Revised: 15 March 2019 / Accepted: 19 March 2019 / Published online: 11 April 2019

Abstract
We report a case of a 56-year-old woman with an alleged diagnosis of an acute coronary syndrome that was later correctly identified in our Cardiology Unit as antisynthetase syndrome (AS) with inflammatory cardiac involvement. In this case report, we focus on clinical features of this rare autoimmune disease aiming to provide useful tips to achieve correct differential diagnosis according to updated international guidelines and recommendations, especially in cases of concurrent disease-related myocarditis.

Keywords Acute coronary syndrome · Antisynthetase syndrome · Myocarditis

Background

The antisynthetase syndrome (AS) is an autoimmune disorder characterized by myopathy, interstitial lung disease, cutaneous involvement, arthritis, fever, and the presence of myositis-specific autoantibodies directed against tRNA-synthetases. Among these, anti-histidyl (Jo-1) antibody is the most common autoantibody, with a prevalence of 15–25% in overall patients with inflammatory myositis [1, 2]. AS can be considered as a rare auto-inflammatory systemic disorder and concurrent cardiac involvement has a prevalence of approximately 3–4% [3].

Cardiac involvement in AS syndrome could possibly include coronary artery inflammation leading to vasculitis, intimal proliferation, microvascular disease, or coronary vasospasm, all of which may contribute to impaired left ventricular function and conduction abnormalities; evidence suggest however that myocardial inflammation could not necessarily be linked to autoantibody specificity and the exact pathophysiological effect of AS antibodies on the heart still remains unclear [3].

✉ Paolo Diego L'Angiocola
paolo.doc@gmail.com; paolo.langiocola@aas2.sanita.fvg.it

[1] Department of Cardiology, San Giovanni di Dio Hospital, Via Fatebenefratelli, 34, 34170 Gorizia, GO, Italy

[2] Department of Cardiology, San Giovanni di Dio Hospital, Gorizia - San Polo Hospital, Monfalcone, Italy

Clinical case

A 56-year-old woman was admitted to the emergency room for a clinical picture characterized by ankle swelling and oliguria. Two weeks before hospital admission, she reported transient, self-limiting erythema, and edema of the face. The patient's husband was the main caregiver.

In her past clinical history, the patient reported systemic hypertension and Alzheimer disease treated with donepezil and memantine. No antihypertensive drug was ever prescribed. The patient's father died from pulmonary neoplasia. She reported two non-complicated pregnancies and the sons were in good health.

At admission in the emergency department, the clinical examination revealed a regular heartbeat (88 bpm), no evidence of murmurs and no relevant abdominal findings. But there was evidence of ankle swelling and roughening and cracking of the skin of the tips and sides of the fingers: the skin of the hands was clearly thickened. This clinical finding was underestimated at first and wrongly related to possible irritant contact dermatitis: blood pressure was 130/60 mmHg and SpO_2 was 98% breathing room air. The electrocardiogram showed sinus rhythm and abnormal, negative T-waves in antero-lateral peripheral leads, and whole precordial leads (from V1 to V6), Fig. 1. The high-sensitivity troponin I resulted in 496 ng/l on first determinations: creatine phosphokinase was 3693 U/L, lactate dehydrogenase was 1456 U/L, aspartate aminotransferase was 210 U/l, alanine aminotransferase was 180 U/l, and albumin was 2.58 g/dl. The patient was then

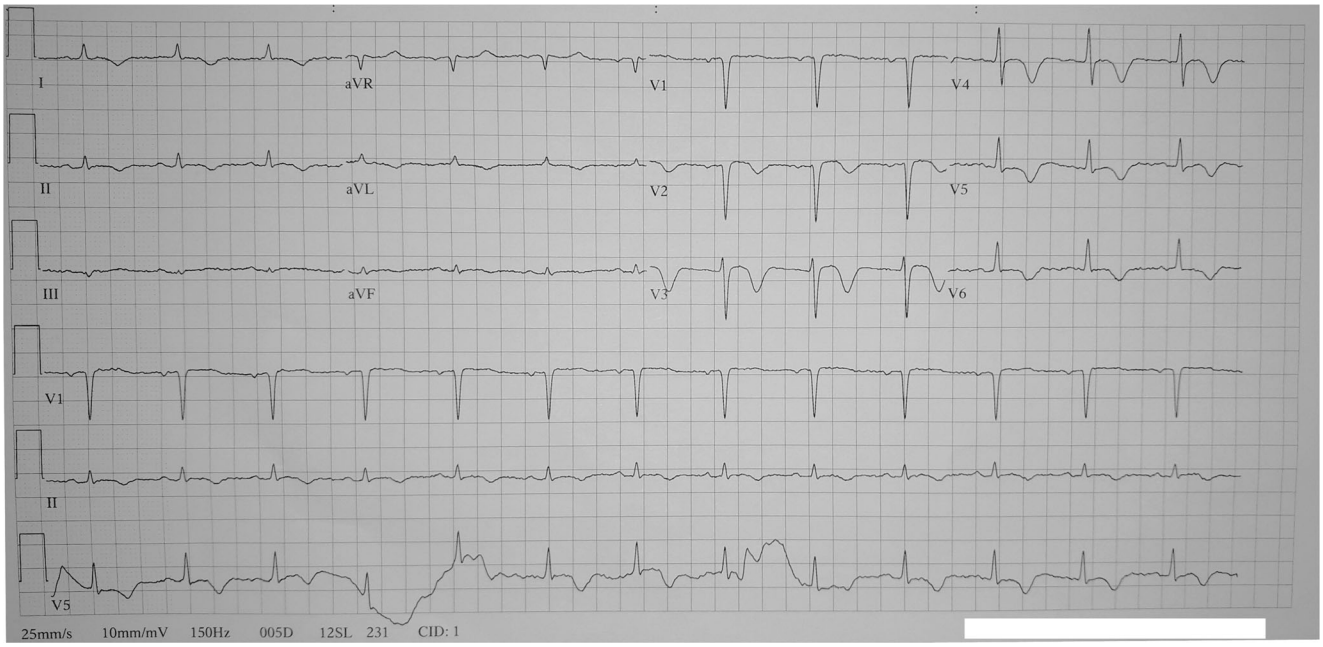

Fig. 1 12-lead ECG at emergency room admission showing abnormal, negative T-waves in II and aVL peripheral leads and from V1 to V6 on precordial leads

admitted to our cardiology unit with an alleged diagnosis of the acute coronary syndrome in the context of malnutrition state complicated by rhabdomyolysis. A chest X-ray was performed that revealed increased bilateral interstitial markings described by the radiologist as an increased, thickened, and reticular pattern in the lower fields of the lungs.

A transthoracic echocardiogram was performed on the first and seventh days of hospitalization, and in both cases revealed normal systolic function (ejection fraction was as high as 60%), no relevant echocardiographic abnormal findings.

High-sensitivity troponin I resulted slightly increased on several determinations during the hospital stay but overall slowly decreasing from the first determination with atypical "plateau" trend when considering the alleged diagnosis of the acute coronary syndrome.

Moreover, a normal systolic function raised doubts about a suspected acute coronary syndrome, and a consultation with a neurologist was performed in order to rule out any possible implication of collateral effects related to memantine or donepezil use injuring myocardial tissue. Overall, renal function parameters were within normal limits and nephritic syndrome was ruled out considering normal values after 24-h proteinuria. Considering increased hepatocellular necrotic parameters and normal serological results about hepatitis-related etiological markers (including HBV, HCV, CMV, and Borrelia B.), a rheumatologic consultation was requested in order to clarify the diagnosis. Reconsidering the "mechanic hands" examination finding, more accurate inspection of the distal limb skin was achieved. The "Hiker's feet" (resembling a callousing pattern on the feet, more typical of avid hikers or long-distance walkers) was actually identified upon clinical examination; the rheumatologist underlined the importance of hands and feet skin clinical findings that were faultlessly underestimated by the emergency and cardiology staff, and considering the whole clinical examination and the concurrent abovementioned radiological interstitial lung findings ANA, ENA, and ANCA serological screening determination was then requested. ANA titer was negative (immunofluorescent assay Hep2 cells). ANCA titer was within normal limits (p-ANCA/MPO, < 2.0 U/ml; c-ANCA/PR3. 4 U/ml); rheumatoid factor plasma concentration was within normal limits (12.0 UI/ml). Anti-CCP titer was normal (< 7 U/ml). C-reactive protein plasma concentration was increased (2.18 mg/dl). ENA screening determination revealed positive anti-Jo-1 antibodies, Ab-anti beta2GP IgG was positive (44.1 U/ml), ACA IgG was positive (54 U/ml), and thus antisynthetase syndrome diagnosis was then confirmed.

During hospitalization, ECG monitoring revealed a couple of non-sustained, asymptomatic, and self-limiting episodes of ventricular tachycardia; and clinical examination revealed signs of increasing congestive heart failure.

The following therapy was prescribed: bisoprolol 10 mg OD, ramipril 5 mg OD, prednisone 1 mg/kg/day, cyclophosphamide 2 mg/kg/day, immunoglobulin infusion i.v., furosemide 40 mg i.v. BID.

After 2 weeks of hospitalization, a new transthoracic echocardiogram was performed and revealed a mild left ventricular systolic dysfunction with apical and inferior hypokinesis and mild, circumferential pericardial effusion with no echocardiographic signs of cardiac tamponade.

A cardiac magnetic resonance (CMR) with dye (gadopentetate DMG, 0.2 ml/kg) was performed that

confirmed the presence of mild pericardial effusion, revealed pleural bilateral effusion, and moderate to severe systolic dysfunction (left ventricle ejection fraction, 38%) with no typical signs of cardiac inflammatory involvement in T1, T2, and STIR-weighted scans (Fig. 2).

Cyclophosphamide was then replaced by cyclosporine administration (2.5 mg/kg/dye) maintaining immunoglobulin and prednisone intravenous infusion.

After 1 month of hospitalization with cyclosporine therapy, a remarkable, clinical improvement was achieved. High-sensitivity troponin values fell into normal limits, ECG revealed partial regression of T-wave inversion in precordial leads Fig. 3, and echocardiography showed complete recovery of left ventricular systolic function and absence of pericardial effusion. Prednisone and furosemide administration was progressively down-titrated and at last suspended.

The patient was then discharged at home with prednisone 5 mg OD and cyclosporine 75 mg BID with a schedule of strict, clinical outpatient follow-up.

An echocardiographic exam performed after 2 months from hospital discharge showed normal systolic function and no other abnormal findings.

Discussion

We managed the case of a 56-year-old woman admitted to the emergency room complaining of ankle swelling and oliguria; NSTE-ACS diagnosis was at first suspected considering increased blood levels of high-sensitivity troponin I and later disconfirmed, with a consequently correct diagnosis of antisynthetase syndrome complicated by myocarditis. Immunosuppressive therapy was administered with benefit and correct clinical management of the patient and was achieved with complete regression of clinical and cardiac abnormal findings.

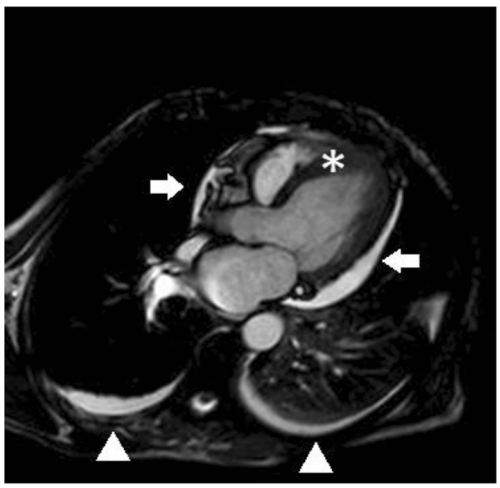

Fig. 2 Cine CMR: *white arrows* pericardial effusion; *head arrows* pleural effusions; A single asterisk indicates a normal myocardial tissue signal

Myocarditis is defined as an inflammatory, pathological involvement of the myocardium [4, 5]; it often results from common viral infections but has been associated with several systemic autoimmune disorders as well [6].

Myocarditis can range from mild clinical pictures (such as presence of chest pain associated with absent or mild ventricular dysfunction) to life-threatening conditions (malignant arrhythmias and severe heart failure) [7]. The outcomes of patients are consequently heterogeneous according to clinical severity of inflammatory involvement, varying from partial or full clinical recovery to irreversible, advanced heart failure, or death [8].

This case report implies interesting considerations about inflammatory cardiac involvement in an autoimmune disease such as AS: myocarditis occurs in 3–4% of all AS cases [3], thus representing a rare complication of a rare immunologic disease.

Few cases of cardiac inflammatory involvement in AS are reported in literature. Dieval C. et al. report a small group of 12 patients with cardiac inflammatory involvement affected by AS; myocarditis was the first AS manifestations in 42% of cases, it was always associated with active myositis, with evidence of extracardiac symptoms and signs, and could be asymptomatic (17%) or with acute (33%) or subacute onset (50%) associated with cardiac failure signs and symptoms. Moreover, myocarditis was associated with pericarditis in 50% of the cases [9]. Sharma et al. report two cases of AS complicated by myocarditis and congestive heart failure; both patients underwent cardiac MRI, skeletal muscle and endomyocardial biopsy and showed extracardiac signs and symptoms and active myositis with typical signs of a chronic inflammatory state, confirming the recurrent clinical picture of AS complicated by inflammatory involvement with extra cardiac signs and skeletal myositis. A histopathologic pattern showed cellular infiltrates in myocardial and skeletal muscle with cardiac myocyte damage and mononuclear inflammatory cell infiltrate within the endomysium and perivascular areas [3]. Meudec et al. report a case of a 55-year-old woman with a 3-month history of polyarthritis, myalgia, and dyspnea with AS complicated by cardiac inflammatory involvement, ECG pattern within normal limits and CMR indicating active myocarditis; active myositis was clear in this patient as well [10]. Kulkarni et al. report a case of a 43-year-old patient presenting with acute worsening of dyspnea, showing a severe and rapidly worsening clinical systemic inflammatory condition involving heart and lungs with interstitial inflammatory lung disease and myocarditis confirmed by chest CT scan and CMR. In this case, extracardiac manifestations are reported and they are associated with severe

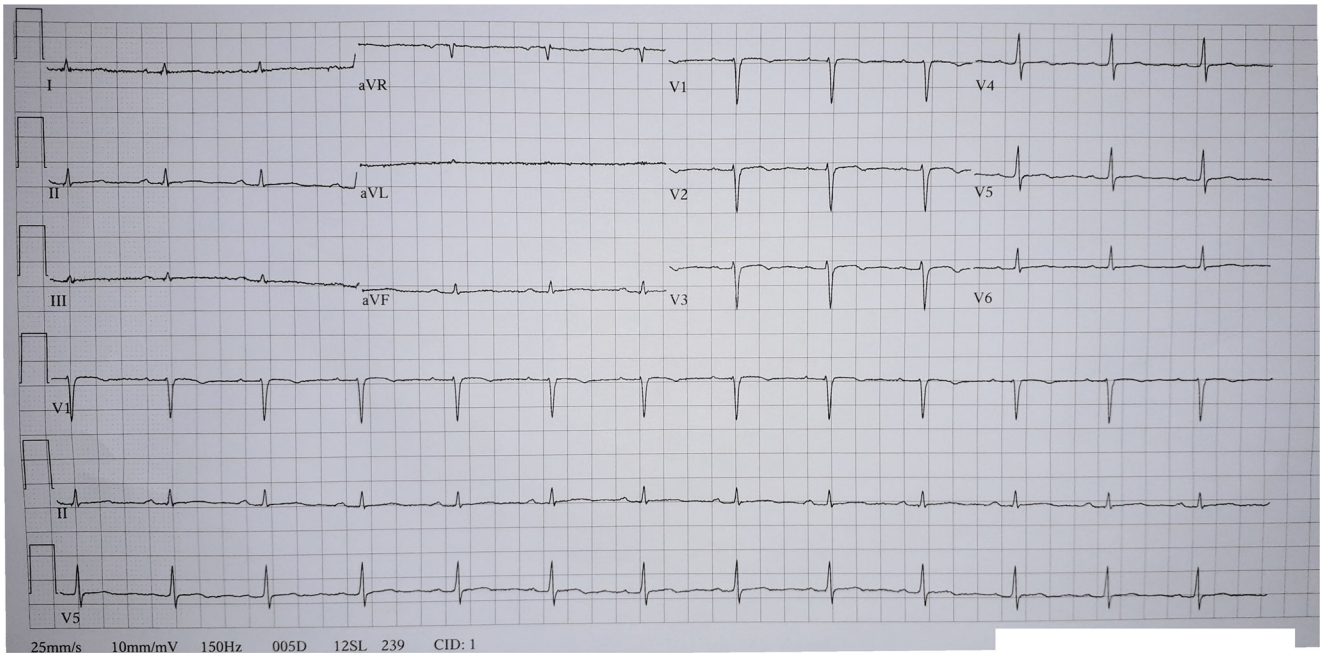

Fig. 3 12-lead ECG at hospital discharge showing partial regression of abnormal, negative T-waves in II and aVL peripheral leads and from V1 to V6 on precordial leads

myocardial damage as well [11]. Mahfoudhi M and Battikh AG report a case of AS characterized by a clinical picture of myalgia, polyarthritis, and dyspnea. In this case, an inflammatory state was diagnosed and myositis confirmed considering fivefold increased level blood levels of creatine phosphokinase. A chest CT scan revealed a honey-combing radiological lung pattern and a severe restrictive respiratory pattern was then highlighted. Despite confirmation of AS made by Jo-1 Ab positivity and administration of cyclophosphamide and steroids i.v., the clinical condition of the patient rapidly got worse leading to death due to cardiogenic shock related to concurrent myocarditis [12].

Controversies remain about choice of the more suitable and effective therapy to be administered and our case highlights the initial inefficacy of cyclophosphamide versus following, beneficial cyclosporine administration. Allanore et al. in a very small number of patients highlight the efficacy of treatment with methylprednisolone followed by prednisone and immunosuppressive therapy for myocardial involvement in patients with idiopathic inflammatory myopathies, considering that specific therapy in this cases remains empirical anyway [13]. Moreover, controversies remain about indications to endomyocardial biopsy (EMB) versus CMR in specific clinical conditions like AS and our case underlines the misleading role of CMR that underestimated the inflammatory cardiac involvement.

CMR is a usefully proven imaging technique able to detect inflammation, edema, necrosis, and fibrosis within the myocardial tissue [14, 15]. However, in acute phase myocarditis, it sometimes could be less feasible and possibly diagnostically misleading, especially in fulminant or rapidly evolving myocarditis, underestimating inflammatory cardiac involvement [16].

EMB is the gold standard for the diagnosis of myocarditis according to international consensus papers but it is not a recommended routine procedure to rule out or confirm the diagnosis: EBM should be reserved to specific clinical cases characterized by hemodynamic instability associated with signs and symptoms of rapidly worsening heart failure [17, 18]. In our patients, EMB was debated but it was finally not performed considering frailty and co-morbidities of the patient. Myocarditis diagnosis was however set considering clinical features and high-sensitivity troponin values.

CMR-driven diagnosis of myocarditis is based on an evaluation of three radiological markers of inflammation/myocardial injury, possibly but not necessarily associated with evidence of pericardial effusion: *myocardial edema* (T2-weighted high intensity images signals), *hyperemia/interstitial edema* (T1-weighted early gadolinium enhancement signals), and *necrosis/fibrosis* (T1-weighted late gadolinium enhancement signals). CMR cannot provide information about microstructural damage. This information can be provided by EMB only, thus essential to distinguish specific histological features, such as in giant-cells myocarditis, eosinophilic myocarditis and sarcoidosis, and from other specific clinical conditions such as lymphocytic myocarditis. Specific etiologies require disease-oriented treatments. In this case, EMB becomes essential [4, 5]. In suspected myocarditis, CMR with gadolinium dye could be useful to give a picture of a specific anatomical distribution of inflammatory disease involving myocardial tissue

in order to properly guide identification of correct sampling sites for EMB procedure and increase its sensitivity. Moreover, confirming inflammatory myocardial substrate with EMB in doubtful cases of suspected myocarditis could postpone indications to implantable cardioverter defibrillators considering the potentially reversible proarrhythmic substrate in case of beneficial and early immunosuppressive therapy. It becomes clear that complementary use of CMR and EMB can add greater value to the diagnostic and therapeutic pathway, accurately choosing to achieve one technique or the other, or both, according to the patient-specific clinical picture.

However, in any case of cardiac inflammatory suspicion in the context of a possibly systemic inflammatory condition, cornerstones of diagnosis to detect myocarditis are electrocardiogram, transthoracic echocardiography, myocardial specific necrosis markers determination (troponin I and troponin T—if high sensitivity available troponin I and T assay the better) that always have to be performed as a first-level diagnostic exams [15].

AS cardiac manifestations, management and possible outcomes are briefly summarized in Table 1.

Follow-up and possible treatments

Immunosuppressive therapy is the cornerstone of treatment for eosinophilic myocarditis, giant-cell myocarditis, cardiac sarcoidosis, and other forms associated with systemic autoimmune diseases. The recommended usual treatment is a combination of cyclosporine, prednisone, and antithymocyte globulins [19, 20]. Intravenous immunoglobulins, mycophenolate mofetil, methotrexate, rituximab, and azathioprine can be used as second-line therapies [21]. A complex immunological condition such as AS with inflammatory cardiac involvement necessarily implies a rheumatologically consultation and multidisciplinary team evaluation. Considering the systemic nature of AS, the choice of best immunosuppressor or multiple drug therapy to be administered needs to be carefully evaluated in multidisciplinary teamwork as the best choice of pharmacological treatment still remain controversial, especially in rare autoimmune diseases such as AS [22]. In our case, cyclophosphamide was not beneficial in the first weeks of hospitalization while cyclosporine achieved the therapeutic goal. In order to reduce in-hospital mortality rates, rapid referral to hub centers for aggressive treatment and early EMB should be considered in case of doubtful management or not properly equipped/specialized centers.

Conclusions

AS is a rare autoimmune disease. Myocarditis can be considered a rare complication of autoimmune disorders and of AS as well but whenever identified can be a dangerous clinical feature leading to cardiac failure and severe, permanent left ventricular systolic impairment compromising the outcome for the patient.

CMR and EMB can be usefully and complementary performed to establish the diagnosis of myocardial inflammatory involvement in autoimmune systemic disease but need to be tailored on an individual basis according to patient overall clinical conditions, co-morbidities in a proper cost-benefit perspective, avoiding useless exposure to iatrogenic injury. Early diagnosis has to be reached to begin appropriate immunosuppressive treatment and identify histological features in case of

Table 1 Clinical cardiac signs and symptoms, management and outcomes

	Clinical cardiac related manifestations	Management	Outcomes
Dieval C. et al. [9]	Dyspnea Thoracic pain	Steroids (not specified) Oral immunosuppressive drugs (mycophenolate mofetil, methotrexate, azathioprine—dosage not specified) I.v. immunosuppressive drugs (rituximab, cyclosporine—dosage not specified)	Good clinical cardiac response and recovery in 7 out of 12 patients; residual left ventricular systolic impairment in 3 patients; 1 patient lost in follow-up
Meudec L. et al. [10]	Dyspnea	Rituximab 1000 mg × 2 Prednisone (0.5 mg/kg/day) Methotrexate 20 mg/week	Good clinical cardiac response and recovery
Kulkarni HS et al. [11]	Dyspnea	Rituximab 1000 mg i.v. Mycophenolate mofetil 1000 mg bid Prednisone 60 mg od	Good clinical cardiac response and recovery
Mahfoudhi M, Battikh AG. [12]	Dyspnea	Steroids (not specified) cyclophosphamide (not specified)	Death from cardiogenic shock
Our case report	Ankle swelling, oliguria	Prednisone 1 mg/kg/day Cyclosporine 2,5 mg/kg/die i.v.	Complete clinical cardiac recovery

rapidly worsening autoimmune myocarditis. The choice of appropriate treatment can be controversial and a multidisciplinary teamwork including expert rheumatologist consultation or hub medical center quick referral have to be necessarily considered.

References

1. Yoshida S, Akizuki M, Mimori T, Yamagata H, Inada S, Homma M (1983) The precipitating antibody to an acidic nuclear protein antigen, the Jo-1, in connective tissue diseases. A marker for a subset of poly-myositis with interstitial pulmonary fibrosis. Arthritis Rheum 26:604–611
2. Brouwer R, Hengstman GJ, Vree Egberts W, Ehrfeld H, Bozic B, Ghirardello A et al (2001) Autoantibody profiles in the sera of European patients with myositis. Ann Rheum Dis 60:116–123
3. Sharma K, Orbai A-M, Desai D, Cingolani OH, Halushka MK, Christopher-Stine L, Mammen AL, Wu KC, Zakaria S (2014) Brief report: antisynthetase syndrome-associated myocarditis. J Card Fail 20:939–945
4. Cooper LT Jr (2009) Myocarditis. N Engl J Med 360:1526–1538
5. Sagar S, Liu PP, Cooper LT Jr (2012) Myocarditis. Lancet 379:738–747
6. Elamm C, Fairweather D, Cooper LT (2012) Pathogenesis and diagnosis of myocarditis. Heart 98:835–840
7. Sinagra G, Anzini M, Pereira NL, Bussani R, Finocchiaro G, Bartunek J et al (2016) Myocarditis in clinical practice. Mayo Clin Proc 91:1256–1266
8. Ammirati E, Cipriani M, Lilliu M, Sormani P, Varrenti M, Raineri C, Petrella D, Garascia A, Pedrotti P, Roghi A, Bonacina E, Moreo A, Bottiroli M, Gagliardone MP, Mondino M, Ghio S, Totaro R, Turazza FM, Russo CF, Oliva F, Camici PG, Frigerio M (2017) Survival and left ventricular function changes in fulminant versus nonfulminant acute myocarditis. Circulation 136:529–545
9. Dieval C, Deligny C, Meyer A, Cluzel P, Champtiaux N, Lefevre G, Saadoun D, Sibilia J, Pellegrin JL, Hachulla E, Benveniste O, Hervier B (2015) Myocarditis in patients with antisynthetase syndrome: prevalence, presentation, and outcomes. Medicine (Baltimore) 94:e798
10. Meudec L, Jelin G, Forien M, Palazzo E, Dieudé P, Ottaviani S (2018) Antisynthetase syndrome and cardiac involvement: a rare association. Joint Bone Spine. https://doi.org/10.1016/j.jbspin.2018.09.019
11. Kulkarni HS, Gutierrez FR, Despotovic V, Russell TD (2015) A 43-year-old man with antisynthetase syndrome presenting with acute worsening of dyspnea. Chest 147(6):e215–e219. https://doi.org/10.1378/chest.14-2402
12. Mahfoudhi M, Battikh AG (2015) Antisynthetase syndrome complicated with severe myocarditis. Pan Afr Med J 21:4. https://doi.org/10.11604/pamj.2015.21.4.6871
13. Allanore Y, Vignaux O, Arnaud L, Puéchal X, Pavy S, Duboc D, Legmann P, Kahan A (2006) Effects of corticosteroids and immunosuppressors on idiopathic inflammatory myopathy related myocarditis evaluated by magnetic resonance imaging. Ann Rheum Dis 65(2):249–252
14. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E (2013) Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized Protocols. Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update. J Cardiovasc Magn Reson 15(91):2013
15. Lurz P, Luecke C, Eitel I, Föhrenbach F, Frank C, Grothoff M, de Waha S, Rommel KP, Lurz JA, Klingel K, Kandolf R, Schuler G, Thiele H, Gutberlet M (2016) Comprehensive cardiac magnetic resonance imaging in patients with suspected myocarditis: the MyoRacer-trial. J Am Coll Cardiol 67:1800–1811
16. Veronese G, Ammirati E, Cipriani M, Frigerio M (2018) Fulminant myocarditis: characteristics, treatment, and outcomes. Anatol J Cardiol 19(4):279–286. https://doi.org/10.14744/AnatolJCardiol.2017.8170
17. Caforio AL, Pankuweit S, Arbustini E et al (2013) Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 34(33):2636–2648, 2648a-2648d. https://doi.org/10.1093/eurheartj/eht210
18. Schultheiss HP, Kuhl U, Cooper LT (2011) The management of myocarditis. Eur Heart J 32:2616–2625
19. Brambatti M, Matassini MV, Adler ED, Klingel K, Camici PG, Ammirati E (2017) Eosinophilic myocarditis: characteristics, treatment, and outcomes. J Am Coll Cardiol 70:2363–2375
20. Cooper LT Jr, Hare JM, Tazelaar HD, Edwards WD, Starling RC, Deng MC, Menon S, Mullen GM, Jaski B, Bailey KR, Cunningham MW, Dec GW (2008) Usefulness of immunosuppression for giant cell myocarditis. Am J Cardiol 102:1535–1539
21. Ammirati E, Oliva F, Belli O, Bonacina E, Pedrotti P, Turazza FM, Roghi A, Paino R, Martinelli L, Frigerio M (2016) Giant cell myocarditis successfully treated with antithymocyte globuline and extracorporeal membrane oxygenation for 21 days. J Cardiovasc Med (Hagerstown) 17(Suppl 2):e151–e153
22. Barba T, Fort R, Cottin V, Provencher S, Durieu I, Jardel S, Hot A, Reynaud Q, Lega JC (2019) Treatment of idiopathic inflammatory myositis associated interstitial lung disease: a systematic review and meta-analysis. Autoimmun Rev 18(2):113–122. https://doi.org/10.1016/j.autrev.2018.07.013