Diagnosis and management of myocardial involvement in systemic immune-mediated diseases: A position statement of the ESC Working Group on Myocardial and Pericardial Disease.

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Abstract

The myocardium is a critical target in systemic immune-mediated diseases (SIDs), even in asymptomatic patients, with negative prognostic implications. This multidisciplinary position paper from the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Disease focuses on inflammatory and degenerative myocardial diseases. Their type and frequency markedly differ in individual SIDs, thus here a disease-specific approach has been used. However, some general considerations and recommendations have been made. It is hoped that this document will provide a first orientation to cardiologists and non cardiology physicians in selecting an appropriate multidisciplinary diagnostic work-up in SIDs-related myocardial disease, as well as personalised treatment, setting the stage for future controlled studies.

Key words: myocarditis; cardiomyopathy; immune-mediated disease; autoimmunity.

Introduction

Systemic immune-mediated diseases (SIDs) include autoimmune and autoinflammatory diseases affecting at least two-organ systems.[1] Autoinflammatory diseases refer to a growing family of conditions characterised by episodes of unprovoked inflammation in the absence of high autoantibody titers or auto reactive T lymphocytes, reflecting a primary innate immune system dysfunction.[1] Conversely, autoimmune diseases are characterised by aberrant B, T and dendritic cell responses, leading to a break in tolerance against self-antigens, with predominantly cell-mediated or autoantibody-mediated responses in genetically susceptible individuals.[2-11] Autoantibodies (AAbs), when detectable, can promote inflammatory responses via immune complex formation and may directly affect target organ function,[10] e.g. resulting, in cardiac autoimmunity, in electrical disturbance, cardiomyocyte dysfunction or loss and heart failure.[12-15] However, a dichotomous classification does not reflect clinical evidence and a continuum from purely autoinflammatory to purely autoimmune diseases should be considered (Figure 1).[1]

Cardiac involvement in SIDs is associated with adverse outcomes.[16-18] Currently there is a lack of up to date cardiological diagnostic work-up in the scientific literature and in clinical practice, leading to poor scientific knowledge, late recognition or under diagnosis and under treatment of cardiac involvement.[16-18] Specific limitations include the use of scores only based on clinical findings (e.g. heart failure symptoms) to stratify patients with cardiac involvement as well as limited information based on state-of-the art non-invasive and invasive methodology.[16-18] Although all heart structures may be affected (Suppl Table 1 online), we will focus on inflammatory and degenerative myocardial diseases, which may include: 1) myocarditis evolving to a dilated cardiomyopathy (DCM) or a hypokinetic non-dilated cardiomyopathy; 2) endomyocarditis and endomyocardial fibrosis.[19-22] The aim of this multidisciplinary position paper by the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Disease is to help cardiologists and non-cardiac specialists to select the appropriate diagnostic work-up in SIDs, setting the stage for future therapeutic choices.[11, 23-27]

General approach to diagnosis of myocardial involvement in SIDs

The type and frequency of myocardial involvement markedly differ in the main SIDs, making a general diagnostic algorithm too cumbersome to be clinically useful; therefore here a disease-specific approach has been used. However, some general considerations and recommendations can be made.

Clinical features suggesting myocardial involvement

- Clinical presentation of myocarditis is unspecific. *Red flags* may include: unexplained dyspnoea, palpitations, chest pain with or without increased troponin, syncope, arrhythmia and acute or chronic congestive heart failure, sudden cardiac death, fulminant cardiogenic shock.[22]

- Since in many SIDs accelerated coronary artery disease (CAD) as well as coronary microvascular dysfunction may be predominant or contributory to cardiac signs and symptoms,[28] an ischaemic aetiology should be ruled out first, whenever clinically indicated, by standard non-invasive and invasive means.[22, 28-29] The specific work-up should be tailored to the individual case and clinically oriented.

Biomarkers, ECG, old and new imaging techniques

- An increase in troponin and/or NT-pro BNP may be indicative of myocardial involvement, regardless to its aetiology.[22] In addition troponin may be increased in extracardiac disease (e.g. pulmonary embolism).[22, 29] Conversely myocarditis may occur in the absence of troponin release.[22]

- Some disease-specific biomarkers, e.g. AAbs,[8-11] are available for the various SIDs and are part of the multiparametric diagnostic criteria (see section on specific SIDs), but so far it is unknown whether they may be markers associated with myocarditis.

- Myocarditis may occur in association with any unexplained abnormality on standard 12 lead electrocardiography (ECG) or twenty-four hour-ECG Holter monitoring.[22]

- Cardiological non-invasive imaging plays a pivotal role in the detection of myocardial involvement in SIDs, although findings are often unspecific in relation to aetiology (Suppl. Table 2 online). The first-line method is standard echocardiography with Doppler analysis[30-32] as well as advanced methods, e.g. deformation imaging, to detect subclinical myocardial involvement.[33-34] Echocardiography is also essential in the diagnosis of pericardial and valvular involvement.[35-38] Transesophageal echocardiography particularly in association with 3D imaging may be useful in particular cases, such as Libman-Sacks endocarditis in systemic Lupus Erythematosus (SLE).[39-40] The assessment of tricuspid and pulmonary regurgitation gradients plays a key role in noninvasive diagnosis of pulmonary hypertension (PH).[40-41]

- Other non-invasive techniques, in particular cardiac magnetic resonance (CMR) imaging with tissue characterisation sequences and positron emission tomography (PET) may refine the clinical suspicion of non-ischaemic inflammatory myocardial involvement, and help in the patient's follow-up and in assessing response to treatment. CMR provides complementary information and is particularly useful when echocardiography is inconclusive. Cardiac involvement in SIDs can be assessed by CMR tissue characterisation with T1 and T2 weighted imaging and late gadolinium enhancement (LGE), as well as with parametric mapping. The characteristic subepicardial or midmyocardial LGE pattern seen in SIDs allows differential diagnosis from CAD and has been shown to correlate with disease activity in rheumatoid arthritis (RA),[42] and in systemic sclerosis (SSc).[43-44] CMR with LGE and T1 mapping can also identify early changes in SSc and RA.[45, 46] Myocardial perfusion CMR abnormalities have been reported to correlate with C–reactive protein (CRP) in SSc.[44]

- Computed Tomography (CT) is mainly used for the diagnosis of aortic disease and coronary atheroma as well as pericardial disease, if other tests fail to provide sufficient information. CT shows coronary and aortic calcification, which is more prevalent and severe in RA than in controls [47]. In patients at low and intermediate risk with symptoms and/or ventricular

dysfunction, CT coronary angiography may substitute invasive coronary angiography. CT can also be used as an adjunct to echocardiography in PH work-up.[41]

- Positron Emission Tomography (PET) is particularly useful to detect inflammation in specific settings, such as sarcoidosis.[16, 48] Myocardial perfusion PET, using short-lived radionuclides such as ^{13}N-NH$_3$, offers noninvasive quantitation of myocardial blood flow (MBF). Abnormal MBF is a strong predictor of adverse outcome in CAD, reflecting microvascular dysfunction and impaired coronary flow reserve.[49]

- Endomyocardial biopsy (EMB) is the gold standard for suspected myocarditis with or without associated SIDs; using current histological, immunological, immunohistochemical and molecular tools, it provides differentiation between infectious and non-infectious myocarditis.[22, 50-55] In addition it can identify cardiac vasculitis and/or other non-inflammatory (degenerative or infiltrative) myocardial diseases applying special histological and immunohistochemical techniques (Figures 2-3).[22, 50-55] It may be particularly useful at diagnosis in SIDs if cardiac clinical, non-invasive and invasive findings suggest non-ischaemic myocardial involvement as well as if there is an unexplained and unexpected change in cardiac status and the histological confirmation is expected to change management. This is especially true if the diagnosis cannot be made with biopsies of more accessible tissues, e.g. in cardiac amyloidosis.[52-55] The clinical drawbacks of the method include low complication rate (0-0.8% of serious events) in experienced hands[56-59] and sampling errors. For histology and immunohistochemistry at least three myocardial tissue samples from the right or left ventricle should be investigated,[22,50] immediately fixed in 4% buffered formaldehyde for all histological and immunohistochemical stainings and for special stains of storage diseases. Additionally, at least two samples (fixed in RNA later or snap-frozen in liquid nitrogen and stored at -80°C) should be obtained for molecular analyses including cardiotropic viruses and bacteria by Reverse Transcription (RT-) polymerase chain reaction (PCR) detection.[22, 50]

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- Ideally and whenever possible sophisticated and expensive second-step cardiac tests, e.g. CMR, PET, EMB should be performed in specialised centres, experienced in rare cardiac disease assessment.

Recommendation

1. Echocardiography should be performed in all SIDs patients with suspected cardiac involvement.[30-38] CMR should be considered in uncertain cases and where myocarditis or myocardial infiltration is suspected.[42-46] PET is particularly useful to detect inflammation in specific settings, such as sarcoidosis.[16, 48]

2. EMB has significant clinical value,[22, 50-55] provided that it is taken by experienced investigators and assessed by trained cardiopathologists from specialised laboratories, possibly certified by international organizations in terms of performance and interpretation of up-to date techniques.

3. EMB may foster treatment decisions on the basis of histopathological results, particularly in eosinophilic myocarditis, sarcoidosis and in giant cell myocarditis (GCM).[22, 50-55] In these types of non-infectious myocarditis, immunosuppressive therapy should always be considered, provided that major contraindications are excluded (e.g. active or latent malignancy or extracardiac infection).[22]

4. The use of biomarkers, such as natriuretic peptides should be adapted according to current ESC heart failure guidelines, algorithms and cut-off values.[92] It should not be done routinely but only if clinical suspicion of cardiac symptoms and/or signs, e.g. dyspnea, develop.[92]

General principles of management of myocardial involvement in SIDs

Since type and frequency of cardiac and specifically myocardial involvement are different in various SIDs, a detailed general management algorithm is not realistic, however some general principles can be addressed. Although all heart structures can be involved in SIDs, here we focus on myocardial inflammatory involvement that is under diagnosed and overlooked. Thus, there is also a lack of robust evidence-base for management of affected patients.

Role of disease specific therapies.

Background disease specific therapies in SIDs include immunosuppressive and/or immunomodulatory regimes, particularly in active phases of the disease.[11, 25] There is wide variability in clinical presentation, response to treatment and prognosis in SIDs,[11] therefore immunosuppressive therapy is tailored to the level of disease activity, the involvement of vital organs and the presence of comorbidities, thus requiring a personalised approach targeted to reach the lowest level of disease activity, e.g. treat-to-target strategy.[60] Anyway, when a vital organ failure ensues general supportive management is used, e.g. heart failure or kidney failure therapy. In many SIDs, proven myocarditis is an indication to a more intensive immunosuppression, since it may lead to irreversible organ damage and directly affect survival.[16, 48, 61-72]

Complications of treatment

Main immunosuppressive treatment complications include a higher incidence of acquired infections and/or reactivation of latent or opportunistic infections. The use of corticosteroids, in particular, is associated with adverse cardiovascular outcomes and an unfavourable metabolic profile.[73] Therefore, steroid-sparing strategies are preferred, especially if a chronic immunosuppressive regimen is needed.[11] In addition, teratogenic and oncogenic effects of some immunosuppressants, e.g. methotrexate or mycophenolate mofetil, should be minimized and active screening programs are advisable in this high-risk population.

Systemic Lupus Erythematosus (SLE)

Heart involvement in SLE is common (more than 50% of the patients) and may affect any heart structure (Table 1).[74] SLE myocarditis, which may be associated with mutations in the gene encoding the 3'-5' DNA exonuclease TREX1,[75-76] had an autopsy frequency of up to 8% in the era of corticosteroids and chloroquine and hydroxychloroquine use.[73] It is nowadays presumed to be rare, possibly in relation to better immunosuppressive regimens.[11] Clinical presentation of SLE myocarditis is unspecific and difficult to be recognised, particularly when SLE diagnosis is not yet

established (Suppl. Table 3 online).[77-78] The pathogenesis of SLE myocarditis is thought to be immune complex-mediated, with granular complement and immunoglobulin deposits seen at autopsy and on EMB. Noninvasive diagnostic red flags include an unexplained increase in troponin I and/or NT-pro BNP,[79] global or segmental hypokinesis on transthoracic (TTE) echocardiography. CMR imaging may detect abnormalities even in pre-clinical stages of SLE, showing a non-ischaemic pattern of myocardial LGE and/or oedema.[79] Since accelerated atherosclerosis is well known to occur in SLE, CAD must be ruled out.[28-29] EMB differentiates SLE myocarditis from the rare finding of chloroquine/hydroxychloroquine-induced cardiomyopathy and/or the common coronary vasculitis/vasculopathy.[78, 80] Treatment of SLE myocarditis with high-dose methylprednisolone pulse is typically required, followed by oral corticosteroids in combination with immunosuppressive drugs, such as azathioprine, cyclophosphamide or intravenous immunoglobulin (IVIg).[61] SLE patients are at high risk of infection due to the disease itself, which may be associated with primary immunodeficiency[81] and to immunosuppressive treatment, leading to secondary immunodeficiency. Thus, ruling out infectious myocarditis by EMB may be clinically useful.[22]

Recommendation

4. EMB, applying histology, immunohistology and (RT-) PCR for detection of infectious agents, may be useful for diagnosis of SLE myocarditis, since SLE patients are at high risk of infection due to the disease itself and to immunosuppressive treatment.[22, 81]

Systemic sclerosis (SSc)

Heart involvement in SSc may be primary or secondary to concomitant kidney and/or pulmonary vascular/interstitial disease (Table 2, Suppl. Table 4 online).[82] Primary myocardial involvement is often clinically occult and, when symptomatic, prognosis is poor. It may be related to dysfunction and/or structural damage of the microvascular bed, leading to repeat focal ischaemic injury and irreversible myocardial fibrosis,[83] but it can also be due to a primary systemic myositic disease.[84] Left ventricular systolic dysfunction (LSVD) is the 'hallmark' of primary SSc myocardial

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involvement.[85] Routine echocardiography is clinically useful in diagnosing LVSD, as well as advanced echocardiography, e.g. tissue-doppler and speckle-tracking strain analysis, in heart failure with preserved ejection fraction (HFpEF).[86-87] Left ventricular diastolic dysfunction (LVDD) is common;[86-87] pulmonary hypertension (PH) should be carefully ruled out.[41] Standard 12 lead ECG is abnormal in 50% of patients, the most common abnormality being left bundle branch block (16%), followed by first-degree (8%), or advanced atrioventricular (A-V) blocks (<2%).[88] Twenty-four hour-ECG Holter monitoring may detect supraventricular and/or ventricular arrhythmias; QTc prolongation may be associated with life-threatening tachyarrhythmias.[89] SSc is perceived as having a high arrhythmic burden, with a 5% sudden death rate in patients with both skeletal and cardiac muscle disease.[90] Clinical and non-invasive myocarditis red flags are similar to those seen in SLE, including unexplained increased (more than 3 fold) CPK or troponin,[91] LVSD and/or LVDD,[85-87] non-ischaemic abnormal CMR tissue patterns.[65] Autoimmune myocarditis (Figure 3) should be managed by immunosuppressive treatment,[22, 62-65] while heart failure, arrhythmia and conduction disturbances should be treated according to current ESC guidelines.[92-93]

Recommendation

5. Referral to a cardiologist for further diagnostic work-up is indicated at any time in the screening of SSc patients, if myocardial involvement is suspected based upon clinical and noninvasive diagnostic findings.[22, 62-65,84-89,91]

6. EMB may be considered in patients with clinically suspected myocarditis; immunosuppressive treatment is indicated in EMB-proven infection-negative myocarditis.[22,62,65,84]

Sarcoidosis

Sarcoidosis is a multisystem disorder of unknown cause(s), frequently presenting with hilar lymphadenopathy, pulmonary infiltration, ocular and skin lesions, mainly occuring in the 2nd to 5th decade (Suppl Table 5 online).[94-95] The diagnosis is based upon clinical and non-invasive findings, supported by histological evidence of non-necrotising granulomas. Cardiac involvement can be found in 2-7% of patients,[48] but it may be underestimated: autopsy studies reported myocardial

granulomas in 20-30% of patients. The disease may present with sudden death, particularly in patients aged over 40 years, as well as with "idiopathic" A-V block of various degrees, or ventricular tachycardia in apparently healthy subjects.[48, 94-95] Arrhythmogenic right ventricular cardiomyopathy is high on the list for differential diagnosis.[48, 94-95] In Japanese patients heart involvement accounts for 50-85% of the deaths compared to 13-20% in Caucasians, confirming that racial factors may play a role in disease expression.[16]

Sarcoid granulomas may involve any site of the heart, although left ventricular free wall, posterior interventricular septum, papillary muscles, right ventricle and the atria are most frequently affected. Heart involvement may occur at any time and does not correlate with other extracardiac locations. It should be suspected if a patient with known sarcoidosis develops conduction blocks, tachyarrhythmia, congestive cardiac failure, pericarditis or DCM (Table 3). The extension of myocardial granulomatosis is directly related to bad prognosis.[16] Non-invasive imaging is indicated in all patients with suspected cardiac sarcoidosis and the definitive diagnosis of cardiac involvement requires a combined approach, often including CMR and PET (Table 3) (Figure 4). EMB may be of clinical value, but, since the myocardium is involved in a patchy fashion, its sensitivity may be low due to sampling error. If positive, EMB provides histological and aetiological differential diagnosis from idiopathic GCM and other infectious granulomatous forms (e.g. mycobacteria, Bartonella henselae, Toxoplasma gondii and Yersinia) (Figure 2).[16] Corticosteroids are the gold standard treatment,[16, 48] although response to medical therapy is variable and cardiac transplantation may be the last option (Table 4).

Recommendation

7. Red flags for cardiac involvement in clinically suspected or known extracardiac sarcoidosis, include:

- unexplained brady or tachyarrhythmia, heart failure signs and symptoms, LVDD and/or LVSD on echocardiography or CMR, and/or abnormal tissue patterns on CMR or FDG-PET uptake[16,48,94-95]

- unexplained steroid-responsive cardiomyopathy[16,48,94-95]

8. Corticosteroids are the first line treatment.[16, 48] Other immunosuppressive drugs may be valid alternatives (Table 4).[16, 48]

9. Internal cardioverter defibrillator (ICD) implantation may be considered earlier in patients with cardiac sarcoidosis who had haemodynamically compromising sustained ventricular arrhythmia or aborted cardiac arrest, if survival >1 year with good functional status can be expected. The most effective antiarrhythmic drugs are β-blockers, sotalol and amiodarone. Catheter ablation of ventricular arrhythmia is usually considered after an ICD implantation or failure of antiarrhythmic drug therapy. Primary and secondary sudden cardiac death prevention should be in keeping with current ESC guidelines.[93, 96]

10. A-V block is the most frequent conduction abnormality in cardiac sarcoidosis and pacemaker therapy is often needed.[93, 96] Corticosteroids may improve A-V node recovery, but pacemaker implantation may be preferable, even if the A-V block reverses transiently.[16, 93, 96]

Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome)

EGPA is a rare eosinophilic-rich and necrotizing granulomatous vasculitis often involving the respiratory tract and predominantly affecting small to medium vessels (Suppl. Table 6 online). [17,97,98] Multiple cell types participate in the cellular immune response, including Th2, Th1 and Th17 cells and activated B cells producing antineutrophilic cytoplasmic antibody (ANCA).[17] The pathogenesis of EGPA is multifactorial: it can be triggered by exposure to allergens or drugs, but a genetic background has also been recognized.[17, 99] EGPA involves various organs; the triad of the disease includes asthma, allergic rhinitis and marked peripheral blood eosinophilia (Suppl. Table 6 online).[98,99] EGPA belongs to the spectrum of ANCA-associated vasculitides (AAV), although

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ANCA frequency (30-40% of cases) is lower than in other AAV.[18, 66, 99] Two major clinical subsets have been identified, including ANCA-positive EGPA, with features of small-vessel vasculitis, and ANCA-negative, in which organ damage is mainly mediated by tissue eosinophilic infiltration.[17, 99] Myocardial involvement, in particular as endomyocarditis or endomyocardial fibrosis (up to 60% of cases, with endocavitary thrombosis in about 10%), or cardiomyopathy (up to 20%), is associated with high eosinophilic cell count and the absence of ANCA (Figures 2, 4).[18,67] In eosinophilic EGPA associated myocarditis (Figure 2), long-term prognosis is poor,[17] leading to a restrictive cardiomyopathy or DCM,[17,67] which is an independent risk factor for death.[18]

Cardiac screening should include laboratory assessment (CK-MB and troponin) and ECG, echocardiography and CMR. Echocardiography and/or CMR can detect regional wall-motion abnormalities, pericardial effusion (20% of cases) and intracavitary thrombi.[18,67] Tissue characterization by CMR may show features suggestive for myocarditis and myocardial fibrosis (Figure 4). Coronary abnormalities should be ruled out by coronary angiography. EMB may provide diagnosis of EGPA myocarditis, particularly in ANCA-negative patients with early and/or predominant cardiac involvement.[67] Diagnostic work-up should be aimed to the identification of other causes of hypereosinophilic syndromes with possible heart involvement (toxic, infectious, clonal, hypersensitivity).[100,101] The standard therapeutic approach to EGPA is based on high-dose corticosteroids plus immunosuppressive agents, including cyclophosphamide.[66-67]

Recommendation

11. Red flags and cardiological diagnostic methods are identical to those of other SIDs.[17, 67, 99] Heart involvement is typically associated with high eosinophilic counts and negative ANCA status.[18, 67]

12. The diagnosis of EGPA myocarditis may reinforce the indication to immunosuppression.[66,67]

Granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis)

GPA is a rare necrotizing granulomatous AAV, predominantly affecting small to medium vessels, which usually involves the upper and lower respiratory tract, but any other organ can be affected (Suppl. Table 7 online).[97,98] Cardiac manifestations, such as pericarditis (35% of cases), coronary

arteritis (12%), cardiomyopathy (30%), arrhythmias (6%) and valvular lesions (6%) have been reported.[102] However, the extent and type of cardiac involvement are still poorly defined and mainly based on the composite Birmingham Vasculitis Activity Score, which includes loss of pulses, valvular heart disease, cardiomyopathy, ischaemic cardiac pain, pericarditis, congestive heart failure, not confirmed by routine cardiology methods. Between 1957 and 2005, the French Vasculitis Study Group included 1108 patients with systemic necrotizing vasculitides, among them 311 GPA patients.[103] Cardiac involvement was diagnosed in 13% of GPA subjects and a multivariate analysis identified age, renal and cardiac failure as independent negative prognostic factors.[103] Conversely, in the Vasculitis Clinical Research Consortium longitudinal multicenter cohort study including 517 GPA patients, cardiac involvement was found in only 3.3% of GPA subjects and was not associated with a higher rate of relapse or premature death.[102] In a meta-analysis of long-term follow-up data from 4 European clinical trials including 535 newly diagnosed AAV patients, of whom 53% GPA cases, cardiovascular involvement, found in a minority (5.7%) of patients, was independently associated with a higher risk of relapse.[104] In the absence of immunosuppressive treatment, the outcome of GPA is nearly always fatal.[104] The combination of immunosuppressant drugs including biologic agents such as rituximab has remarkably improved GPA prognosis.[105]

Recommendation

13. Since cardiovascular GPA involvement may predict poor prognosis and/or higher risk of relapse,[103,104] an upgraded immunosuppressive regimen may be considered.[105]

Inflammatory myopathies (IM).

IM are a heterogeneous group of diseases primarily affecting skeletal muscle, including dermatomyositis, polymyositis, necrotizing autoimmune myositis, inclusion-body myositis and overlap myositis, which are characterized by specific IM AAbs with features of the connective tissue disorders.[106] Cardiac involvement in IM is clinically occult in most patients, but may be suspected by non-invasive cardiovascular methods[68, 106-107] and is related to bad outcome.[107-108]

Myocarditis occurs in up to 30% of autopsied patients, with or without concomitant coronary or vessel vasculitis.[106] Biopsy-proven lymphocytic or giant cell myocarditis may be found in IM patients with or without myositis-specific (anti- tRNA-synthetase) AAbs[68,109-111] and is a negative prognostic factor.[110, 69, 111] Red flags and cardiological diagnostic methods are identical to those in clinically suspected myocarditis in other SIDs.[68, 106-107,111] Myocardial ischaemia (due to coronary vasculitis), pericardial or valve disease may also occur.[107] Cardiovascular mortality ranges from 5-17%, most frequently caused by myocardial infarction, heart failure and myocarditis.[107] Myocarditis seems to respond to an intensification of standard immunosuppression.[69,107,109-111]

Recommendation

14. Myocarditis may be found in IMs patients with or without myositis-specific Abs and it may be an indication to a more intensive immunosuppressive regimen.[69,107, 109-111]

Rheumatoid arthritis (RA).

RA exhibits a high risk of cardiovascular disease (CVD) and of heart failure, resulting in premature morbidity and mortality and reduced life expectancy compared to subjects without RA.[112] Positive AAbs status, joint pain severity and conventional risk factors were all strongly associated with increased CVD risk.[112] At present, accelerated atherosclerosis is considered a main complication, resulting from the cumulative effect of chronic systemic inflammation, oxidative stress and classical CVD risk factors.[113] All cardiac structures can be affected in RA resulting in pericarditis (common, but symptomatic in less than 1%), myocarditis, myocardial fibrosis, brady- and tachyarrhythmia, epicardial CAD, valvular disease (usually a single valve, resulting mainly in regurgitation and rarely in stenosis), PH and cardiomyopathy.[114-116] In 3-30% of patients the RA-associated cardiomyopathy may be caused by focal lymphocytic, diffuse necrotizing or granulomatous myocarditis.[114, 116] The granulomas show a predilection for the left ventricle and are morphologically identical to the subcutaneous RA nodules (Figure 3).[114] Recent CMR-based studies

suggest that RA myocarditis may be more prevalent than previously suspected, even in asymptomatic patients, but more correlative data with EMB are needed (Figure 4). [46]

Recommendation

15. Since RA patients have a high burden of CVD, mainly because of accelerated atherosclerosis,[112-113] a multidisciplinary management including a cardiologist is indicated and should be driven by a clinical suspicion from the attending physician .

Spondyloarthritis (SA)

SA primarily affects joints and the axial skeleton and is associated with increased cardiovascular morbidity and mortality, although the contributory role of CVD risk factors and of anti-inflammatory treatment needs to be further defined;[117] in psoriatic arthritis, CVD is the leading cause of death (36.2%) and the death risk is 1.3 times greater than in the general population. Cardiovascular symptoms are present in 10% of AS patients and clinical presentations may include CAD, valvular disease, mainly aortitis and aortic insufficiency (1-34%), and conduction defects, anecdotally myocarditis.[117-119.] An association between disease activity and CVD risk has been suggested in AS, but statin therapy is still under scrutiny.[120]

Myasthenia gravis (MG)

MG is an autoantibody and T helper cell mediated autoimmune disease, most often associated with thymic hyperplasia or thymoma, less frequently (up to 8% of patients) with thyroid diseases, RA and SLE, affecting patients of either sex, at any age.[70] Diagnosis is established by patient history, (e.g. fluctuating muscular weakness involving ocular, bulbar and, less frequently, nuchal or proximal limb muscles), electromyography and detection of AAbs interfering with the acetylcholine receptor (AChR).[70] Patients without anti-AChR AAbs often have AAbs against the muscle-specific receptor tyrosine kinase and other postsynaptic neuromuscular junction components. In addition, AAbs against striated muscular antigens, such as anti-titin, anti-ryanodine and anti-Kv 1.4 AAbs,

can be detected almost exclusively in thymoma patients.[121] In Japanese patients, anti-Kv 1.4 AAbs specifically correlate with severe MG, myasthenia crisis, myocarditis, and ECG abnormalities.[122] Cardiac involvement in MG may include Takotsubo cardiomyopathy, myocarditis, abnormal ECG findings such as QT-prolongation, anticholinesterase induced A-V block, and sudden cardiac death.[122] Heart rate variability is disturbed, due to autonomic dysfunction[123]. Since coronary arteries dilate in response to acetylcholine, cases of diffuse coronary spasm associated with anticholinesterase therapy have been reported.[124] Nevertheless, there is no association between MG and CAD. Takotsubo or stress induced cardiomyopathy is typically observed during myasthenia crisis episodes, older patients being at a higher risk.[125] Myocarditis typically affects thymoma-related elderly MG patients and is associated with skeletal muscle cross-reactive striational anti-heart AAbs;[122] diagnosis is often delayed because heart failure symptoms may be misinterpreted. Biopsy-proven GCM may be associated with MG and carries a worse prognosis, compared to other forms of myocarditis.[71-72]

Recommendation

16. The threshold for suspecting GCM should be low in MG, particularly in elderly patients and in those with skeletal muscle cross-reactive striational anti-heart AAbs. If GCM is clinically suspected, particularly in life-threatening heart failure and/or arrhythmias presentations, EMB is indicated.[22, 51, 96]

17. MG patients with GCM myocarditis should be promptly treated with adequate immunosuppression according to the patient's age and the clinical condition.[22, 71-72]

Primary Sjögren Syndrome (SS)

Primary SS is a chronic autoimmune exocrinopathy that mostly affects middle-aged women, leading to xerostomia and xerophtalmia.[126] The diagnosis of primary SS requires an objective immunological abnormality, either focal lymphocytic infiltrates in the minor salivary glands, or the

presence of anti-SSA/SSB AAbs, which are present in 50 to 90% of cases, but are not specific for primary SS, being found in SLE or in other connective tissues diseases.[126] In more than one third of cases, SS also involves extra glandular sites, such as lungs, kidneys, and joints. Fatigue is one of the most common symptoms.[126] Only few isolated cases of clinically suspected myocarditis have been described in primary SS, one of which associated with cryoglobulinemic vasculitis.[127-128] An echocardiographic study in 107 consecutive primary SS patients without cardiac symptoms and 112 healthy controls, matched for age and gender, has shown a higher prevalence of valvulopathies, pericardial effusion, higher systolic pulmonary pressure, LVDD[129].

Congenital heart block (CHB) may be associated (2% of cases) with maternal AAbs against SSA (Ro) or SSB (La) proteins (neonatal lupus syndrome).[130] Some infants with CHB, usually young (less than 2 year-old), or older (greater than 10 year-old), may develop endomyocardial fibroelastosis leading sometimes to heart failure despite early pacemaker implantation.[131-132] This encourages a long follow-up of CHB children of mothers with anti-SSA/SSB AAbs.

Recommendation

18. Long follow-up of CHB children of mothers with anti-SSA/SSB AAbs is recommended.[131-132]

Autoinflammatory diseases (AD)

Monogenic AD usually start in infancy, most commonly involve the skin, serous membranes, joints, gastrointestinal tract, eyes and, less frequently, the nervous system; they are associated with elevated levels of acute phase reactants, e.g. CRP, but a relative lack of high titer AAbs or antigen-specific T cells (Figure 1, Suppl. Table 8 online).[133] Complications include severe inflammatory anaemia and AA amyloidosis, which usually does not affect the heart.[133]

Nonhereditary polygenic AD include adult-onset Still's disease (AOSD) and systemic-onset juvenile idiopathic arthritis (sJIA), as well as other immune-mediated conditions, such as Behçet's disease, and inflammatory bowel disease (IBD) that overlap with autoimmune diseases.[133-134]

18

Among monogenic AD, Mediterranean fever (MF) and tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS) occasionally may cause recurrent pericarditis, clinically suspected myocarditis has been anecdotally described only in TRAPS[135].

Myocarditis, usually a neutrophilic form, can be an uncommon complication of Behçet, AOSD and Crohn's disease.[135] GCM has been reported in association with Crohn's disease and Behçet's disease. [136,137]

Recommendation

19. Myocarditis, although uncommon, should be suspected in some nonhereditary AD, such as Still's disease and Behçet's disease if cardiac red flags similar to other SIDs are present.[136-137]

Conclusions

The cardiovascular system and in particular the myocardium are often critical targets in SIDs, even in asymptomatic patients, leading to a relevant negative burden on prognosis. However, there are at present no studies to recommend cardiac screening in all patients regardless of the clinical suspicion. Therefore, management of patients with SIDs should always include prospective cardiological screening and follow-up in patients with clinically suspected cardiac involvement and when felt necessary by the attending physician. It is hoped that this document will provide a first orientation to cardiologists and non-cardiology physicians in selecting an appropriate multidisciplinary diagnostic work-up in SIDs-related myocardial disease, as well as personalised treatment. Furthermore, it is hoped that cardiologists will actively participate to conception and design of future immunosuppressive/immunomodulatory trials in well-characterized groups of SIDs patients with early/subclinical as well as established myocardial involvement. In fact, at present there is a relative paucity of evidence-based treat-to-target regimens in SIDs patients with myocardial involvement besides empirically driven intensification of conventional immunosuppression.

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Figure legends.

Figure 1. Classification of Systemic Inflammatory Diseases

Adapted from reference 1. Abbreviations (see also text): ALPS, autoimmune lymphoproliferative syndrome; AOSD, adult-onset Still's disease; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome; CANDLE, Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CMRO, chronic multifocal recurrent osteomyelitis; DIRA, Deficiency of interleukin-1 receptor antagonist; DITRA, Deficiency of the interleukin-36-receptor antagonist; FCAS, Familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinaemia D with periodic fever syndrome; HLA, human leukocyte antigen; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; MAS, Macrophage activation syndrome; MHC, major histocompatibility complex; NOMID (also known as CINCA), Neonatal onset multisystem inflammatory disease; PAPA, pyogenic arthritis, pyoderma gangrenosum, and severe cystic acne; PFAPA, Periodic fever, aphthous stomatitis, pharyngitis and adenitis; TRAPS, tumour necrosis factor receptor–associated periodic fever syndrome

Figure 2 and 3. EMB examples of myocarditis in SIDs.

Typical examples of histologically and immunohistologically proven myocarditis in different SIDs (EGPA (a, x100), sarcoidosis (b, x100) in Figure 2, RA (c, x200) and SSc (d, x200) in Figure 3). As shown by Masson Trichrome stains fibrosis (blue areas) is present in all cases of myocarditis, indicating an ongoing or chronic inflammation, which is characterized by presence of T lymphocytes (CD3), macrophages (CD68) and major histocompatibility complex (MHC) class II expression. In addition, in EGPA a significant infiltration of eosinophilic granulocytes (Giemsa stain of B and D (D=inset of B)) is observed in presence of a severe necrotizing vasculitis. In sarcoidosis (b) numerous CD68+ MHCII expressing giant cells (C, D) are present within non-caseating epithelioid granulomas.

Figure 4: CMR findings in SIDs

Top, panel a. Late gadolinium enhanced CMR of a 38 year old patient with cardiac sarcoidosis. The images show the typical pattern of multiple focal areas of enhancement throughout the heart consistent with granulomatous infiltration.

Middle, panel b. Late gadolinium enhanced CMR of a 54 year old patient with EGPA. Note the characteristic widespread subendocardial enhancement of the left ventricle.

Bottom, panel c. Late gadolinium enhanced CMR of a 63 year old patient with long standing RA. There is midmyocardial enhancement in the basal infero-lateral wall as a unspecific sign of previous myocarditis.

Table 1: Cardiac involvement in Systemic Lupus Erythematosus[74]

Cardiac involvement	Presentation/ Clinical Frequency
Pericardium	Pericarditis /30%
Myocardium and coronary vessels	- Autoimmune Myocarditis /1% - CAD due to premature atherosclerosis / <1% - CQ/HCQ-induced cardiomyopathy / <1% - CAD due to coronary thrombosis associated to antiphospholipid AAbs < 1% - Small vessel vasculitis / <1%
Endocardium	- Valvular involvement / 10% usually associated to antiphospholipid AAbs - Libman-Sacks endocarditis Abs / <1% usually associated to antiphospholipid AAbs
Cavities	Thrombosis / < 1% usually associated to antiphospholipid AAbs
Pulmonary arteries	- Pulmonary arterial hypertension - Pulmonary hypertension related to pulmonary embolism usually associated to antiphospholipid AAbs

Abbreviations: Abs= autoantibodies; CAD=coronary artery disease; CQ=chloroquine; HCQ= hydroxychloroquine.

Table 2: Cardiovascular involvement in systemic sclerosis (SSc)[82,85]

Cardiac involvement	Presentation/ Clinical Frequency	Comments
Reduced LVEF	About 5%	High risk in: male gender, diffuse cutaneous SSc, history of digital ulceration, renal crisis and muscle involvement
Reduced LV filling	About 30%	Post-capillary PH: increasing occurrence
Reduced RVEF	5-10%	Related to PH but can also be related to primary heart disease and RV fibrosis
Valvular abnormalities	Similar frequency as matched controls	
Pericarditis	10 to 20%	Usually mild, asymptomatic. When large, recurrent and/or symptomatic it reflects the disease progression with high risk of PH or renal crisis.
Pulmonary arteries	PH in about 5 to 10%	Mainly late complication in limited cutaneous SSc and positive anti-centromere AAbs. Systematic annual screening recommended
Myocarditis	To be suspected particularly in SSc patients with concomitant peripheral myopathy	Usefulness of ECG Holter, troponin, cardiac MRI, EMB to confirm the diagnosis

Table 3. Diagnostic work-up in cardiac sarcoidosis[16,48,96]

Test	Findings	Comments
ECG	- PR prolongation, fragmented QRS - A-V nodal block - atrial or ventricular premature beats	It should be a part of the initial evaluation.
Echocardiography	- hypokinesis or dyskinesia; chamber enlargement, aneurysms - wall thinning and wall motion abnormalities - ventricular dilatation; depressed ejection fraction - valvular dysfunction; papillary muscle involvement - pericardial effusion	Data may be not specific, but echocardiography may help to assess cardiac size and function at diagnosis and during follow-up.
EMB	- presence of granulomas is confirmatory of the diagnosis. - yield of EMB is low being only 30% in initial biopsy - sampling using ^{18}FDG -PET increases diagnostic yield	Its sensitivity is low. In the absence of an alternative aetiology, sarcoidosis must be suspected in presence of heart dysfunction or ECG abnormalities, even if EMB is negative.

CMR	• Gadolinium enhanced CMR can show patchy focal enhancement in regions with granulomatous myocardial infiltration. • T2 weighted CMR can show myocardial oedema in acute inflammatory myocardial involvement.	Cine CMR shows similar findings as echocardiography. CMR can contribute unique information to the non-invasive diagnosis of cardiac sarcoidosis and is well suited to follow the course of cardiac involvement. It may also serve as a prognostic indicator for disease severity.
PET/CT	• Increased uptake of ^{18}FDG occurs within activated macrophages and CD4+ T cells forming granuloma • Patchy and focal cardiac uptake is specific for sarcoidosis • Increased myocardial uptake most frequently observed in the basal and lateral LV wall	PET represents a key method to evaluate cardiac areas involved by sarcoidosis. Pooled estimates demonstrated a sensitivity of 89% and specificity of 78%.

Abbreviations: A-V=atrioventricular; CT= computed tomography; CMR=cardiac magnetic resonance; ECG=electrocardiography; EMB=endomyocardial biopsy; FDG-PET= fluorodeoxyglucose Positron Emission Tomography; LV=left ventricular

Table 4: Treatment of cardiac sarcoidosis[16, 48, 96]

Medical and surgical therapy	Modality	Comments
Corticosteroids	• Pulse of iv methylprednisolone (500 mg daily) • Oral prednisone (initial dose ~ 1 mg/kg/ day) • Prednisone is gradually tapered to a maintenance therapy (5-10 mg/die) for 6-9 months	Steroids represent the gold standard therapy. Randomized trials are lacking; thus, appropriate dose and duration have not been defined.
Other medical therapies	• hydroxychloroquine (400 mg/daily) • Methotrexate (10-20 mg weekly) • Azathioprine (100-150 mg daily) • Mycophenolate mofetil (1.0-2.0 gr daily) • Pulse of iv cyclophosphamide (500-1000 mg every 3-4 weeks)	Randomized trials have not been done. Additional immunosuppressive treatment alone or together with steroids may represent an effective alternative therapy in aggressive cardiac sarcoidosis.
Biologics	• Infliximab • Adalimumab • Rituximab	Data are insufficient to ensure the efficacy of biologics. Off-label biologics may be considered in subjects who do not respond to other therapies. A careful examination of the benefit/risk ratio must be considered before beginning such therapies.

Adjuntive cardiac therapy	• Antiarrhythmics • Catheter ablation • Implantable Cardioverter Defibrillators (ICD)	The efficacy of antiarrhythmic is variable. An ICD may be considered earlier (see recommendation 9). Ventricular tachycardia resistant to medical therapy and ICD may require ablation therapy.
Surgical therapies	• Surgical resection of ventricular aneurysms • Pericardiectomy • Heart transplantation	Surgical resection of ventricular aneurysms or pericardium may be necessary in selected cases. Cardiac transplantation is the only option for patients with end-stage heart failure refractory to medical therapy.

Figure 1. Classification of Systemic Inflammatory Diseases

AUTOIMMUNE — **AUTOINFLAMMATORY**

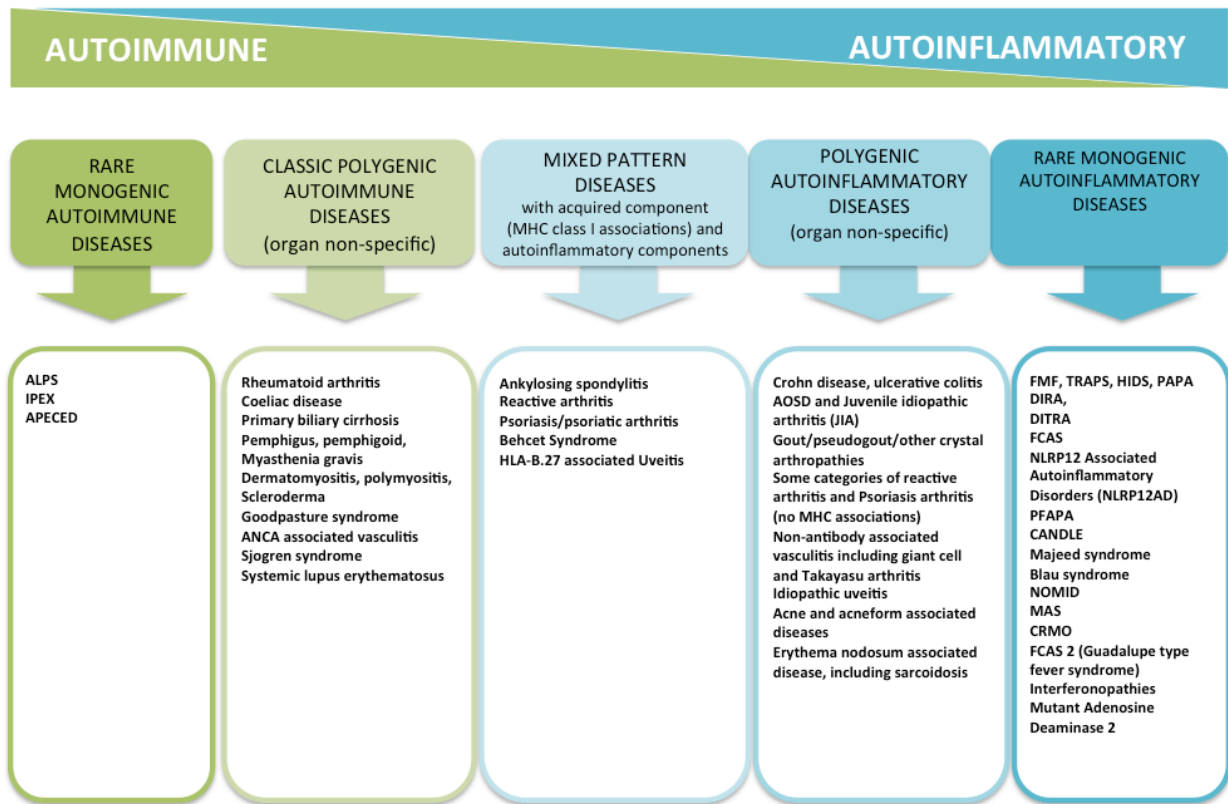| RARE MONOGENIC AUTOIMMUNE DISEASES	CLASSIC POLYGENIC AUTOIMMUNE DISEASES (organ non-specific)	MIXED PATTERN DISEASES with acquired component (MHC class I associations) and autoinflammatory components	POLYGENIC AUTOINFLAMMATORY DISEASES (organ non-specific)	RARE MONOGENIC AUTOINFLAMMATORY DISEASES
ALPS IPEX APECED	Rheumatoid arthritis Coeliac disease Primary biliary cirrhosis Pemphigus, pemphigoid, Myasthenia gravis Dermatomyositis, polymyositis, Scleroderma Goodpasture syndrome ANCA associated vasculitis Sjogren syndrome Systemic lupus erythematosus	Ankylosing spondylitis Reactive arthritis Psoriasis/psoriatic arthritis Behcet Syndrome HLA-B.27 associated Uveitis	Crohn disease, ulcerative colitis AOSD and Juvenile idiopathic arthritis (JIA) Gout/pseudogout/other crystal arthropathies Some categories of reactive arthritis and Psoriasis arthritis (no MHC associations) Non-antibody associated vasculitis including giant cell and Takayasu arthritis Idiopathic uveitis Acne and acneform associated diseases Erythema nodosum associated disease, including sarcoidosis	FMF, TRAPS, HIDS, PAPA DIRA, DITRA FCAS NLRP12 Associated Autoinflammatory Disorders (NLRP12AD) PFAPA CANDLE Majeed syndrome Blau syndrome NOMID MAS CRMO FCAS 2 (Guadalupe type fever syndrome) Interferonopathies Mutant Adenosine Deaminase 2

Figure 2. EMB examples of myocarditis in SIDs.
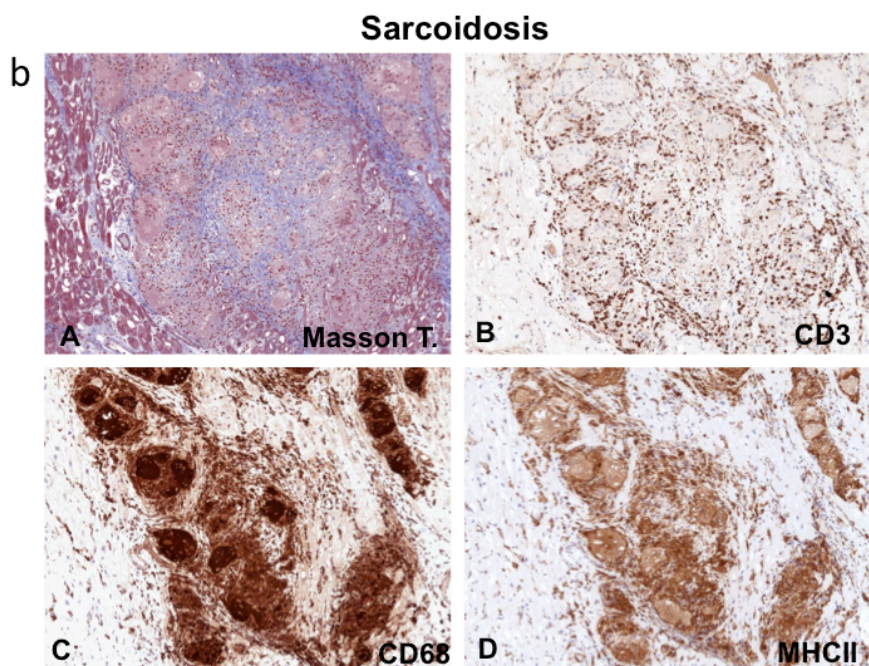

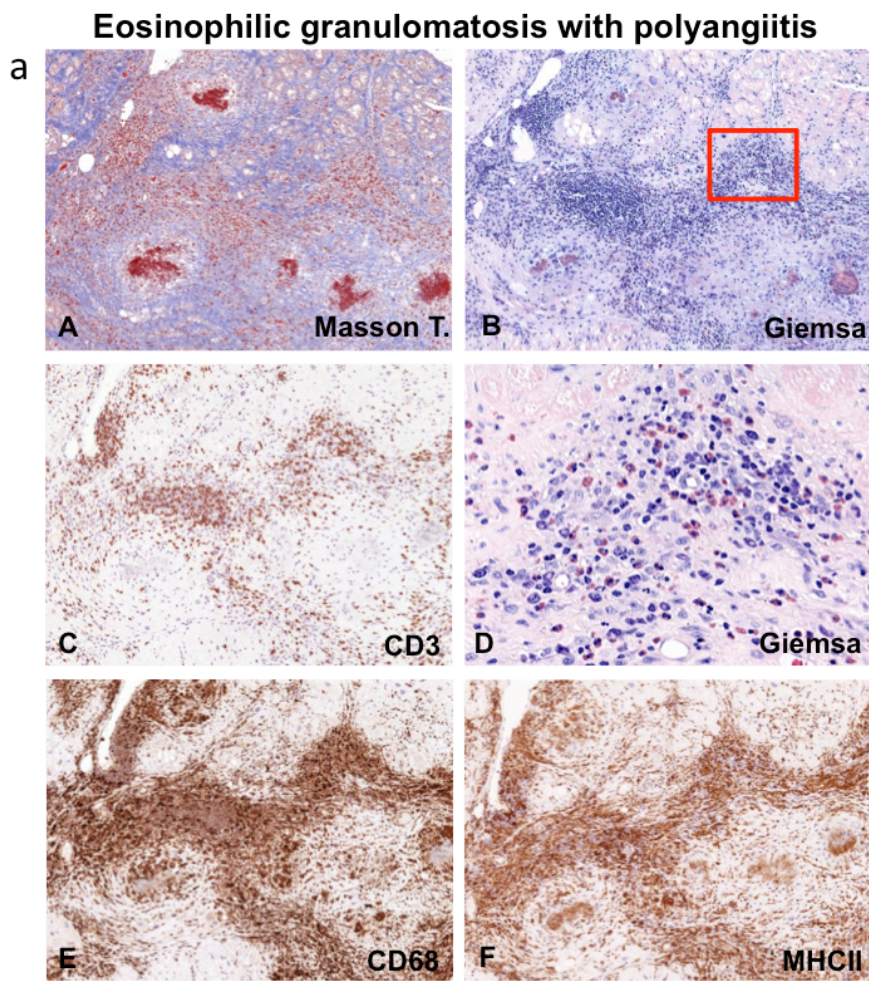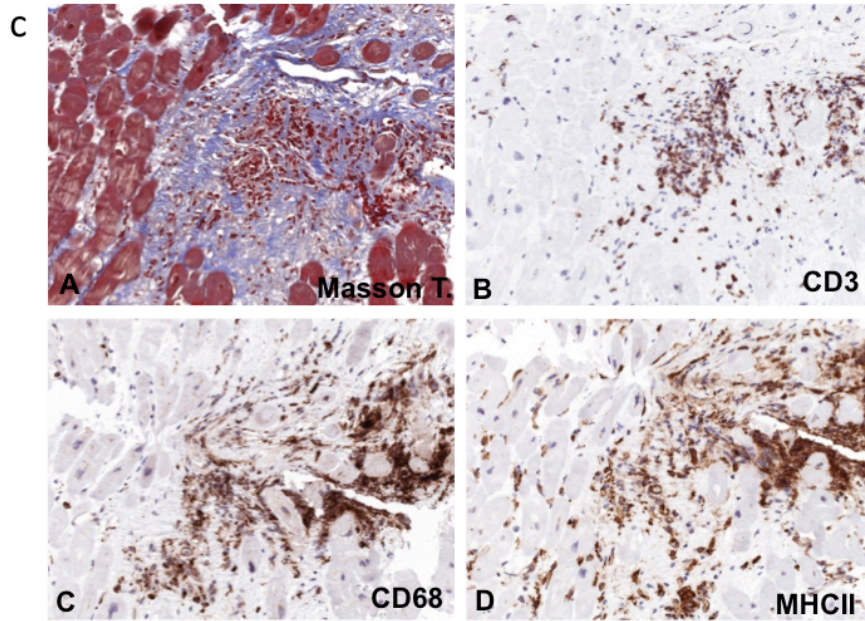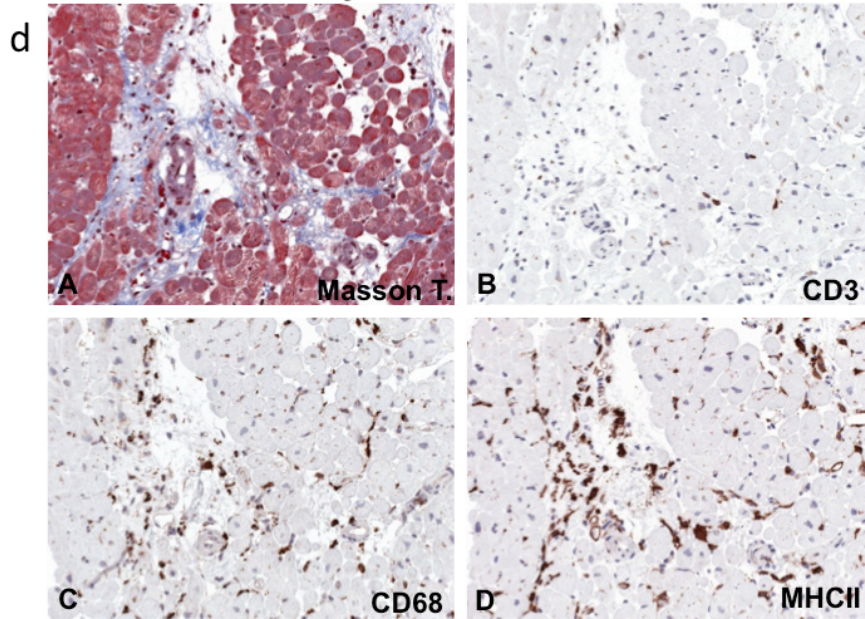Eosinophilic granulomatosis with polyangiitis

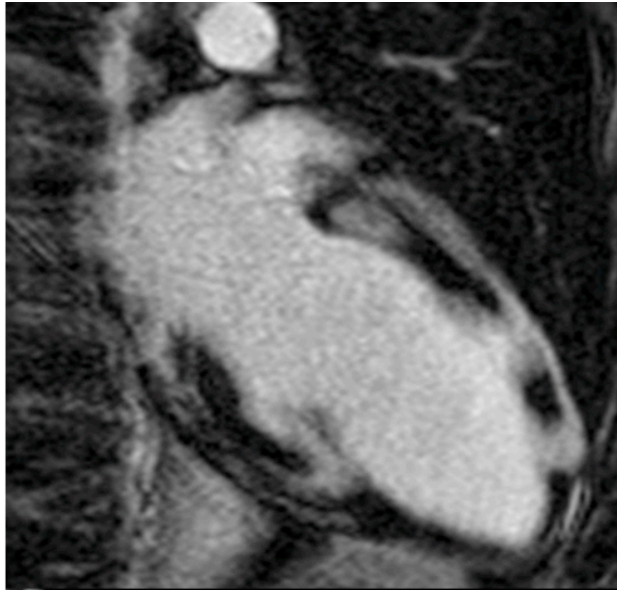**Figure 3. EMB examples of myocarditis in SIDs**.

Rheumatic arthritis

Systemic sclerosis
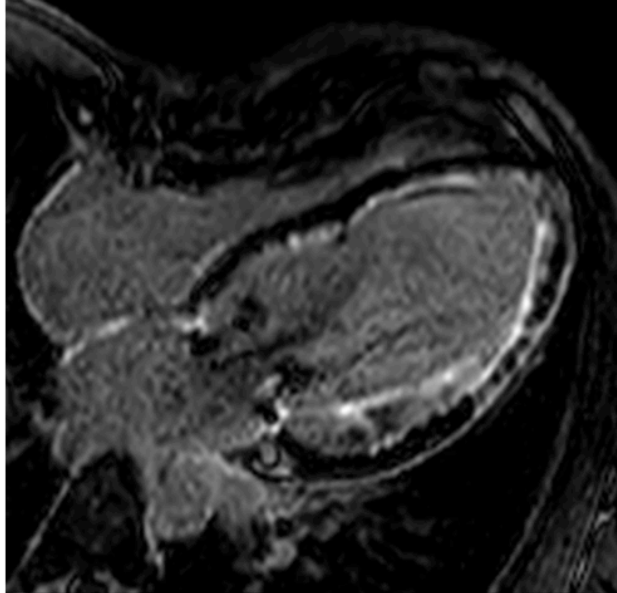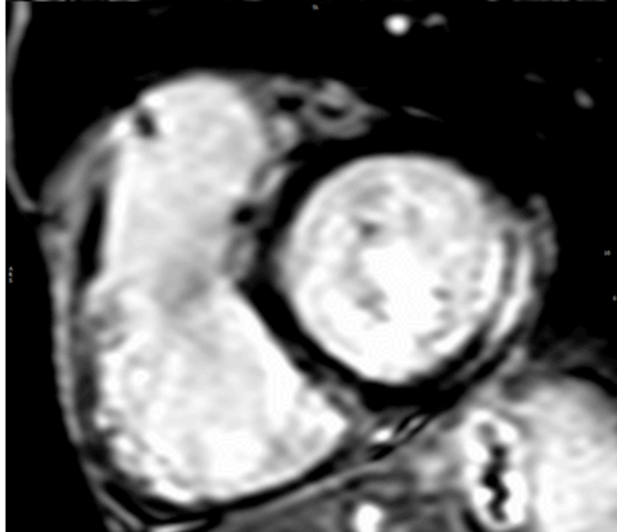

Figure 4: CMR findings in SIDs

Supplementary Table 1 (online): Diversity and estimated frequency of cardiac involvement in SIDs

Cardiac involvement	Presentation/ Clinical Frequency
Systemic lupus erythematosus	pericarditis 30%, myocarditis 1%, valvular involvement 10%, endocarditis <1%
Systemic sclerosis	reduced left ventricular ejection fraction (LVEF) 5%, diastolic dysfunction 30%, reduced right ventricular ejection fraction (RVEF) 5-10%, pericarditis 10-20%, reports on myocarditis
Sarcoidosis	clinical (arrhythmias) 5-7%; granulomas in autopsy 20-30%
Eosinophilic granulomatosis with polyangiits	endomyocarditis, endomyocardial fibrosis up to 60%, cardiomyopathy 20%
Granulomatosis with polyangiitis	pericarditis 35%, coronary arteritis 12%, cardiomyopathy 30%, arrhythmias 6%, valvular lesions 6%
Inflammatory myopathies	myocarditis in up to 30% of autopsies
Rheumatoid arthritis	main complication: accelerated atherosclerosis; cardiomyopathy or myocarditis 3-30%, all cardiac structures may be affected
Ankylosing spondylitis	cardiovascular disease as leading cause of death 36% in psoriatic arthritis, valvular disease 1-34%, anecdotally myocardits
Myasthenia gravis	reports on cardiomyopathy, giant cell myocarditis
Sjögren syndrome	reports on valvulopathies, pericardial effusion, arrhythmias
Auto-inflammatory disease	pericarditis, reports on myocarditis

Supplementary Table 2 (online): Overview of imaging methods to assess cardiovascular involvement in SIDs.

	Myocardial contractile function	LV/RV mass	Scar/ Fibrosis	Ischaemia	Valve involvement	Pericardial involvement	Aortic involvement
Echo	++	++	-	++	++	++	+
CMR	++	++	++	++	+	++	++
CT	+	++	+	+	+	++	++
Nuclear Imaging	+	+	+	++	-	-	–

- no indication

+ limited indication

++ strong indication

Abbreviations: CMR=cardiac magnetic resonance; CT=computed tomography;

Echo=echocardiography.

Updated American College of Rheumatology Classification Criteria for SLE [77]

Criterion*	Definition
1. Malar rash	Fixed, flat or raised erythema over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging (older lesions may demonstrate atrophic scarring)
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving at least 2 peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	(A) Pleuritis: Convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion *or* (B) Pericarditis: Documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	(A) Persistent proteinuria >0.5 g/day or >3+ if quantitation not performed *or* (B) Cellular casts: May be red blood cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	(A) Seizures: In the absence of offending drugs or known metabolic derangements (eg, uraemia, ketoacidosis, electrolyte imbalance) *or* (B) Psychosis: In the absence of offending drugs or known metabolic derangements (eg, uraemia, ketoacidosis, electrolyte imbalance)
9. Hematologic	(A) Hemolytic anaemia: With reticulocytosis

disorder	*or* (B) Leukopenia: < 4000/mm^3 total on =2 occasions *or* (C) Lymphopenia: < 1500/mm^3 on =2 occasions *or* (D) Thrombocytopenia: < 100,000/mm^3 in the absence of offending drugs
10. Immunologic disorder	(A) Anti-DNA: Antibody to native DNA in abnormal titer *or* (B) Anti-Sm: Presence of antibody to Smith (Sm) nuclear antigen *or* (C) Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) a positive test result for lupus anticoagulant using a standard method, or (3) a false-positive serologic test for syphilis known to be positive for =6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption tests
11. Antinuclear antibody (ANA)	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome

Abbreviations: ECG = electrocardiogram; Ig = immunoglobulin; SLE = systemic lupus erythematosus

*=SLE can be diagnosed if any 4 or more of the following 11 criteria are present, serially or simultaneously, during any interval of observation.

Supplementary Table 4 (online): Systemic sclerosis (SSc) 2013 ACR/EULAR classification[82]

Item*	Sub-item(s)	Weight/Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	–	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpo-phalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies (anticentromere, anti-topoisomerase I [anti-Scl-70], anti-RNA polymerase III) *(maximum score is 3)*	Anticentromere	3
	Anti-topoisomerase I	
	Anti-RNA polymerase III	

* These criteria are applicable to any patient to include in an SSc study. The criteria are not applicable to patients with skin thickening sparing the fingers or having a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy). The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥9 are classified as having definite SSc.

Supplementary Table 5 online: Main extracardiac features of sarcoidosis[94-95]

Acute sarcoidosis

- *General concepts*: the acute onset is characterised by the triad of erythema nodosum, arthritis and hilar lymphadenopathy (Lofgren's syndrome)

- *Epidemiology*: commonly recognised in Caucasians, especially Scandinavians, aged about 25 years, and in pregnant or lactating women.

Chronic sarcoidosis

- *General concepts*: an insidious onset is usually followed by relentless, progressive fibrosis at all diseased sites.

- *Epidemiology*: multisystem disease occurring more frequently in some ethnic groups.

- *Main organ involvements*

  o *Lung (*about 80-90% of patients): Dyspnoea, dry cough, or chest discomfort are usual symptoms. Conventional radiography need to be complemented by high resolution CT scanning. Pulmonary function tests usually reveal a restrictive defect and a lowered TLCO/KCO

  o *Skin:* Skin lesions include erythema nodosum, lupus pernio, granuloma annulare, plaque, maculopapular eruptions scars and keloids.

  o *Eyes:* anterior and posterior uveitis may be present. Other ocular findings include choroidoretinitis, periphlebitis retinae; retinal, macular and optic nerve oedema and retinal haemorrhage.

Abbreviations: CT= computed tomography; TLCO/KCO= transfer factor for carbon monoxide/ "volume–corrected" value of TLCO.

Supplementary Table 6 (online): The diagnosis of eosinophilic granulomatosis with polyangiits (EGPA): Classification criteria by the 2012 Chapel Hill Consensus conference and the 1990 American College of Rheumatology (ACR)[97-98]

1990 ACR criteria for classification of Churg-Strauss-Syndrome[97]	Churg-Strauss syndrome if at least 4 of these 6 criteria are positive.* The presence of any 4 or more of the 6 criteria yields a sensitivity of 85% and a specificity of 99.7%
	Asthma
	Eosinophilia > 10%
	Neuropathy (mono or poly)
	Pulmonary infiltrates, non-fixed
	Paranasal sinus abnormality
	Extravascular eosinophils
2012 CHCC statements for the definition of EGPA[98]	
	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract and necrotizing vasculitis predominantly affecting small to medium vessels and associated with asthma and eosinophilia
	Nasal polyps are common
	ANCA is more frequent when glomerulonephritis is present. 100%

	with documented necrotizing glomerulonephritis have ANCA
	Limited expressions of EGPA confined to the upper or lower respiratory tract may occur.
	Granulomatous and nongranulomatous extravascular inflammation, such as nongranulomatous eosinophil-rich inflammation of lungs, myocardium, and gastrointestinal tract, is common.

*Three overlapping phases of EPGA that progress at variable intervals have been described: In the first stage, nonallergic eosinophilic asthma and other allergy symptoms such as rhinosinusitis and/or nasal polyposis are the defining feature. The second phase is characterized by tissue and blood eosinophilia. In the third phase, the characteristic findings are eosinophilic infiltration in tissue, eosinophilic vasculitis of the small arteries and veins, and eosinophilic granulomas.

Supplementary <mark>Table 7 (online):</mark> The diagnosis of granulomatosis with polyangiitis (GPA): classification criteria by the 2012 Chapel Hill Consensus conference and the 1990 American College of Rheumatology (ACR)[97-98]

1990 ACR criteria for GPA classification [97]	
	Wegener's granulomatosis is defined by the presence of at least 2 of the following 4 criteria (sensitivity of 88.2% and a specificity of 92.0%):
	abnormal urinary sediment (red cell casts or greater than 5 red blood cells per high power field)
	abnormal findings on chest radiograph (nodules, cavities, or fixed infiltrates)
	oral ulcers or nasal discharge
	granulomatous inflammation on tissue biopsy
2012 CHCC statements for GPA definition[98]	
	Necrotizing granulomatous inflammation and necrotizing vasculitis associated with antineutrophil cytoplasmic antibody (ANCA).
	Predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries and veins) are affected.
	The upper and lower respiratory tract is usually involved.
	Necrotizing glomerulonephritis is common.

	Ocular vasculitis and pulmonary capillaritis with hemorrhage are frequent.

Supplementary Table 8 (on-line). The expanding spectrum of autoinflammatory diseases

Monogenic syndromes:

- Familial Mediterranean fever (FMF)

- Tumour necrosis factor receptor-associated periodic syndrome (TRAPS)

- Hyper-IgD syndrome (HIDS)

- Cryopyrin-associated periodic syndromes (CAPS): Familial cold autoinflammatory syndrome, Muckle-Wells syndrome, Neonatal onset multisystem inflammatory disease/chronic Infantile neurologic cutaneous arthropathy syndrome (NOMID/CINCA)

- Juvenile systemic granulomatosis (Blau syndrome, early onset sarcoidosis)

- Syndrome of pyogenic arthritis, pyoderma gangrenosum and acne (PAPA syndrome, PAPAS, PAPGA syndrome)

- Majeed syndrome

- Deficiency of interleukin-1 receptor antagonist (DIRA)

- Mevalonic aciduria

Nonhereditary or polygenic disorders:

- Adult-onset Still's disease (AOSD) and Systemic-onset juvenile idiopathic arthritis (sJIA)

- Syndrome of periodic fever, aphthous stomatitis, pharyngitis and adenitis (PAPAS, PFAPA syndrome)

- Schnitzler syndrome

- Other proposed autoinflammatory diseases: Behçet's disease, psoriatic arthritis, Crohn's disease, Sweet's syndrome, relapsing polychondritis, urticarial vasculitis, etc.