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CURRENT OPINION
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Diagnosis and management of myocardial involvement in systemic immune-mediated diseases: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Disease

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Introduction

Systemic immune-mediated diseases (SIDs) include autoimmune and autoinflammatory diseases (AD) 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 titres 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

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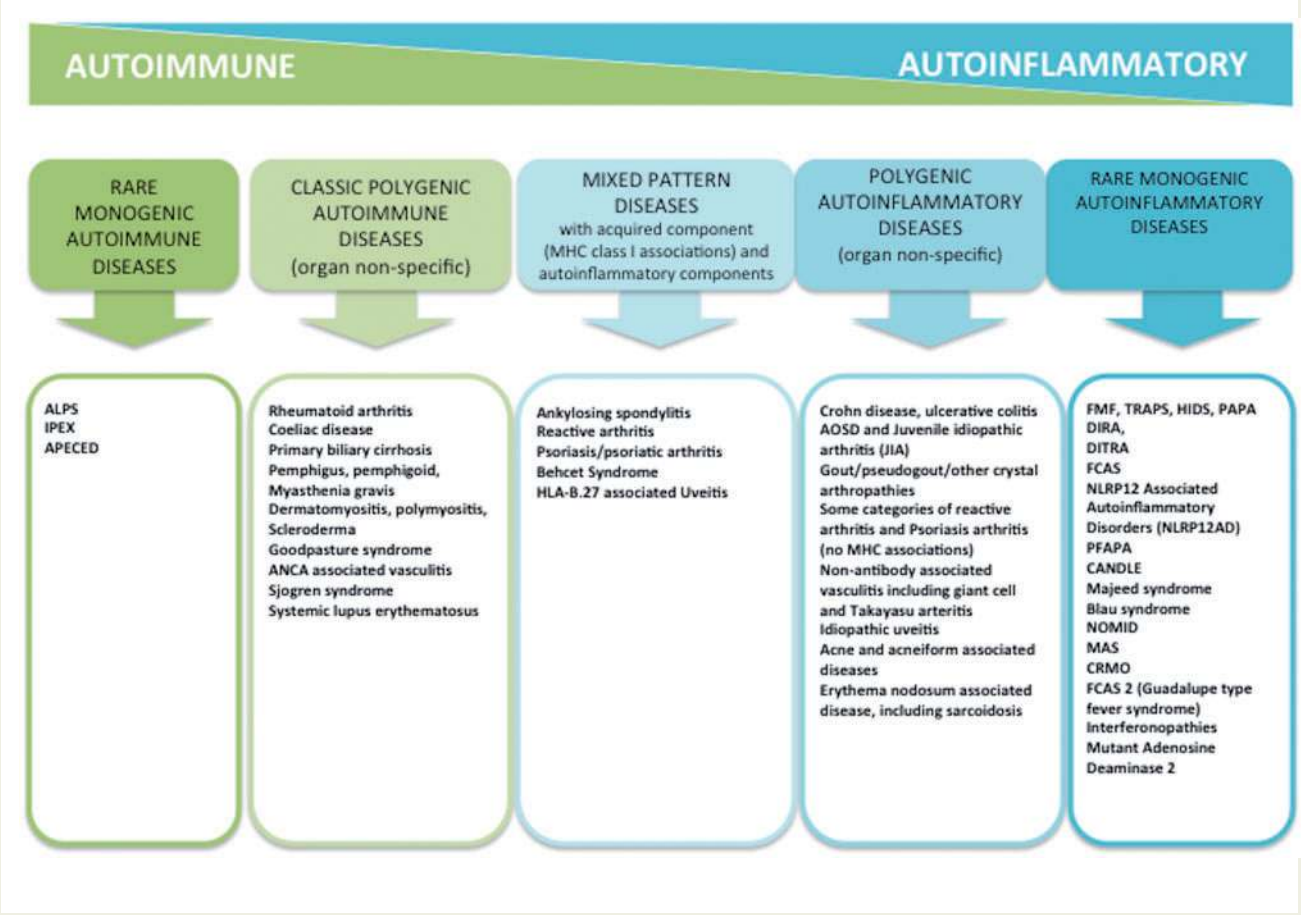

Figure 1 Classification of systemic inflammatory diseases. Adapted from reference[1]. ALPS, autoimmune lymphoproliferative syndrome; AOSD, adult-onset Still's disease; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome; CANDLE, Chronic atypical neutrophilic dermatosis with 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.

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 workup 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 (see Supplementary material online, *Table S1*), we will focus on inflammatory and degenerative myocardial diseases, which may include: (i) myocarditis evolving to a dilated cardiomyopathy (DCM) or a hypokinetic non-dilated cardiomyopathy; (ii) 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 workup in SIDs, setting the stage for future therapeutic choices.[11,23–27]

General approach to diagnosis of myocardial involvement in systemic immune-mediated diseases

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, aborted 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 workup should be tailored to the individual case and clinically oriented.

Biomarkers, electrocardiography, 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 24-h-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 (see Supplementary material online, *Table S2*). 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] Transoesophageal 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 non-invasive 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 mid-myocardial 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 workup.[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 non-invasive 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 (*Figure 2*).[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]
- 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) Endomyocardial biopsy 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.

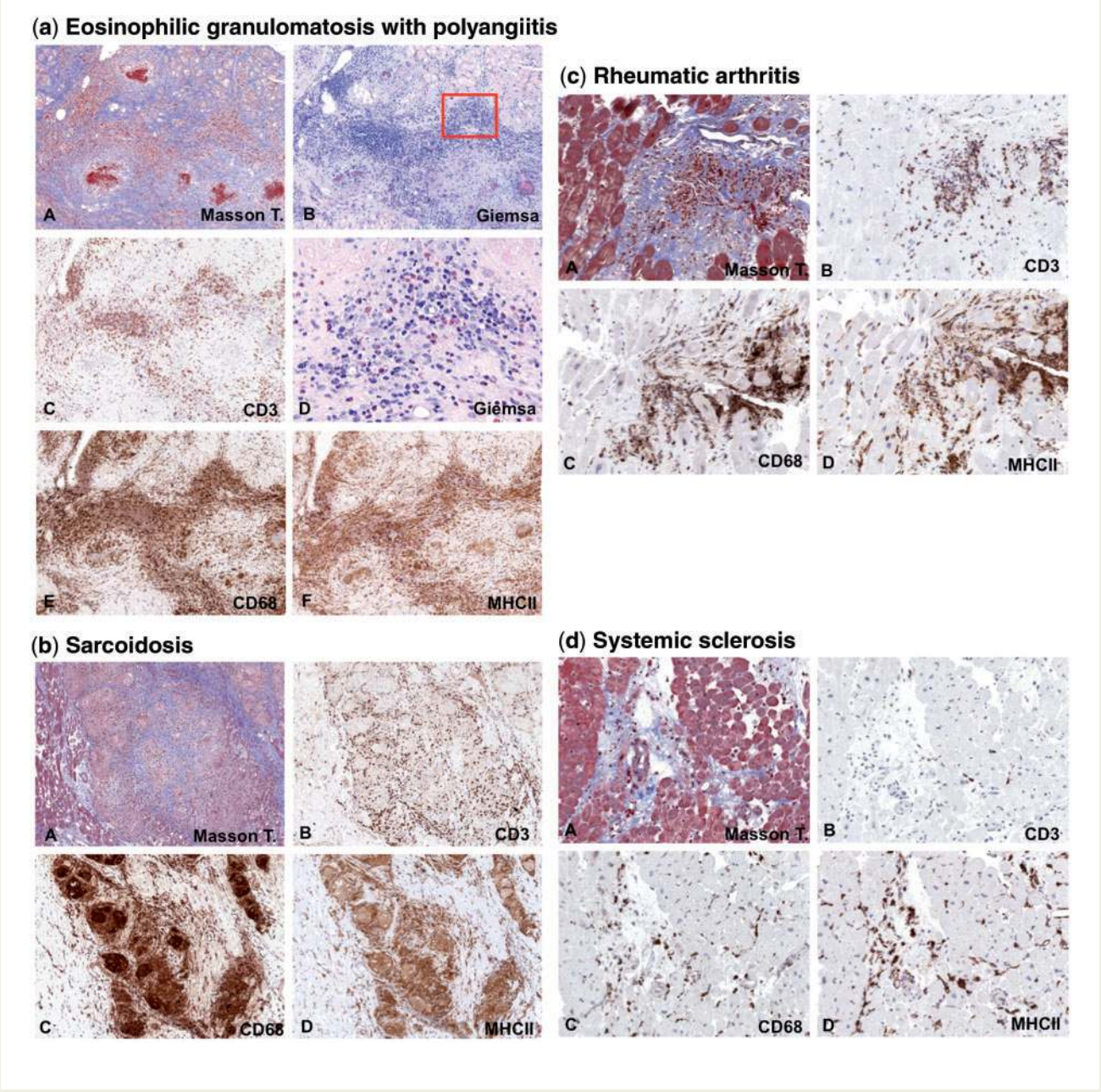

Figure 2 Endomyocardial biopsy examples of myocarditis in systemic immune-mediated diseases (SIDs). Typical examples of histologically and immunohistologically proven myocarditis in different SIDs [eosinophilic granulomatosis with polyangiitis, EGPA (**a**, ×100), sarcoidosis (**b**, ×100), rheumatoid arthritis, (**c**, ×200) and systemic sclerosis, SSc (**d**, ×200)]. 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**) 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.

(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.[60] It should not be done routinely but only

if clinical suspicion of cardiac symptoms and/or signs, e.g. dyspnea, develop.[60]

General principles of management of myocardial involvement in systemic immune-mediated diseases

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.[61] 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.[16,48,62–73]

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.[74] 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

Heart involvement in SLE is common (more than 50% of the patients) and may affect any heart structure (see Supplementary material online, *Table S3*).[75] SLE myocarditis, which may be associated with mutations in the gene encoding the 3′-5′ DNA exonuclease TREX1,[76,77] had an autopsy frequency of up to 8% in the era of corticosteroids and chloroquine and hydroxychloroquine use.[74] 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 (see Supplementary material online, *Table S4*).[78,79] The pathogenesis of SLE myocarditis is thought to be immune complex-mediated, with granular complement and immunoglobulin deposits seen at autopsy and on EMB. Non-invasive diagnostic red flags include an unexplained increase in troponin I and/or NT-pro BNP,[80] 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.[80] 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.[79,81] 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).[62] SLE patients are at high risk of infection due to the disease itself, which may be associated with primary immunodeficiency[82] and to immunosuppressive treatment, leading to secondary immunodeficiency. Thus, ruling out infectious myocarditis by EMB may be clinically useful.[22]

Recommendation

(1) 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.[22,82]

Systemic sclerosis

Heart involvement in SSc may be primary or secondary to concomitant kidney and/or pulmonary vascular/interstitial disease (see Supplementary material online, *Tables S5* and *S6*).[83] 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,[84] but it can also be due to a primary systemic myositic disease.[85] Left ventricular systolic dysfunction (LSVD) is the 'hallmark' of primary SSc myocardial involvement.[86] 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).[87,88] Left ventricular diastolic dysfunction (LVDD) is common[87,88]; 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%).[89] Twenty-four hour-ECG Holter monitoring may detect supraventricular and/or ventricular arrhythmias; QTc prolongation may be associated with life-threatening tachyarrhythmias.[90] SSc is perceived as having a high arrhythmic burden, with a 5% sudden death rate in patients with both skeletal and cardiac muscle disease.[91] Clinical and non-invasive myocarditis red flags are similar to those seen in SLE, including unexplained increased (more than 3 fold) CPK or troponin,[92] LVSD and/or LVDD,[86–88] non-ischaemic abnormal CMR tissue patterns.[66] Autoimmune myocarditis (*Figure 2*) should be managed by immunosuppressive treatment,[22,62–65] while

heart failure, arrhythmia, and conduction disturbances should be treated according to current ESC guidelines.[60,93]

Recommendation

(1) Referral to a cardiologist for further diagnostic workup is indicated at any time in the screening of SSc patients, if myocardial involvement is suspected based upon clinical and non-invasive diagnostic findings.[22,63–66,85–90,92]

(2) EMB may be considered in patients with clinically suspected myocarditis; immunosuppressive treatment is indicated in EMB-proven infection-negative myocarditis.[22,63,66,85]

Sarcoidosis

Sarcoidosis is a multisystem disorder of unknown cause(s), frequently presenting with hilar lymphadenopathy, pulmonary infiltration, ocular and skin lesions, mainly occurring in the 2nd to 5th decade (see Supplementary material online, *Table S7*).[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 with 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 (see Supplementary material online, *Table S8*). 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 (see Supplementary material online, *Table S8*) (*Figure 3*). 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 (see Supplementary material online, *Table S9*).

Recommendation

(1) 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]

(2) Corticosteroids are the first line treatment.[16,48] Other immunosuppressive drugs may be valid alternatives (see Supplementary material online, *Table S9*).[16,48]

(3) 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]

(4) 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 (formerly Churg-Strauss syndrome)

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare eosinophilic-rich and necrotizing granulomatous vasculitis often involving the respiratory tract and predominantly affecting small to medium vessels (see Supplementary material online, *Table S10*).[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 (see Supplementary material online, *Table S10*).[98,99] EGPA belongs to the spectrum of ANCA-associated vasculitides (AAV), although ANCA frequency (30–40% of cases) is lower than in other AAV.[18,67,99] 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* and *3*).[18,68] In eosinophilic EGPA associated myocarditis (*Figure 2*), long-term prognosis is poor,[17] leading to a restrictive cardiomyopathy or DCM,[17,68] 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.[18,68] Tissue characterization by CMR may show features suggestive for myocarditis and myocardial fibrosis (*Figure 3*). Coronary

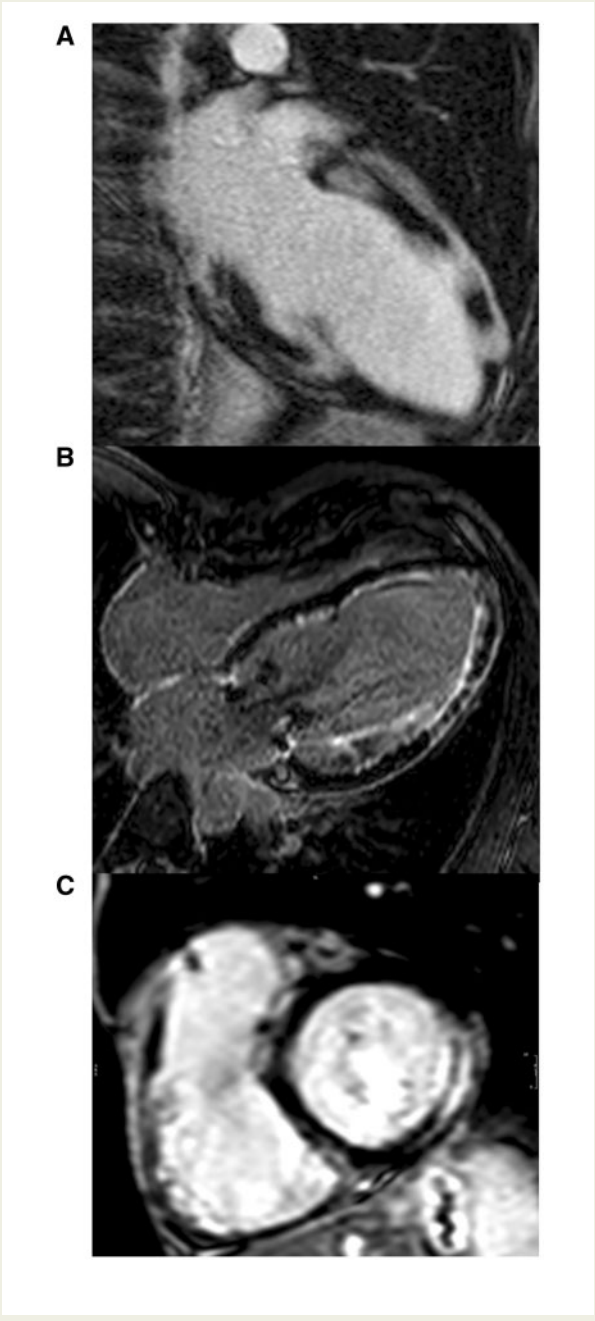

Figure 3 Cardiac magnetic resonance (CMR) findings in systemic immune-mediated diseases (SIDs). (Top, panel *A*) Late gadolinium enhanced CMR of a 38 year old patient with cardiac sarcoidosis. The images show the typical pattern of multiple focal areas of enhancement throughout the heart consistent with granulomatous infiltration. (Middle, panel *B*) Late gadolinium enhanced CMR of a 54 year old patient with eosinophilic granulomatosis with polyangiitis. 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 rheumatoid arthritis. There is mid-myocardial enhancement in the basal infero-lateral wall as a unspecific sign of previous myocarditis.

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.[68] Diagnostic workup 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.[67,68]

Recommendation

(1) Red flags and cardiological diagnostic methods are identical to those of other SIDs.[17,68,99] Heart involvement is typically associated with high eosinophilic counts and negative ANCA status.[18,68]
(2) The diagnosis of EGPA myocarditis may reinforce the indication to immunosuppression.[67,68]

Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)

Granulomatosis with polyangiitis (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 (see Supplementary material online, *Table S11*).[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

(1) 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

Inflammatory myopathies (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 [69,106,107] 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[69,109–111] and is a negative prognostic factor.[110,70,111] Red flags and cardiological diagnostic methods are identical to those in clinically suspected myocarditis in other SIDs.[69,106,107,111] Myocardial ischaemia (due to coronary vasculitis), pericardial or valve disease may also occur.[107] Cardiovascular mortality ranges from 5 to 17%, most frequently caused by myocardial infarction, heart failure and myocarditis.[107] Myocarditis seems to respond to an intensification of standard immunosuppression.[70,107,109–111]

Recommendation

(1) 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.[70,107,109–111]

Rheumatoid arthritis

Rheumatoid arthritis 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 2*).[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 3*).[46]

Recommendation

(1) 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

Spondyloarthritis (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

Myasthenia gravis (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.[71] 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).[71] 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.[72,73]

Recommendation

(1) 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]

(2) Myasthenia gravis patients with GCM myocarditis should be promptly treated with adequate immunosuppression according to the patient's age and the clinical condition.[22,72,73]

Primary Sjögren syndrome

Primary Sjögren syndrome (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

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

Autoinflammatory diseases

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 titre AAbs or antigen-specific T cells (*Figure 1*, Supplementary material online, *Table S12*).[133] Complications include severe inflammatory anaemia and AA amyloidosis, which usually does not affect the heart.[133]

Non-hereditary 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]

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

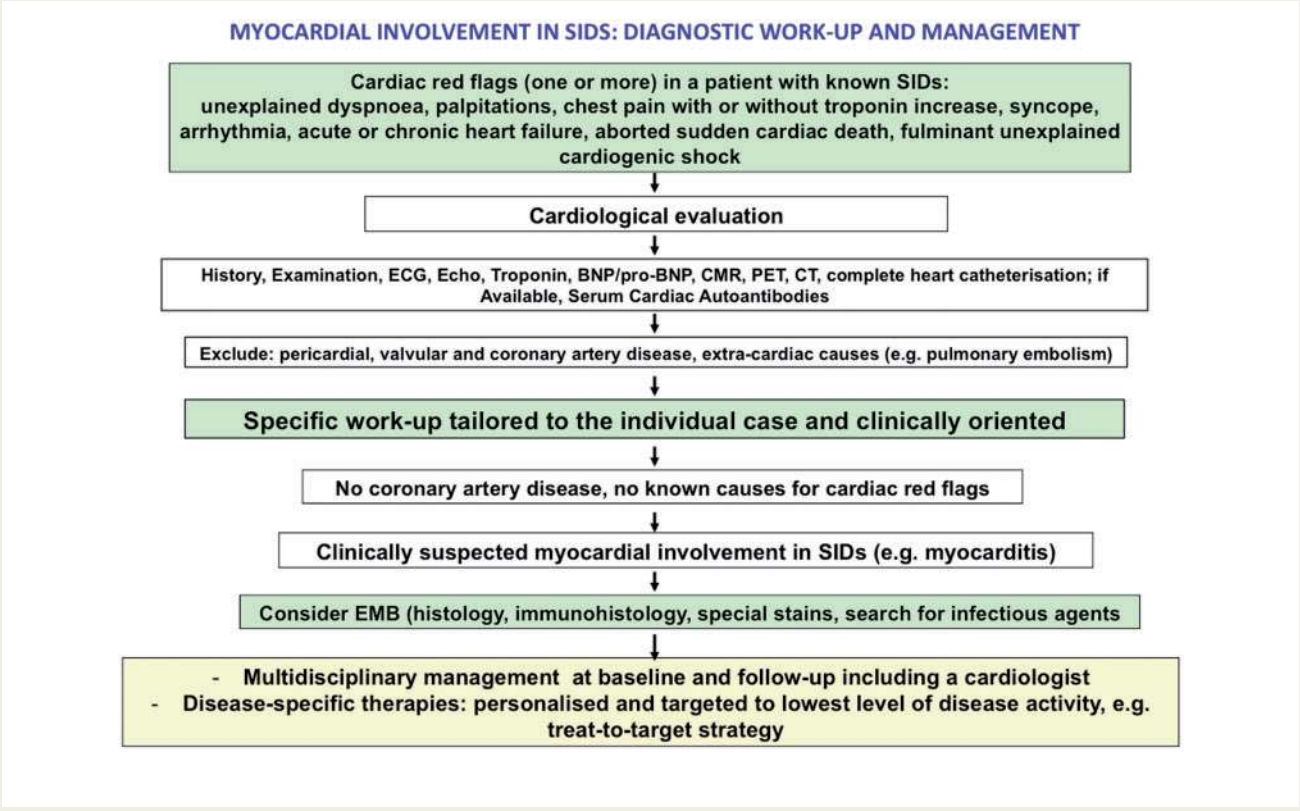

Figure 4 Myocardial involvement in SIDs: diagnostic workup and management. CMR, cardiac magnetic resonance; CT, computed tomography; EMB, endomyocardial biopsy; SIDs, systemic immune-mediated diseases.

been reported in association with Crohn's disease and Behçet's disease.[136,137]

Recommendation

(1) Myocarditis, although uncommon, should be suspected in some non-hereditary 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 cardiological screening and follow-up in patients with clinically suspected cardiac involvement (*Summarizing Figure 4*). It is hoped that this document will provide a first orientation to cardiologists and non-cardiology physicians in selecting an appropriate multidisciplinary diagnostic workup 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.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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CARDIOVASCULAR FLASHLIGHT

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'Pericarditis intestinalis': a rare complication of esophageal resection

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A 57-year-old patient presented 6 months after a thoracolaparoscopic Ivor Lewis esophageal resection for T3N1M0 esophageal adenocarcinoma after neoadjuvante chemoradiotherapy, at our surgical unit with acute abdominal pain and vomiting. An intestinal obstruction was suspected.

The cardiologist was consulted pre-operatively, as he had a history of acute anterior infarction, and his pain radiated to his chest with positive cardiac markers. Acute coronary syndrome was unlikely, but could not be fully excluded.

We found an ECG typical for pericarditis. Echocardiography revealed a fluid collection with pocket formation within the pericardial cavity [*Figure 1*, *Panel A* (see Supplementary material online, *Video clip 1*)]. There were no signs of tamponade and wall motion abnormalities were absent. As the origin of the pocketed fluid collection remained unclear computed tomography of the thorax and abdomen was performed (*Figure 1*, *Panel B*), which revealed intrathoracic intestinal herniation of the small bowel.

The patient was immediately taken into the operating room for laparoscopic exploration. The surgeons found intestinal herniation of the small bowel into the thorax, and into the pericardial cavity. Twenty centimetres of short bowel was withdrawn from the pericardial cavity [(*Figure 1*, *Panels C* and *D* (see Supplementary material online, *Video clip 2*)]. Most likely, this case of herniation of the short bowel into the pericardium appeared to be a rare complication of the patient's previous transthoracic esophageal resection, during which the pericardium had accidentally been opened due to post-radiotherapy adhesions of the esophagus to the pericardium.

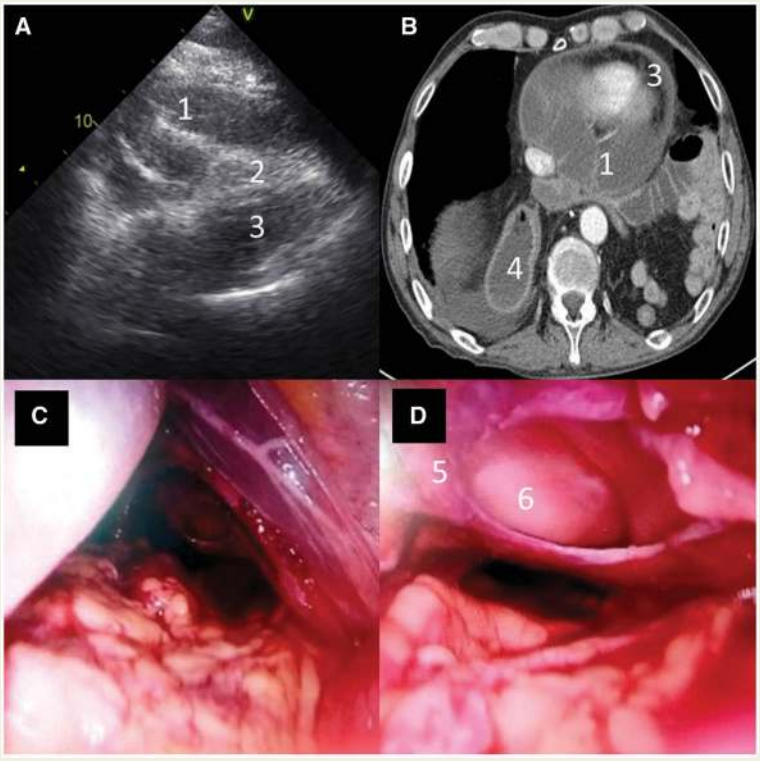

Figure 1 Panel A: Cardiac ultrasound, subcostal view. (1) pericardial cavity with small bowel, (2) right ventricle, and (3), left ventricle. Panel B: Cardiac tomography, axial view. (4) dilated esophagogastric anastomosis. Panel C: Video 2 still image. Per-operative view. Panel D: Video 2 still image. Per-operative view, detailed. (5) pericard and (6) heart.

The protruded small bowel segment appeared to be necrotic, was resected and a side-to-side anastomosis was performed. Post-operative recovery was uncomplicated.

Supplementary material is available at *European Heart Journal* online.