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Sarcoidosis – a multisystem disease

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Summary

Sarcoidosis is a systemic inflammatory disease, characterised by granuloma formation upon an unknown trigger in genetically predisposed individuals. The inflammation is characterised by an activation of both the innate immune system, with macrophages differentiating into epitheloid cells and dendritic cells, and the adaptive immune system, particularly T helper (Th) 1 and Th17 cells. Since all organs can be affected to varying extents, clinical presentation is often diverse. Most commonly, the lungs, lymph nodes, skin and eyes are involved, whereas cardiac, renal and neurological manifestations are less common but associated with higher morbidity. Depending on the clinical symptoms, a detailed evaluation including thorough clinical examination, imaging and laboratory tests should explore all possible organ involvements. In some patients, fatigue manifests as a para-sarcoidosis symptom impacting quality of life, even if sarcoidosis is in remission.

Some acute syndromic presentations, such as Löfgren's syndrome, have a good prognosis and are commonly self-limiting. If possible, a topical treatment, for example for cutaneous sarcoidosis or bronchial involvement, should be applied. Treatment of severe cases with persisting disease activity necessitates long-term immunosuppressive drugs, with glucocorticoids as the first-line option. Steroid-sparing and second-line drugs include methotrexate, azathioprine, mycophenolate mofetil and immunomodulators such hydroxychloroquine, with the latter being first-line therapy in cutaneous sarcoidosis. Tumour necrosis factor-alpha inhibitors (particularly adalimumab and infliximab) are used as third-line agents but are administered earlier in cases of persistent disease activity, severe organ-involvement or intolerance to conventional drugs. Treatment decisions should be based on a multidisciplinary approach, depending on organ involvement and treatment tolerability. Para-sarcoidosis manifestations, particularly fatigue, should also be carefully addressed, where the patient could also be enrolled in multidimensional rehabilitation programmes.

With various organ involvement and different phenotypes, larger studies including real-world data from registries are necessary to evaluate different sarcoidosis endotypes and preferential treatment pathways.

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Introduction

Sarcoidosis is a systemic inflammatory disease, characterised by granuloma formation upon an unknown trigger. Innate and adaptive immune response in genetically predisposed individuals has been associated with its pathogenesis [1] .

Pulmonary involvement is the most common manifestation in sarcoidosis, although all organs can be affected, with several distinguishable clinical phenotypes. The disease course can vary significantly (table 1), ranging from spontaneous recovery, through chronic active inflammation to a post-inflammatory state, eventually resulting in an irreversible impairment of organ function such as pulmonary fibrosis, congestive heart failure or renal failure. In addition, quality of life is often substantially compromised ow-

ing to direct organ damage, but also because of sarcoidosis-associated comorbidities, of which fatigue has been increasingly recognised and investigated in recent past years [2].

The incidence of sarcoidosis is variable, depending on age, gender and ethnicity, with seasonal and geographic variations, indicating the possible influence of environmental factors such as microorganisms or inorganic materials in genetically predisposed individuals, carrying certain human leucocyte antigen (HLA) variants.

The formation of non-necrotising epithelioid cell granulomas, which are surrounded by activated T helper 1 (Th1) and Th17 cells suggests that specific antigens trigger an inflammatory process. Interestingly, in multiple individuals with sarcoidosis, identical $CD4^+$ T cell receptor (TCR) repertoires, so called public TCRs, have been found. These T cells recognise the specific sarcoidosis-associated epitopes in the context of HLA-DR3 [3, 4]. Thus, these public TCRs could explain how similar (public) T cell responses are triggered in multiples individuals by certain antigens and lead to a sarcoidosis phenotype.

Histological confirmation should be sought whenever possible to strengthen diagnosis and exclude differential diagnoses such as infection or cancer. Assessments include laboratory, imaging and organ-specific investigations (table 2). Recent diagnostic approaches, such as ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET), cardiac magnetic resonance imaging (cMRI), detection of perfusion deficits in the myocardium with 13N-ammonia or ^{82}Rb PET, allow early diagnosis and risk stratification. Although data are still limited, certain HLA types are associated with a self-limiting, rather than a chronic, course and could add information towards risk stratification. Finally, based on more diagnostic possibilities, a more personalised therapeutic approach can be pursued, leading towards a tailored selection of immunosuppressive treatment in selected cases, including glucocorticoids (GCs) and steroid-sparing agents such as azathioprine, methotrexate, leflunomide, hydroxychloroquine, mycophenolate mofetil and biologicals such as tumour necrosis factor-alpha (TNFα) inhibitors (TNFis).

The awareness that sarcoidosis is recognised increasingly as an inflammatory, systemic granulomatous disease, requires also the inclusion of a multidisciplinary team if multi-organ involvement is suspected.

Epidemiology

The incidence and prevalence of sarcoidosis vary across geographical regions, age, sex and ethnicities [5–7]. The highest incidence is found in Scandinavian countries (11–24 cases per 100,000 individuals per year) [8–10] and African Americans (18–71 cases per 100,000 individuals per year) [11-13], and the lowest incidence is found in Asian countries (1 case per 100,000 individuals per year) [14–16]. The incidence in Switzerland was reported to be 7

Table 1:
Organ involvements and symptoms in sarcoidosis.

Organ	Possible related signs and symptoms	Prevalence
Lung	Cough, wheezing, stridor, dyspnoea, chest pain	80–90%
Lymph nodes	Lymphadenopathy, pain	90% hilar/paratracheal/mediastinal, 40% in the periphery
Eyes	Red eye, pain, vision loss	25–50%
Skin	Mild to moderate tender, itchy, papules, nodules, plaques, subcutaneous nodules, infiltrated scars and tattoos, lupus pernio, erythema nodosum	Up to 25%
Liver	Abdominal pain and elevated liver enzymes	Up to 20%
Nervous system	Cranial mononeuropathy (facial palsy, visual loss,trigeminal neuralgia, hearing loss, vertigo), gait abnormality, headache, seizure, weakness, numbness, paraesthesia, paresis, fatigue	510% (facial palsy up to 50%)
Arthropathy	Pain, tenderness, stiffness, swelling, dysfunction, inflammation, warm erythematous skin, weakness	Up to 15%
Muscle	Usually asymptomatic; could also involve diaphragm or extraocular muscles	Up to 10%
Heart	Pain, arrhythmias, conductance disturbances, dyspnoea, syncope, fatigue	27%, in post-mortem studies up to 83%
Spleen	Abdominal pain, swelling	Up to 6%
Kidney	Decreased renal function (reduced eGFR) due to interstitial nephritis, hypercalcaemia or nephrocalcinosis; flank/abdominal pain due to nephrolithiasis; interstitial nephritis (urinalysis normal or displaying sterile pyuria or mild tubular proteinuria, rarely haematuria or glycosuria); sarcoidosis patients may present with glomerulonephritis although causal relationship to sarcoidosis has not been proven	Nephrocalcinosis about 5%, interstitial nephritis about 20%
Exocrine glands (parotid and salivary)	Sicca syndrome, xerostomia	About 5%
Bone and bone marrow	Pain, tenderness, and sometimes swelling; cytopenia (anaemia, leukopenia, lymphopenia)	About 5%
Gastrointestinal tract	(Apart from liver) most commonly oral cavity and stomach, rarely oesophagus, small intestine, appendix, colon, rectum, pancreas, peritoneum	About 1%
Upper respiratory tract (laryngeal and sinonasal)	Dysphagia, dyspnoea, cough, stridor and hoarseness. Nasal obstruction / crusting / polyps, anosmia, epistaxis	About 1%
Parasarcoidosis symptoms	Fatigue, sleep disturbances, cognitive deficits. hypercalcaemia, hypercalciuria	Up to 70%. Up to 20% and 40%, respectively

eGFR: estimated glomerular filtration rate

per 100,000 individuals per year with a higher regional occurrence in areas with metal industry and intense agriculture, especially production of potatoes, artificial meadows and bread grains [17].

The average age of onset is 40–55 years, with a peak in younger men between the ages of 30 and 50 years and middle-aged women between 50 and 60 years of age, without gender predilection [15, 18, 19]. African American ethnicity and low income are associated with more severe disease at diagnosis [20–22].

Risk factors

Genetic susceptibility has been shown in genome wide association studies with several HLA risk alleles predisposing for prognostic outcome [23, 24]. For example, DRB1*01 and DQB1*0501 seem to be protective, whereas DRB1*12 and *14 are associated with lung involvement [25]. Also, non-HLA different risk variants, for example in *BTNL2*, have been associated with sarcoidosis [26], and shown in Japanese [27] as well as British or Dutch [28] patients. However, sarcoidosis will occur in these susceptible individuals only if an external trigger is present, which activates the immune system. Since lung involvement is the most prevalent manifestation of sarcoidosis, inhalational exposure is a possible driving cause. Several studies have investigated associations between occupational exposures and sarcoidosis [17, 29]; for example an association in New York City Fire Department rescue workers after 09/11 has been suggested [30]. On the other hand, cigarette smoking and oestrogens, possibly due to immunomodulatory effects, are associated with lower risk of developing sarcoidosis [1].

Pathogenesis

Granuloma formation occurs to isolate potentially non-degradable antigens, such as pathogenic organisms such as certain *Mycobacterium* spp. or inorganic particles. In addition, granulomas may form as a result of drug reactions (interferon, immune checkpoint inhibitors, BRAF inhibitors, TNFis, antiretroviral therapy or immune reconstitution,), or due to potential self-antigens such as vimentin [31–34]. It is important to note that these peptide remnants, particularly from bacteria or viruses (e.g., mycobacterial catalase–peroxidase [KatG], superoxide dismutase, early-secreted antigenic target of 6 kDa [ESAT6] or heat-shock proteins), are seen as an initial and temporary trigger for the immune reaction rather than being continuously present [35–42].

Epithelioid non-necrotising granulomas (fig. 1) represent the pathological hallmark of sarcoidosis with an innate immune response characterised by activated macrophages (transforming into epithelioid cells fusing into giant cells) and dendritic cells. This fosters an adaptive immune response with a polarisation towards Th1 and Th17 cells and

Table 2:
Diagnostic approach for minimum organ screening assessment.

Diagnostic approach	Measures
Medical history	Environmental and occupational factors (dust, beryllium, etc.), comorbidities, medication (current and former), family history of sarcoidosis
Symptom evaluation	All organ systems: particularly lungs, heart, central nervous system, eyes and skin
Physical examination	
Laboratory (minimal screening)	Differential blood count, liver (AP, γGT) and kidney (creatinine, eGFR) values, serum calcium, 25- and 1,25-OH vitamin D (calcidiol, calcitriol), total IgG (incl. subclasses), IgA, IgM, CRP
	Sarcoidosis-associated biomarkers: ACE, sIL-2Rα, neopterin
	Urine: urine sediment, urine calcium/24 h, calcium/creatinine, urine protein/creatinine and albumin/creatinine ratios
	Microbiology: IFNγ release assay, e.g., QuantiFERON-TB Gold®
Possible laboratory assessments in certain clinical settings (not mandatory)	CK, SAA, ESR, protein electrophoresis and further cytokines like TNFα or IL-17
	HLA typing
Specific organ assessment	
Heart	Screening: ECG, 24h-ECG, echocardiography
	In symptomatic patients or suspicion of cardiac involvement: troponin T, pro-BNP. cardiac MRI and cardiac PET-CT
Eyes	Ophthalmological work-up
Lungs	High-resolution chest CT, spirometry, plethysmography, DLCO.
	Bronchoscopy with BAL and histological confirmation in case of positive CT findings (or at the place lowest invasive burden, see text)
	In symptomatic individuals: cardio-pulmonary exercise testing / 6-minute walking test
Abdomen / lymph nodes	Sonography
In the case of symptoms or suspicious organ involvement	
Skin	Biopsy
Kidney	Ultrasound or abdominal CT (highly sensitive for nephrocalcinosis or nephrolithiasis), renal biopsy
CNS	In the case of symptoms, cranial and spinal MRI, lumbar puncture (cerebrospinal fluid analyses: cell count, protein, immunoglobulins, oligoclonal band, ACE, sIL-2R, CD4/CD8 ratio)
Joints	Rheumatological referral, possibly ultrasond, MRI, puncture
Exocrine glands	Sonography, sicca assessment (e.g., sialography), Schirmer's test
Hypothalamic-hypophyseal system	Endocrinologist referral

ACE: angiotensin converting-enzyme; AP: alkaline phosphatase; BAL: bronchoalveolar lavage; CK: creatine kinase; CRP: C-reactive protein; CT: computed tomography; DLCO: diffusing capacity of lung for carbon monoxide; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; γGT: gamma-glutamyltransferase; HLA: human leucocyte antigen; Ig: immunoglobulin; IFNγ: interferon gamma; IL: interleukin; MRI: magnetic resonance imaging: PET: positron emission tomography; pro-BNP: pro-B-type natriuretic peptide; SAA: serum amyloid A; sIL-2Rα: soluble interleukin-2 receptor alpha; TNFα: tumour necrosis factor-alpha

increased production of interferon-γ (IFN) and interleukin (IL)-17, as well as TNFα, IL-12, IL-18, IL-6, transforming growth factor β and IL-10. The activation of the Janus kinase (JAK)–STAT signaling pathway by INFγ for STAT1 has been shown in peripheral blood, lung tissue and lymph nodes of sarcoidosis patients [43–46] and IL-17 for STAT3 [47]. Additionally, activation of mechanistic target of rapamycin complex 1 (mTORC1) in progressive disease [48] and Toll-like or NOD-like receptors (TLRs, NLRs) have been associated with innate immune activation [49]. Maintenance and progression of granuloma formation can lead to chronic inflammation and tissue fibrosis.

Abundance of TCR-restricted, for example TRAV2.3$^+$, T cells in bronchoalveolar lavage (BAL) fluid of HLA-DR3$^+$ patients is associated with a good prognosis in Löfgren's syndrome [50, 51]. Vimentin-specific TRAV2.3$^+$ TRBV22$^+$ T cells and production of anti-vimentin antibodies have been found in BAL of sarcoidosis patients [52, 53]. Increased production of serum amyloid A by macrophages and its accumulation in granulomas could provide an additional mechanism for Th1 activation and disease progression in the absence of a microbiological trigger [36].

The immune activation is accompanied by impaired regulatory T cell-mediated immune controls [1] and their survival [54]. TNF receptor-2 positive (TNFR2$^+$) regulatory T (Treg) cells and soluble TNFR2 were also shown to be elevated in sarcoidosis patients with higher levels correlating with treatment response [55]. Additionally, in Löfgren's syndrome, higher levels of Tregs were found, which could explain its self-limiting course [56].

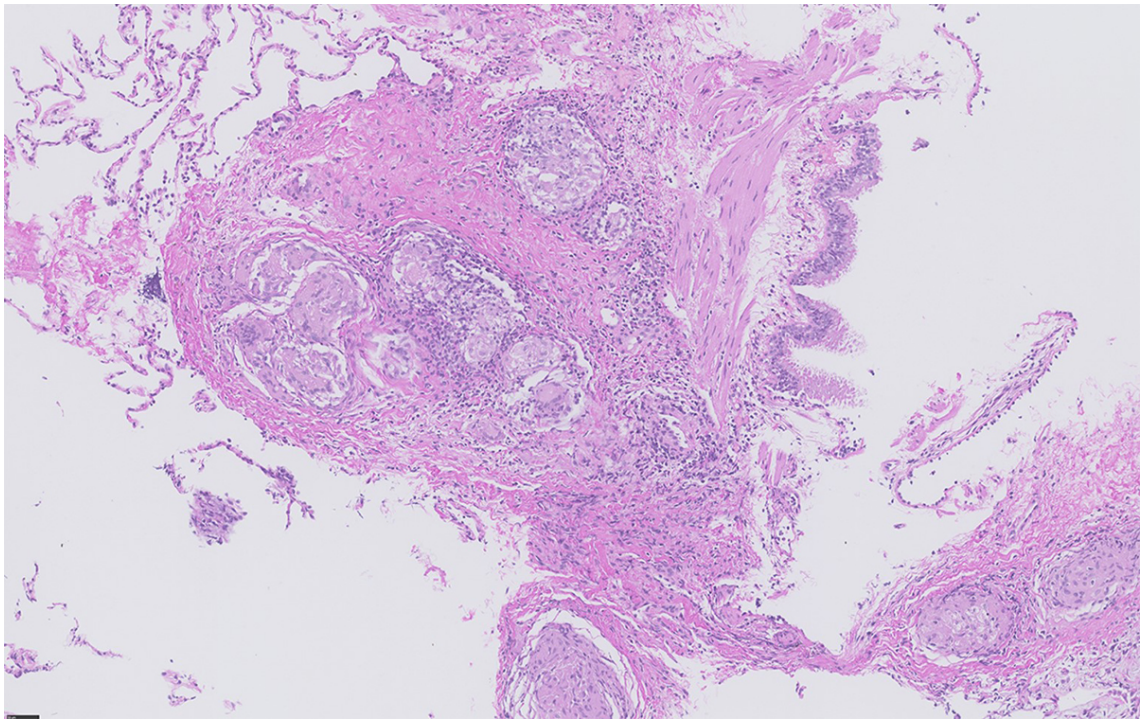
Clinical presentation

Sarcoidosis is a multisystem disease, which may present with a broad range of symptoms, over various time-points, and organ manifestations (see table 1). It can be defined by onset (acute or gradual), disease course (self-limiting, chronic-stable or chronic-progressive) and major organ involvement. The most severe and potentially life-threatening organ manifestations include pulmonary, cardiac and neurological sarcoidosis. The disease resolves within approximately two years in 50% of patients. Conversely, full remission is less probable after a disease course of five years [57].

Pulmonary sarcoidosis includes involvement of the lungs and/or mediastinal/hilar lymph nodes and is the most common manifestation, affecting 80–90% of sarcoidosis patients. Clinical presentation includes cough, dyspnoea, and chest pain, which can be accompanied by fatigue, weight loss, fever and malaise [58]. The classification by John 'Guy' Scadding based on chest radiography is still in use and associated with a prognostic value [59]. However, there are several limitations of this system, such as lack of information on disease severity due to extrapulmonary involvement or on the risk of progression [1]. Lung function test findings are highly nonspecific, since pulmonary sarcoidosis can present with obstructive, restrictive, mixed or normal patterns, but are important tools for disease severity assessment, treatment indication and response. Interstitial lung disease (ILD) is typically present in Scadding stages 2, 3 and 4, ranging from subclinical manifestations to end-stage pulmonary fibrosis (stage 4). The latter is irreversible organ damage, whereas mild to moderate ILD due to sarcoidosis is a potentially treatable and reversible condition (fig. 2).

Extrapulmonary manifestations occur in up to 30% of patients, and basically every organ can be affected including skin (about 25%), eye (about 25–50%), liver (about 20%), secondary lymphoid organs (lymph nodes 40% in the pe-

Figure 1: Transbronchial biopsy showing multiple non-necrotising granulomas situated in close proximity to the bronchial mucosa (bronchovascular distribution) (courtesy Dr Bart Vrugt, Cantonal Hospital Muensterlingen).



riphery, spleen about 6%), heart (2–7%), nervous system (5–10%), kidney (interstitial nephritis 20%, nephrocalcinosis 5%), arthropathy (up to 15%), muscle (up to 10%), exocrine glands (parotid and salivary, about 5%), bone marrow, gastrointestinal tract (about 1%) and upper airways (about 1%) [20, 60–62]. Manifestations vary based on gender, age and ethnicity, for example skin and eye involvements are more common in African Americans [63].

Ocular sarcoidosis is found in 25–50% of cases [64]. The most frequent ocular manifestation is uveitis. Although anterior uveitis occurs more frequently, the presence of intermediate or posterior uveitis often decreases visual prognosis [64]. It can be the first sign in 20% of sarcoidosis cases and may precede pulmonary manifestations by several years. Almost all parts of the eye, adnexa and orbit may be affected by granulomatous involvement, which is usually bilateral [65].

Cutaneous involvement is seen in up to 25% of patients, often presenting with papules and plaques, followed by subcutaneous nodules, scar or lupus pernio and plenty of rare manifestations resembling other diseases. These manifestations show non-caseating granulomas in histology. Erythema nodosum is the most common nonspecific cutaneous lesion, characterised as a reactive process without granuloma formation, and associated with a good prognosis. Treatment indication depends on symptoms and cosmetic disfigurement, usually beginning with topical treatments (mainly glucocorticoids), which can be extended to systemic treatments in refractory cases [66, 67].

Cardiac sarcoidosis is a rare but potentially life-threatening manifestation, which is observed in 2–7% of sarcoidosis patients and in up to 83% of cases in autopsy series [68–72]. Thus, it is assumed that a significant proportion of at least subclinical cardiac involvement is unrecognised. This applies also to other organs that are not routinely biopsied. According to unpublished data from several authors of this article (DF, JN, AK, JDS), a high prevalence of cardiac involvement (approximately 50%) can be observed in highly specialised sarcoidosis clinics, where modern imaging technologies may lead to detection of early cases and increased diagnostic yield in general. Cardiac involvement can result in ventricular arrhythmias, high-degree heart blocks or progressive heart failure due to myocardial granulomatous infiltration and/or fibrosis at a later stage of the disease (fig. 3). Symptoms include chest pain, palpitations, dizziness and syncope. As sudden cardiac death can occur in up to 25% of patients with cardiac sarcoidosis, an early diagnosis and appropriate treatment is crucial [73].

Neurosarcoidosis occurs in 5–10% of patients. Any level of the neuroaxis can be affected, which is reflected by the wide spectrum of symptoms (fig. 4) and varying disease severity. Whereas 10% of patients remain asymptomatic, one third to half of the patients with neurosarcoidosis exhibit more than one neurological manifestation [74]. Cranial nerve palsies occur frequently (50–70%), with (bilateral) facial nerve palsy being predominantly observed [75, 76], followed by involvement of the optic or vestibulo-

Figure 2: Axial chest computed tomography (CT) images of a 41-year-old female with histologically proven sarcoidosis. Upper panel: extensive, bilateral pulmonary consolidation along peri-bronchovascular bundle (blue arrow) and multiple micronodular changes in upper lobes. Lower panel: extensive mediastinal and bi-hilar lymphadenopathy (red arrow). Clearly less nodular changes in lower lobes (courtesy Dr D. Franzen, USZ).

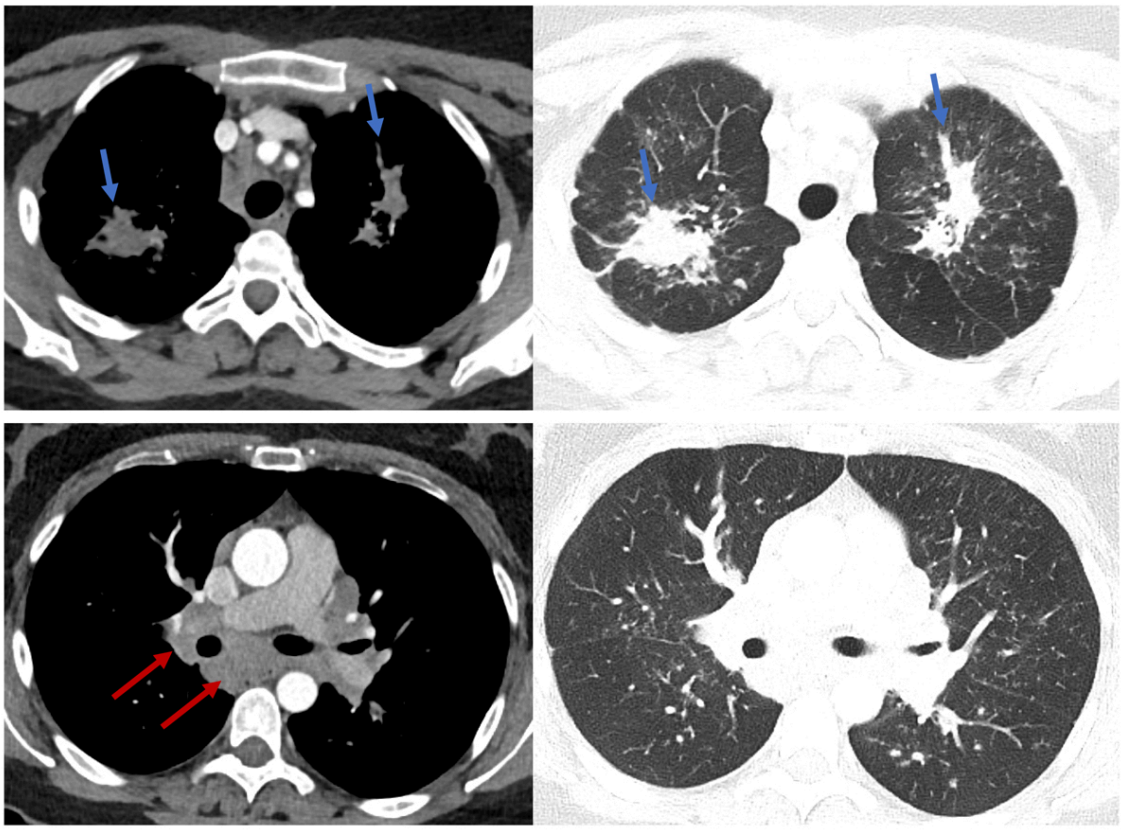
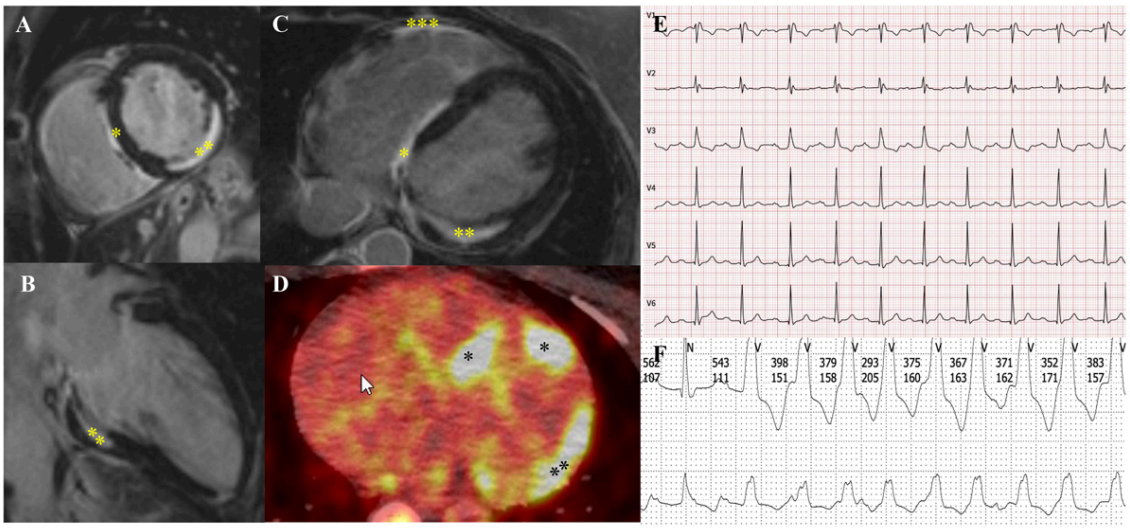


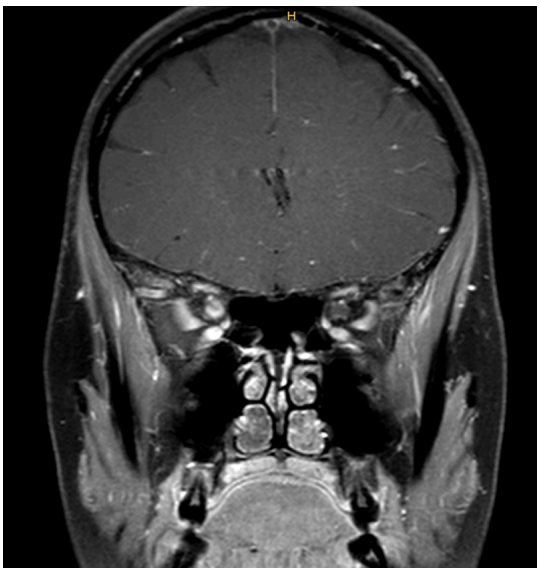
Figure 3: 51-year-old woman with sarcoidosis and cardiac involvement. A–C demonstrates myocardial fibrosis in the interventricular septum (*), inferolateral wall (**) and the right ventricle (***) on cardiac magnetic resonance imaging. D shows the corresponding cardiac FDG-PET/CT with mild inflammation of the septum (*) and the lateral wall (**). E: Her ECG shows a compromised conduction system with first degree atrioventricular block (PQ time 264 ms) and complete right bundle branch block. F: She had repeated nonsustained ventricular tachycardia on Holter monitor. With consideration of all findings together, she was recommended to undergo insertion of a two-chamber intracardiac cardioverter defibrillator for primary prophylaxis of sudden cardiac death (courtesy Dr C. Gruner, USZ).



cochlear nerves. If multiple nerves are affected a chronic course can be assumed, whereas isolated cranial neuropathies often resolve spontaneously. Aseptic meningitis (mostly affecting the basal meninges) ranks second to the most common manifestations, showing a considerable variety from asymptomatic to acute or chronic forms. Chronic granulomatous inflammation can impair cerebrospinal fluid (CSF) circulation leading to a hydrocephalus. The third most common manifestation is cerebral parenchymal infiltration, mainly involving the hypothalamus and the pituitary gland. As a result, neuroendocrine dysfunction can occur, including disturbances in appetite, thirst, temperature, sleep and/or libido [77]. Polyuria is usually caused by diabetes insipidus, which develops either centrally as a result of hypothalamic involvement or peripherally due to hypercalcaemia-related renal dysfunction [78]. Cortical involvement can cause cognitive or behavioural impairments, focal neurological deficits and seizures. Cognitive or behavioural disturbances were reported in up to 20% of neurosarcoidosis patients [79]. Encephalopathy can be caused by both vasculopathy or diffuse parenchymal inflammation. Granulomatous invasion of cerebral vessels is prevalent, though vascular complications such as ischaemic stroke solely occur [80, 81]. Cerebral mass lesions are also a rare finding. Compared with older reports, the emergence of MRI revealed a considerably higher involvement of the spinal cord [82], with lesions spreading over several segments of mostly the cervical and thoracic spinal cord [83]. In addition, radiculitis and cauda equina syndromes can occur. In later stages of the disease extracerebral manifestation can involve the peripheral nervous system (4–14% of the cases; including mononeuropathy, mononeuritis multiplex, and generalised motor, sensorimotor and sensory polyneuropathies) [84] and the muscles (sarcoidosis-related myopathy in 7–12% of the cases) [85].

Renal sarcoidosis occurs in up to one third of patients and can manifest in several ways [60, 86]. The most common is granulomatous interstitial nephritis leading to acute or chronic renal failure. Since this manifestation is clinically asymptomatic until severe renal failure occurs, it must be actively sought. Obstructive uropathy leading to abdominal/flank pain and/or deteriorating renal function is typically caused by nephrolithiasis, but may also be a consequence of retroperitoneal fibrosis or obstructing retroperitoneal lymph nodes. Chronic renal failure may also be a result of diffuse nephrocalcinosis caused by persistent hypercalciuria. Glomerular involvement is rare and, if present, may manifest with various degrees of albuminuria and glomerular haematuria.

Figure 4: Coronal T1-weighted magnetic resonance imaging scan of the brain showing contrast-media enhancement of the right optic nerve (arrow) in a 43-year-old woman who presented with progressive vision loss on the right. Meningioma was expected; however a biopsy showed non-necrotising granulomas leading to the diagnosis of neurosarcoidosis (courtesy Dr H. Hayward-Könnecke, USZ).



Para-sarcoidosis syndromes are not caused by organ-specific granuloma manifestations but result from release of mediators and can even persist after adequate treatment and disease remission. Post-sarcoidosis fatigue syndrome is one of the most challenging manifestations, as no specific treatment options exist and quality of life is severely affected. This is also the case for depression and cognitive impairment [87]. Clinically relevant in patients with systemic sarcoidosis is the development of a small-fibre neuropathy (in up to 70% of the cases). Apart from a painful hyper- or hypoaesthesia, life-threatening autonomic dysfunction, including cardiac arrythmia, can occur [88]. Hypercalcaemia (up to 20% of patients) and hypercalcuria (up to 40% of patients) are caused by extensive synthesis of calcitriol by activated macrophages increasing gastrointestinal calcium absorption and osteoclast-mediated bone resorption [89].

Sarcoidosis syndromes

Löfgren's syndrome is an acute form of sarcoidosis presenting with fever, bilateral ankle arthritis, and/or erythema nodosum and bilateral hilar lymphadenopathy [90]. It has a good prognosis with a remission in 70–80% of these patients [91].

Heerfordt's Syndrome is an extremely rare variant defined by uveitis, enlargement of the parotid and submaxillary salivary glands and paresis of the cranial nerves, particularly the facial nerve.

Differential diagnosis

Sarcoidosis is characterised by compact non-necrotising granulomas with a lymphangitic distribution along the bronchovascular bundle, interlobular septa and pleura. In open lung biopsies sarcoidosis is frequently associated with a granulomatous vasculitis without destruction of the vessel walls. During progression of the disease hyalinised fibrosis with remnants of granuloma dominate the picture. The main differential diagnoses are berylliosis and infliximab-induced granulomatous disease, especially because these entities are histologically indistinguishable from sarcoidosis. Other differentials include conditions associated with sarcoid-like disorders such as malignancies (lymphoma, carcinoma), collagen vascular diseases (systemic lupus erythematosus, Sjögren's syndrome, primary biliary cirrhosis, familial granulomatous arthritis), infections (human immunodeficiency virus, tuberculosis), vasculitis (granulomatosis with polyangiitis, Takayasu arteritis, giant cell arteritis), hypersensitivity pneumonitis, hard metal pneumoconiosis, IgG4-related disease and common variable immunodeficiency [33, 58, 92]. However, morphology and distribution of the granulomas in these diseases differ from sarcoidosis.

Infectious diseases such as tuberculosis, *Mycobacterium avium*, histoplasmosis, coccidiomycosis and Whipple disease demonstrate a peribronchial or random distribution of the granulomas and are frequently associated with necrosis. The application of special stains (Ziehl-Neelsen, auramin and silver stains] or polymerase chain reaction (PCR) tests for *Mycobacterium tuberculosis* complex and atypical mycobacteria help to identify the microorganisms. In contrast to sarcoidosis, hypersensitivity pneumonitis is characterised by loose aggregates of histiocytes in close proximity of the bronchiole. Granulomatosis with polyangiitis (formerly Wegener's granulomatosis) is characterised by basophilic, geographic necrosis surrounded by a cellular infiltrate containing giant cells. Nodular sarcoid granulomatosis, currently regarded as a variant of sarcoidosis, also shows extensive necrosis, which, in contrast to granulomatosis with polyangiitis, is eosinophilic, demarcated from numerous compact granulomas and accompanied by granulomatous vasculitis without destruction of the vessel walls. Differential diagnosis in the case of a neurological manifestation should be based on MRI findings (predominant periventricular, focal lesions vs parenchymal mass lesions or meningeal lesions). New MRI techniques increased sensitivity; however, due to the lack of specificity the spectrum of diseases to be considered is extensive. They range from autoimmune, inflammatory or idiopathic (e.g., multiple sclerosis, neuromyelitis optica spectrum disease, systemic lupus erythematosus, Sjögren`s syndrome, Behçet disease, primary central nervous system vasculitis) to infectious (e.g., tuberculosis, Lyme disease, neurosyphilis, toxoplasmosis) entities and neoplasms (primary central nervous system neoplasms, lymphomas and others).

Comorbidities

Sarcoidosis patients bear an increased risk of comorbidities, such as infections (hazard ratio [HR] 2.13, depending on immunosuppressive therapy) [93, 94], autoimmune diseases (Sjögren`syndrome: HR 11.6; ankylosing spondylitis: HR 3.8; systemic lupus erythematosus: HR 3.0; and autoimmune thyroiditis: HR 1.3) [93–95], cerebrovascular diseases (HR 3.3) [96], venous thromboembolism (HR 2–4) [97, 98], congestive heart failure (HR 1.7–2.7) [96, 99], and also cancer (skin: relative risk [RR] 2.00; haematological: RR 1.92; upper digestive: RR 1.73; colorectal: RR 1.33; liver: RR 1.79,;and kidney: RR 1.55) [100]. A Swiss analysis compared hospitalisations for sarcoidosis to hospitalisations for other causes and demonstrated an increased re-hospitalisation rate and significantly more comorbidities in sarcoidosis patients [101].

Mortality

The mortality of sarcoidosis is higher if patients have more severe disease manifestations at time of diagnosis. Overall, it ranges from 9–14 cases per 1000 person-years. The 5-year overall survival is estimated to be 93–95%. The mortality risk varies depending on gender and race, with a 2.4-fold increase in African American women [102–107]. A Swiss evaluation showed a significantly higher in-hospital mortality of sarcoidosis patients compared with age matched controls (2.6% vs 1.8%) with age being a risk factor [101].

Diagnosis

As sarcoidosis is a multisystem disease and shows varying courses, we recommend an interdisciplinary approach for a minimum organ screening assessment (see table 2). Organ involvement can change over time leading to new symptoms. Hence, follow-up examinations are highly recom-

mended and depend on disease severity and activity, symptoms and treatment (see below).

Histological confirmation should be sought in almost all cases, whenever possible [108], to foster diagnosis and exclude other causes of organ dysfunction, particularly those in which immunosuppressive treatment could cause an adverse outcome. However, a clinical diagnosis alone is sufficient in Löfgren's syndrome presenting with its pathognomonic triad of ankle arthritis, erythema nodosum and bi-hilar lymphadenopathy, or in Heerfordt's syndrome (see above) [109]. In principle, histological specimens should be sampled at the site with the lowest invasive burden and the highest chances for diagnosis – this is typically done via flexible bronchoscopy. Extrapulmonary biosampling, such as from the skin, parotid or lacrimal glands, palpable lymph nodes or conjunctival lesions, is also possible, but somewhat less specific. In any case, histology needs to be associated with compatible clinical and radiographic manifestations and exclusion of other diseases. If there is a histological confirmation at extrapulmonary sites and concomitant lung involvement with suspicion of infection, such as cavitary pulmonary disease, bronchoscopy may still be required to exclude infectious causes such as mycobacteria and fungi.

So far, no specific test for sarcoidosis exists. We recommend that minimum screening laboratory tests include differential blood count, liver (alkaline phosphatase [AP], gamma-glutamyltransrease [γGT] and kidney (creatinine, glomerular filtration rate [GFR]) tests, serum calcium, 25- and 1,25-OH vitamin D (calcidiol and calcitriol), total IgG including IgG subclasses, IgM, IgA, C-reactive protein (CRP) and sarcoidosis-associated biomarkers such angiotensin converting-enzyme (ACE), soluble IL-2 receptor alpha (sIL-2Rα) and neopterin. Urine assessment includes urine sediment, and calcium/creatinine, albumin/creatinine and protein/creatinine ratios.

Serum amyloid A A, erythrocyte sedimentation rate and certain cytokines such TNFα were found to be elevated and can be useful but are not widely available or performed. Certain centres perform HLA typing to assess risk alleles for potential major organ involvement. For example, *DRB1 *0803* is associated with increased risk for developing cardiac or neurosarcoidosis [25]. Furthermore, interferon-γ release assay (e.g., QuantiFERON-TB GOLD®) to exclude a (latent) *M. tuberculosis* infection and serological testing of *Histoplasma* and *Coccidioides* infection can be potentially useful and should be considered during initial diagnostic work-up [110].

Since the lung is affected in most cases, bronchoscopy serves as a safe and minimally invasive procedure (table 2). There are several diagnostic procedures during a bronchoscopy with different diagnostic yields, indications, and risks, including endobronchial (mucosa) biopsy, transbronchial lung biopsy (TBLB), transbronchial needle aspiration (TBNA) of hilar/mediastinal lymph nodes and bronchoalveolar lavage (BAL). The latter is the least invasive procedure, but the exclusive finding suggestive of sarcoidosis, with lymphocytosis and an increased $CD4^+/CD8^+$ T cell ratio (>3.5), has a low sensitivity of 54% [111] but a high specificity of 94–96% [112]. Therefore, BAL fluid analysis is only a supportive finding in addition to other bronchoscopy biopsy techniques. Endobronchial ultrasonography-guided transbronchial needle aspiration (EBUS-TBNA) is an elegant way to provide samples from hilar/mediastinal lymph nodes with a diagnostic yield of up to 79% (sensitivity 84%, specificity 100%), depending on the skill level of the operator [111, 113]. In the case of radiologically evident involvement of lung parenchyma (ILD), escalation to TBLB (including cryobiopsies) can be added. Using a combination of EBUS-TBNA, mucosal biopsies with BAL and/or TBLB with cryobiopsies, the diagnostic yield can be increased to 93–100% [114, 115].

Pulmonary function testing (spirometry, body plethysmography and CO-diffusion) and high-resolution CT (HRCT) are the preferred methods for the assessment of pulmonary involvement and its severity, as well as treatment response (table 2) [116]. HRCT is superior to conventional chest X-ray as it better defines the extent of parenchymatous involvement and fibrosis [117]. However, in some cases, such as Löfgren's syndrome, a chest X-ray may still be sufficient.

Additionally, we recommend ECG, 24-hour ECG and echocardiography, as well as abdominal and lymph node sonography for initial minimum organ screening assessment (table 2).

In the case of clinical signs suggestive of other organ involvement, specific further assessments should be evaluated (table 2). In patients with suspected cardiac sarcoidosis the combination of cardiac MRI and ^{18}F-FDG-PET/CT are considered as the diagnostic tools of choice [118].

If neurosarcoidosis is suspected, a brain MRI and a lumbar puncture should be performed. However, pathognomonic cerebrospinal fluid findings do not exist. In the majority of patients, lymphocytic pleocytosis, elevated protein and IgG can be detected. In up to 50% oligoclonal bands are positive [119, 120], also elevated beta-2-microglobulin values can be found [121]. Elevated ACE CSF levels were shown in only 28% of the individuals in a large retrospective analysis [122], thus ACE levels are not necessarily of help in diagnosing neurosarcoidosis. A biopsy should be obtained, especially in the case of isolated CNS involvement, if accessibility and safety permit it (both are often restrictions).

Monitoring depends on the severity and organ involvement. Patients with active and severe disease during immunosuppression should be seen at least every 12 weeks. Follow-up in patients with a self-limiting course during remission should be seen twice yearly for 2 years, then at yearly intervals for 3 years, followed by on-demand consultations.

Treatment

Generally, the disease course is highly variable ranging from mild courses with spontaneous resolution within several weeks, to irreversible organ damage requiring transplantation in the case of progressive pulmonary or cardiac sarcoidosis. There are currently no uniformly accepted predictors for disease progression or relapses, although high FDG uptake, assessed as standardised uptake value (SUV_{max}) >6.0, was independently associated with disease recurrence [159].

Eventually, it is difficult to decide when and how a treatment should be initiated. In mild forms, topical treatment

and a watch-and-wait approach may be justified, depending on the patients symptoms, but needs a close follow-up to intervene early enough in the case of disease progression. For example, a sudden increase of sarcoidosis-associated biomarkers (e.g., ACE, sIL-2Rα, neopterin), BAL lymphocyte cell count or FDG-uptake in PET/CT may indicate ongoing or progressive inflammation.

Treatment decisions aiming at symptom relief or remission should be personalised during the disease course, with consideration of therapeutic advantage and adverse effects, and depending on organ manifestations [1]. This includes immunosuppression, as well as supportive treatment for comorbidities or complications such as oxygen therapy or an implantable cardioverter–defibrillator (ICD). *Absolute indications* for a systemic treatment in the case of persisting disease activity include clinically apparent impairment of lung function, significant radiographic manifestations or progression towards pulmonary fibrosis, pulmonary hypertension, cardiac involvement (myocardial inflammation, high-degree heart block, ventricular arrhythmias, congestive heart failure), nervous system manifestations, pronounced reduction of hepatic function, hypercalcaemia and renal involvement, lupus pernio, obstructive lymph nodes, eye manifestation, splenomegaly causing thrombocytopenia and diabetes insipidus. As no immunosuppressive drugs are approved for sarcoidosis, selection of an appropriate treatment is based on consensus decisions [1, 123].

It is unknown if, due to better diagnostic procedures, an early treatment intervention in the case of relevant inflammation without concurrent functional impairment yet, will result in a more favourable disease course or outcome, less organ damage and reduced morbidity. Currently, longitudinal data are lacking and need verification over the upcoming years.

Apart from lung, eye and skin/mucosa manifestations (which can be treated topically), oral glucocorticoids are the first-line therapy of choice, although randomised trials are lacking [124–126]. A recent European Respiratory Society (ERS) guideline summarises extensively the current treatment options for sarcoidosis [127]. A typical dose regimen consists of an initial daily dose of 0.5–0.75 mg prednisone per kg body weight for four weeks depending on disease response [1]. Thereafter, glucocorticoid dose can be slowly tapered over 6–12 months (up to 24 months in selected and severe cases). In refractory or chronic active cases, glucocorticoids should be continued at a low dose in combination with one (or even more) steroid-sparing agents. For second-line treatment (in severe organ involvement, in glucocorticoid-refractory, chronic active or relapsing cases) or as steroid-sparing regimen (in the case of intolerable side effects and contraindications to glucocorticoids), there are several alternative immunosuppressants to be considered. Even though drugs, such as azathioprine, methotrexate, mycophenolate mofetil or leflunomide have been investigated only in small randomised trials or case series, beneficial effects have been reported [128–132]. TNFis, particularly infliximab or adalimumab, may serve as further off-label agents, also with some beneficial effects on inflammation, predominantly in extrapulmonary sarcoidosis [133–136]. TNFis were shown to be effective in randomised trials of pulmonary, extrapulmonary (lymph nodes, skin, bone/joint, liver, eyes, muscle, heart, peripheral and central nervous system, nose, spleen, kidney, bone marrow, throat, parotid/salivary glands, ear and gastrointestinal tract) and cutaneous sarcoidosis [137–139]. Chloroquine and hydroxychloroquine, with the latter showing less ocular toxicity, are immunomodulatory agents originally known as antimalarial drugs. Hydroxychloroquine is used as first-line treatment for cutaneous involvement, and shows beneficial effects in hypercalcaemia, in some patients with polymyalgia/arthralgia and fatigue [130]. A treatment algorithm for systemic treatment options is summarised in figure 5.

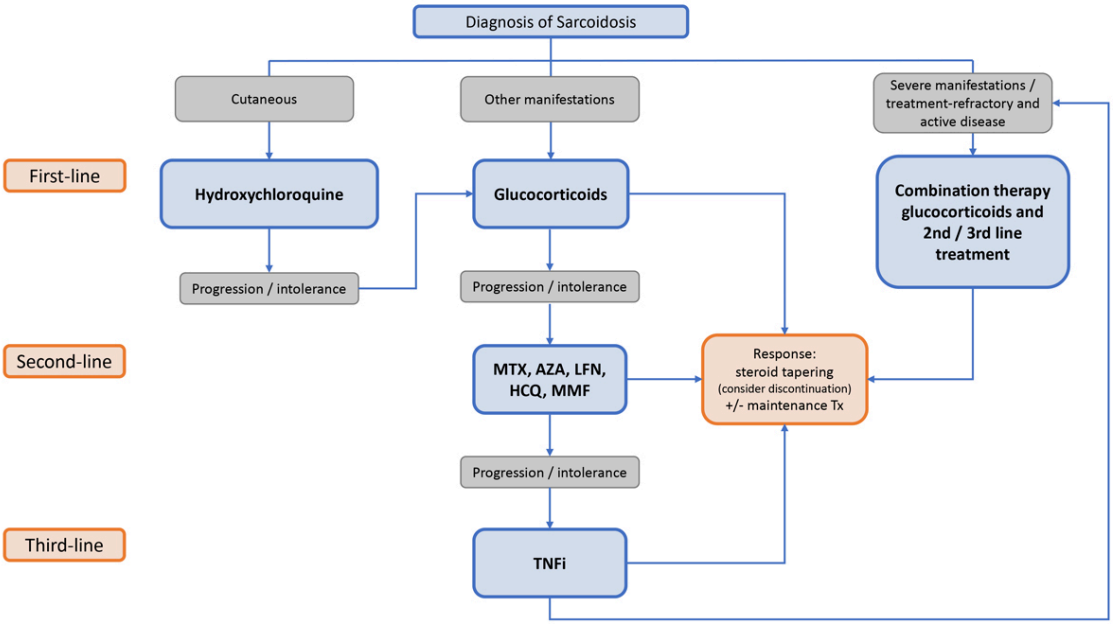
Since TNFα seems to play a key role in the pathogenesis of sarcoidosis, several anti-inflammatory drugs interacting with TNF metabolism, such as thalidomide, lenalidomide, and pentoxifylline, have also shown therapeutic effects in small case series or reports [140–142]. On the other hand, TNFis may also induce sarcoid-like diseases [143, 144]. Eventually, pathogenesis of sarcoidosis seems more complex with derangements in several pathways of acquired and innate immunity, including IL-23/Th17, IL-1 and IL-6 pathways. Thus, alternative approaches have been published in case series and reports with the IL-17 inhibitor secukinumab [143], the IL-6 receptor antagonist tocilizumab [145], or the JAK-1/3 inhibitor tofacitinib [146, 147], and the monoclonal chimeric anti-CD20 antibody rituximab [148]. Studies are currently under way with the phosphodiesterase inhibitor roflumilast and the fusion protein abatacept. In severe, therapy-refractory cases or in neurosarcoidosis, cyclophosphamide can also be considered [149–151], although the evidence level is low.

In general, in the case of persisting disease activity and severe organ involvement, combination therapies should be evaluated early in the treatment process to avoid complications due to long-term glucocorticoid treatment and provide sufficient disease control, with consideration of comorbidities and potential side effects, which could lead to higher hospitalisation rates and higher mortality, especially in older patients [101]. Furthermore, caution is required to avoid overtreatment in cases of burned-out sarcoidosis. This could lead to unnecessary treatment toxicity. If kidney function is decreased, therapy with methotrexate should be executed with great caution and only if no other options are available. When kidney function is severely impaired, methotrexate is contraindicated.

In addition to anti-inflammatory treatments, ICD/pacemaker implantation should be considered in cardiac sarcoidosis with severe ventricular arrhythmias, high degree atrioventricular block or impaired left ventricular function, as well as extensive myocardial fibrosis. Nitedanib, a tyrosine kinase inhibitor, which was approved for idiopathic pulmonary fibrosis, recently received extended approval by the US Food and Drug administration (FDA) for chronic fibrosing interstitial lung diseases with a progressive phenotype, which among others also includes sarcoidosis (12 of 663 participants, about 1.8%) [152, 153].

In end-stage disease, allotransplantation of the lungs, heart, kidney or liver might be the last opportunity. In the case of long-term immunosuppression by glucocorticoids >20 mg/day for longer than one month with an additional immunocompromising factor (immunosuppressive or predisposing disease), prophylaxis against *Pneumocystis jiroveci* with

Figure 5: Algorithm of systemic treatments in sarcoidosis. MTX: methotrexate; AZA: azathioprine; LFN: leflunomide; HCQ: hydroxychloroquine; MMF: mycophenolate mofetil; TNFi: TNFα inhibitor.



trimethoprim-sulfamethoxazole 160/800 mg three times weekly is recommended [154].

Comprehensive care of sarcoidosis patients also includes non-pharmacological measures such as oxygen therapy, physiotherapy and occupational therapy, physical training, pulmonary rehabilitation, cognitive behavioural therapy, psychosocial counselling, multimodal speech pathology therapy, mindfulness-based therapy and more [155]. For regular assessment of quality of life, there are several tools available, such as the 36-item Short Form Health Survey and EuroQol Group 5-dimension questionnaire or disease-specific questionnaires such as the King's Sarcoidosis Questionnaire [156], Sarcoidosis Health Questionnaire [157] or the Sarcoidosis Assessment Tool [158].

Conclusion

As a multi-systemic granulomatous disease with various clinical symptoms, sarcoidosis management requires an interdisciplinary approach to investigate all possibly affected organs and to seek the best treatment approach. Besides organ involvement and pharmacological treatments, comprehensive care also includes non-pharmacological measures and should address the psychosocial burden and para-sarcoidosis symptoms such as fatigue.

The increasing awareness of sarcoidosis as a systemic disease also requires the involvement of a multidisciplinary team. Registries and real-world data of rare diseases, by combining clinical and research efforts, have proven advantageous in multiple medical fields for patients and specialists. Therefore, the authors are currently attempting to generate an inter- and intra-disciplinary national network for sarcoidosis (SARNET).

Conflict of interest statement
DPF received speaker and consultancy honoraries from Boehringer Ingelheim. OD has/had consultancy relationship and/or has received research funding in the area of fibrosis and fibrotic diseases from (last three years): Abbvie, Acceleron Pharma, Amgen, AnaMar, Bayer, Boehringer Ingelheim, Catenion, Drug Development International Ltd, CSL Behring, ChemomAb, GSK, Horizon (Curzion) Pharmaceuticals, Inventiva, Italfarmaco, iQvia, Lilly, Medac, Medscape, Mitsubishi Tanabe Pharma, MSD, Novartis, Pfizer, Roche, Sanofi, Serodapharm, Target Bio Science and UCB. AGAK has served as an investigator, speaker, and/or advisor for AbbVie, Abbott, AstraZeneca, Janssen, Eli Lilly, MSD, Pfizer, Celgene, Novartis, Actelion, Leo, Amgen, Alk-Abello, and does not hold any shares or other financial interest in any related pharmaceutical company. The other authors do not have any conflict of interests related to the manuscript.

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