A case of pulmonary and cutaneous sarcoidosis

Eimear Foley[1], Ahmad Basirat[1], Ankit Yadav[1], Shane O'Brien[1,2], Patrick D. Mitchell[1,2] and Seamas C. Donnelly[1,2]

[1]Respiratory Department, Tallaght University Hospital, Dublin, Ireland. [2]School of Medicine, Trinity College Dublin, Dublin, Ireland.

Corresponding author: Eimear Foley (Eimear.foley@tuh.ie)

Shareable abstract (@ERSpublications)
A case demonstrating refractory cutaneous and pulmonary sarcoidosis, with classic clinical, spirometry and radiological features, despite OCS and low-dose HCQ treatment that responded clinically and functionally to the addition of a TNF inhibitor https://bit.ly/4h8Gix1

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Introduction

Sarcoidosis is a chronic systemic inflammatory disorder of unknown aetiology, characterised by the accumulation of T lymphocytes, mononuclear phagocytes and the formation of noncaseating granulomata in affected tissues [1]. It has a variable clinical presentation and disease course that depends on the organs involved. Diagnosis is based on multiple factors including symptoms, physical examination, radiological abnormalities and histopathological findings of noncaseating granulomas from involved tissues or organs and the exclusion of other causes [2].

Lung or thoracic lymph node involvement occurs in ∼90% of patients with sarcoidosis, and pulmonary disease accounts for the majority of the overall associated morbidity and mortality [3]. ∼50% of patients have extrathoracic manifestations at presentation, including cutaneous sarcoidosis. A minority of patients with sarcoidosis develop sarcoidosis-associated pulmonary fibrosis, which may progress. Progressive and debilitating respiratory impairment occurs in pulmonary sarcoidosis despite the initiation of appropriate therapy in up to 10% of patients. Thus, effective management of sarcoidosis can prove very challenging in the long term both in terms of the disease itself and medication side-effects.

Case presentation

A 45-year-old female of African descent was referred to our specialised sarcoidosis clinic with 6 months of progressively worsening dyspnoea on exertion and a dry cough, which was worse at night. She also reported fatigue and generalised muscle aches. She reported persistent facial plaques, from which she was asymptomatic but which had caused significant cosmetic disfigurement.

She had been diagnosed with pulmonary and cutaneous sarcoidosis 5 years previously. This diagnosis had been supported by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) demonstrating noncaseating granulomas, which were culture negative for mycobacteria. The patient had been followed up on a 6-monthly basis by the Dermatology and Respiratory services in her local hospital, along with cardiology input. She had no other past medical history.

Regular medications on first review at our clinic included hydroxychloroquine 200 mg once daily (commenced 6 months prior to referral) and fluticasone furoate/vilanterol (Relvar) 184/22 µg. She was also taking prednisolone 30 mg at the time of review. This was planned for a slow taper to 5 mg maintenance by her local hospital or pending review at our dedicated clinic, having reported that her breathing and cough were worsening since cessation of the prior steroid course provided by her general practitioner. Co-trimoxazole 960 mg three times weekly had been commenced as *Pneumocystis jirovecii* pneumonia prophylaxis while taking a prolonged corticosteroid course.

She is a lifelong nonsmoker. She works as a stay at home mother, with no known significant occupational exposures. She has no relevant family history.

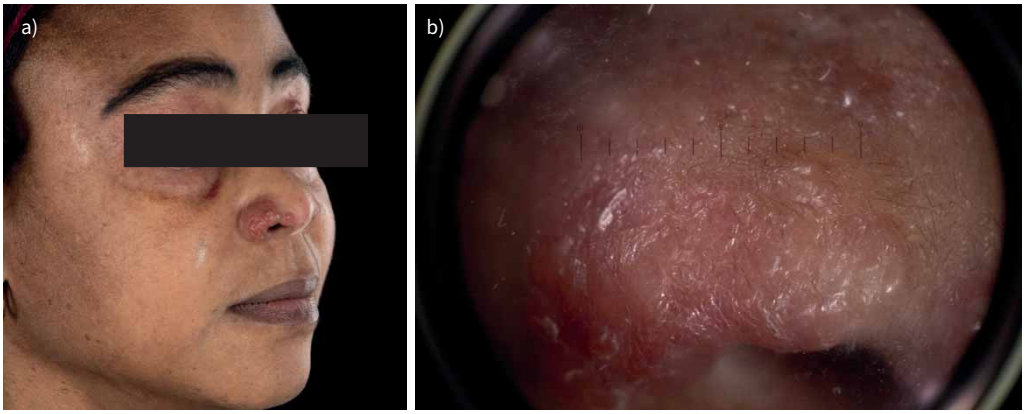

FIGURE 1 a) Photograph showing indolent reddish-purple plaques and nodules on the patient's nose, cheeks and eyelids with associated telangiectasia. b) Close-up image of the right nasal rim.

Clinical examination

She had indolent reddish-purple plaques and nodules on her nose, cheeks and eyelids with associated telangiectasia. Most notable were the crusted lesions on the right nasal rim as shown in figure 1.

Her chest was clear on auscultation and routine fundoscopy assessment was normal.

Task 1

What are the differential diagnoses for the facial lesions shown in figure 2?

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Further investigations

Extensive further workup was carried out, including routine serology, high-resolution computed tomography (HRCT) of the thorax, cardiac magnetic resonance imaging (MRI) and transthoracic echocardiogram, Holter monitor and a 6-min walk test (6MWT), pulmonary function tests (PFTs) and bronchoscopy.

From the routine ILD serology, results of note included angiotensin converting enzyme of 134 $IU \cdot L^{-1}$ (normal range: 8–65 $IU \cdot L^{-1}$). Calcium of 2.40 $mmol \cdot L^{-1}$, corrected calcium of 2.50 $mmol \cdot L^{-1}$, repeatedly within the normal range. Immunoglubulins (IgE, IgG, IgA, IgM) were within the normal range. The CTD screen was negative, CTD ratio was 0.20 (normal range: 0.00–0.69), rheumatoid factor <10 $IU \cdot mL^{-1}$ (normal range: 0.0–20.0 $IU \cdot mL^{-1}$), neutrophil cytoplasmic antibodies were negative and cyclic citrullinated

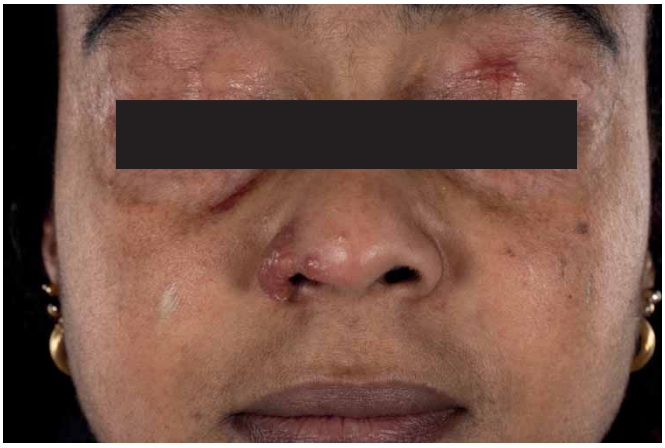

FIGURE 2 Photograph of the patient's facial lesions.

TABLE 1 6-min walk test results

	Peripheral oxygen saturation	Borg
At rest	99%	0
1 min	98%	
2 min	96%	
3 min	99%	
4 min	96%	
5 min	98%	
6 min	96%	

peptide was 1.0 $U \cdot mL^{-1}$ (normal range: 0.0–7.0 $U \cdot mL^{-1}$). Complement C3 was 1.28 $G \cdot L^{-1}$ (normal range: 0.83–1.8 $G \cdot L^{-1}$) and C4 was 0.19 $G \cdot L^{-1}$ (normal range: 0.16–0.7 $G \cdot L^{-1}$). Quantiferon, HIV and hepatitis B and C tests were negative.

Contrast-enhanced cardiac MRI revealed a structurally normal heart without evidence of fibrosis, infarction or infiltration on post-contrast examination. There was no valvular abnormality. The pericardium was normal. Left ventricular (LV) end-diastolic volume, LV mass and global right ventricle assessment were normal.

Transthoracic echocardiogram revealed normal LV systolic function. Ejection fraction was 55% by Simpson's biplane method. Diastolic function was normal; impression of moderate tricuspid regurgitation. Right ventricular systolic pressure was 28 mmHg.

The Holter ECG monitor revealed sinus rhythm throughout, with rare premature ventricular contractions and premature atrial contractions.

6MWT to assess functional capacity showed overall satisfactory oxygen levels with a total of just 300 m total distance covered (table 1), less than the expected distance of 440 m for a healthy patient of this age.

Radiology

Her chest radiograph (figure 3a), taken just prior to our review, showed extensive small nodules with upper zone predominance. HRCT of the thorax (figure 3b) showed multiple peribronchial nodules preferentially affecting the upper lobes with calcified mediastinal and hilar adenopathy that had progressed since the original diagnosis.

Pulmonary function tests

PFTs have shown a progressive decline in lung function since her diagnosis 5 years earlier, despite treatment with hydroxychloroquine 200 mg once daily monotherapy and multiple prolonged intermittent oral corticosteroid courses.

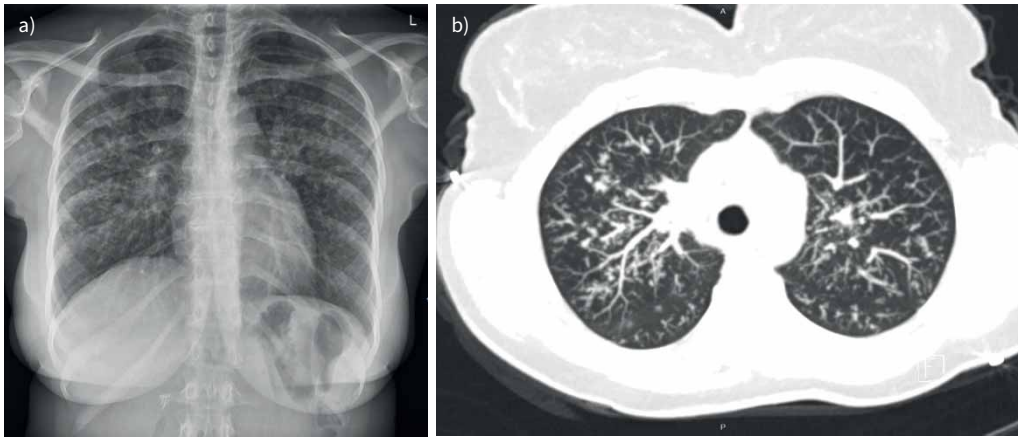

FIGURE 3 a) Chest radiograph. b) High-resolution computed tomography of the thorax.

Forced expiratory volume in 1 s (FEV_1) at diagnosis in 2018 was 2.05 L (72.5% predicted), forced vital capacity (FVC) was 2.51 L (76.7% predicted), FEV_1/FVC was 81.6% and diffusing capacity of the lung for carbon monoxide (D_{LCO}) was 72.4%.

On referral, PFTs showed a restrictive pattern. FEV_1 as shown in table 2 was 1.28 L (49% predicted), FVC was 1.66 L (55% predicted), FEV_1/FVC was 76% and D_{LCO} was down to 55% predicted. Total lung capacity was 2.92 L (61% predicted).

Task 2

As described in [4]:

a) What airway abnormalities might you expect to find on bronchoscopy in a patient with pulmonary sarcoidosis?

b) What percentage of patients with sarcoidosis have evidence of airway abnormalities on bronchoscopy: 10–20%, 20–30%, 30–40% or 40–50%?

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Bronchoscopy

Bronchoscopy was performed as shown in figure 4. Inflamed erythematous airways (figure 4a) and airway nodularity (figure 4b) was noted throughout the airways, particularly in the lower lobes bilaterally. Otherwise the airways were clear, with all segments examined. Bronchoalveolar lavage (BAL) from the right middle lobe medial segment showed cloudy mucoid fluid which was sent for pathology, microbiology and cytology. The cell differential showed: macrophages 83%, lymphocytes 15%, neutrophils 2% and eosinophils 0%. The CD4:CD8 ratio was 10:1.

BAL mycobacteriology was negative. Cytology showed mucosal oedema and infiltration. Malignant cells were not identified. Organisms consistent with normal commensals of the upper respiratory tract were isolated.

Task 3

a) According to the SARCORT study in 2023 [5], what starting dose of steroids would you prescribe in the management of active sarcoidosis?

b) In patients with sarcoidosis refractory to oral glucocorticoid therapy [6], what are the next steps in treatment?

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Treatment and course of disease

This patient was diagnosed with active pulmonary and cutaneous sarcoidosis with worsening respiratory symptoms and radiology, along with extensive lupus pernio on clinical examination. Our investigations,

TABLE 2 Pulmonary function test results at referral

	Pred[#]	Measured	% pred
Spirometry			
FEV_1 (L)	2.60	1.28	49.2
FVC (L)	3.03	1.66	55.0
FEV_1/FVC (%)	80.55	76.72	95.2
$FEF_{25–75\%}$ ($L·s^{-1}$)	3.39	1.01	29.9
PEF ($L·s^{-1}$)	6.34	4.66	73.5
Diffusion studies			
D_{LCO} ($mL·min^{-1}·mmHg^{-1}$)	24.31	13.46	55.4
Lung volumes from FRC plethysmography			
Residual volume (L)	1.62	1.11	68.7
TLC (L)	4.77	2.92	61.3

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25–75\%}$: forced expiratory flow at 25–75% of FVC; PEF: peak expiratory flow; D_{LCO}: diffusing capacity of the lung for carbon monoxide; FRC: functional residual capacity; TLC: total lung capacity. [#]: Pred indicates predicted/reference value.

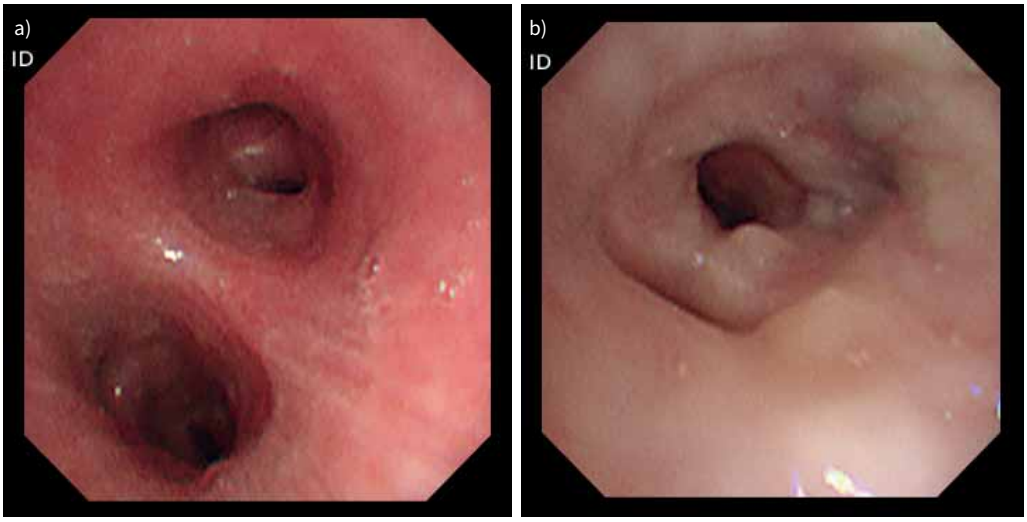

FIGURE 4 a) Endobronchial image captured at bronchoscopy demonstrating inflamed erythematous airways. b) Endobronchial image captured at bronchoscopy demonstrating airway nodularity.

including HRCT which showed the development of multiple peribronchial nodules preferentially affecting the upper lobes with calcified mediastinal and hilar adenopathy, had progressed since the original diagnosis CT, with bronchoscopy showing nodularity and progressive airflow restriction evident on PFTs. The progression of clinical symptoms on hydroxychloroquine and intermittent glucocorticoids, combined with evidence of functional decline led to the decision to advance the patient's treatment plan. The patient was reluctant to persist with further courses of steroids, which had not worked to date.

The decision to progress to a TNF-α antagonist rather than commence MTX or MMF as second-line agents was one made in collaboration with the patient. Given the extent of disease on presentation along with clinician experience with the agents and patient preference, both side-effects and benefits were taken into account as per the guidelines before commencing adalimumab [7]. Adalimumab 40 mg subcutaneously weekly was commenced, following a negative viral screen, with this agent believed to carry less toxicity than infliximab [8].

On follow-up review at our outpatient clinic at 3, 6 and 9 months onwards, the patient continues to report a drastic improvement in both cutaneous manifestations and her pulmonary symptoms, with significant improvement of quality of life. Figure 5 shows the improvement in the lupus pernio. PFTs, 6MWT and radiological follow-up at 9 months also now show stabilisation. 6MWT to assess functional capacity showed overall satisfactory oxygen levels with an increased distance of 315 m covered (table 3).

PFTs show mild improvement from prior to commencement of adalimumab with FEV_1 now up to 1.37 L (57% predicted), FVC of 1.59 L (54% predicted), FEV_1/FVC 85%, D_{LCO} 53% pred. A repeat chest radiograph (figure 6) redemonstrates multiple ill-defined nodules predominantly of the upper zones bilaterally, consistent with known sarcoidosis.

Treatment duration will continue to be decided based on clinical, functional and radiological assessment at 3–6 monthly follow-up.

Discussion

For patients with symptoms due to pulmonary disease, the common presenting complaints tend to include cough, dyspnoea and chest pain. These symptoms are often accompanied by constitutional manifestations including fatigue, malaise, fever and weight loss [9]. Many patients with pulmonary sarcoidosis do not require treatment as most have asymptomatic, nonprogressive disease or will experience spontaneous remission. However, progressive pulmonary fibrosis will occur in ~25% of cases and it is noted that sarcoidosis patients referred to our tertiary centres are more likely to have risk factors associated with the need for systemic treatment [10].

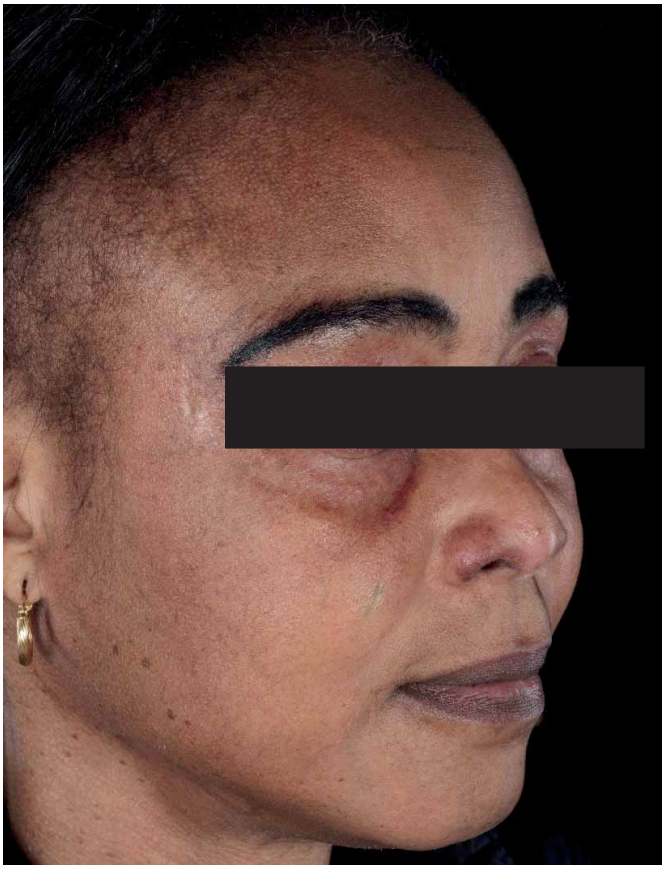

FIGURE 5 Follow-up 4 months after starting tumour necrosis factor-α antagonist treatment.

The incidence and prevalence of sarcoidosis is significantly higher for black than for white individuals, with the highest prevalence for sarcoidosis noted to be in black females [11]. Analyses have shown that that black patients tend to experience more extrapulmonary sarcoidosis. Apart from the skin, it has also been found to affect the bone marrow, liver, extrathoracic lymph nodes and eyes – with calcium dysmetabolism more common in white patients [12]. This prevalence suggests an inherent genetic susceptibility, with first-degree relatives of black sarcoidosis patients found to have a three-fold increase in disease risk [13].

There is diagnostic importance to and demographic variations of skin manifestations in sarcoidosis, with skin often being cited as the second most commonly involved organ [14]. As seen here, lupus pernio is a distinct form of cutaneous sarcoidosis which disproportionally affects black people and females [15]. The presence of lupus pernio appears to be associated with an increased risk for extracutaneous disease, particularly sarcoidosis involving the respiratory tract [16]. It is characterised by indolent violaceous or erythematous, indurated, infiltrative plaques. These are primarily distributed on the central face – usually the alar rim, nasal tip, cheeks, ears and lips [17].

TABLE 3 6-min walk test results at 6 month follow-up

	Peripheral oxygen saturation	Heart rate, beats per min	Borg
At rest	99%	77	0
1 min	98%	86	0
2 min	98%	89	0
3 min	98%	88	
4 min	99%	87	0
5 min	99%	86	
6 min	100%	87	

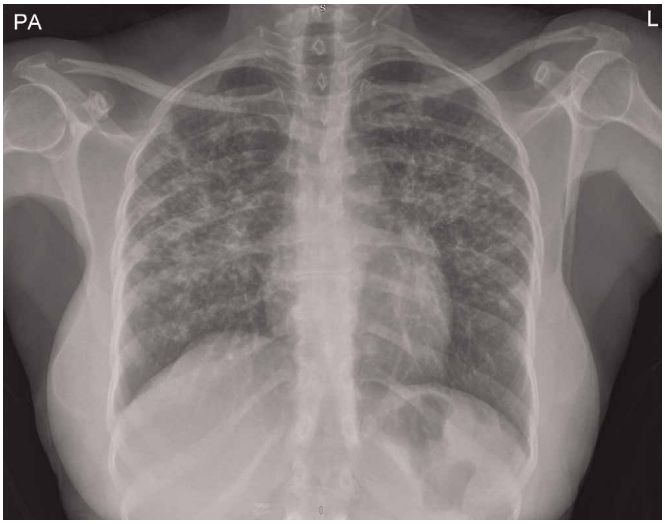

FIGURE 6 Follow-up imaging 9 months after starting tumour necrosis factor-α antagonist treatment.

Lupus pernio is less responsive to treatment than other sarcoidosis lesions, including papular, plaque, nodular and subcutaneous sarcoidosis, and without treatment can progressively infiltrate and indurate, later healing with telangiectatic scars [18]. Lesions on the nasal rim are associated with granulomatous inflammation of the upper respiratory tract and can extend to the nasal septum leading to nosebleeds and crusting [19]. The differential diagnosis for lupus pernio includes acute cutaneous lupus erythematosus, chronic cutaneous lupus erythematosus, lupus vulgaris, tuberculoid leprosy, and cutaneous benign or malignant lymphocytic infiltrates [20].

A substantial proportion of patients diagnosed with cutaneous sarcoidosis will present with cardiac manifestations as their presenting organ of involvement [21]. Higher rates of extracutaneous involvement – particularly cardiac – are again associated with African-American patients, with studies showing these patients are up to 1.7 times more likely to be diagnosed with extracutaneous, cardiac involvement compared with Caucasian patients [20].

The workup for cardiac involvement, including Holter, echocardiogram and cardiac MRI, was normal in this case. Late gadolinium-enhanced cardiac MRI is the reference examination for assessing myocardial involvement with sarcoid infiltrates visible on MRI as intramyocardial focal zones with increased signal intensity on both T2-weighted and early gadopentetate dimeglumine-enhanced images. This is caused by oedema associated with inflammation [22]. A focal myocardial thickening is also often seen because of the oedema, and this feature can mimic hypertrophic cardiomyopathy [23].

There are currently no definitive criteria or cut-offs to determine at what stage of disease progression the patient's treatment regimen should be altered. Therefore, the decision to escalate therapy lies in the hand of the physician and should be made cautiously; however, some markers that should prompt consideration include pulmonary symptoms leading to a relevant impairment in quality of life, a decline in PFTs, progressive worsening of interstitial opacities and a decrease in oxygen saturation on pulse oximetry of ⩾4% at rest or with exercise [24]. As is evident in this case, pulmonary symptoms were inhibiting quality of life along with clear progression of disease on PFTs.

Bronchoscopy, spirometry and radiological imaging all play a significant role in both the diagnosis and management of airway involvement for patients with pulmonary sarcoidosis. The main purpose of bronchoscopy with BAL is to exclude alternative diagnoses including eosinophilic lung disease, malignancy and infections (including fungal and mycobacterial infections). BAL lymphocytosis of >15%, however, confers a 93–96% specificity for the diagnosis of sarcoidosis [24].

The American Thoracic Society guidelines advise against the routine assessment of lymphocyte subsets; however, for patients with suspected sarcoidosis a BAL can be a useful guide with a lymphocytosis ⩾16% and a CD4:CD8 ratio greater than 3.5:1 providing significant support for a diagnosis of sarcoidosis, although not exclusively [25].

On bronchoscopy, the main bronchi and trachea tend to be affected less frequently than the lobar, segmental, subsegmental and distal airways which display mucosal inflammation, endobronchial granulomas, cobblestoning, plaques, bronchial stenosis, distortion, bronchiectasis, bronchiolitis and airway hyperreactivity [4]. Nodularity and increased vascularity are identified as the most prevalent findings in sarcoidosis patients, and parenchymal disease on CT scanning is significantly more common in patients with non-necrotising granulomas on bronchoscopy than those without [26].

It is difficult to estimate the precise incidence of airway dysfunction in pulmonary sarcoidosis; however, an obstructive pattern on spirometry has been reported in between 4% and 75% of patients [27].

The initial mainstay of treatment for pulmonary sarcoidosis is oral glucocorticoid therapy. However, another immunosuppressive agent may need to be added as progressive respiratory impairment complicates up to 10% of patients despite glucocorticoid treatment of at least 3 months of prednisolone 10–20 mg daily. A glucocorticoid sparing agent may be required in those who have been unable to taper below 10 $mg \cdot day^{-1}$ or have had intolerable adverse effects from chronic steroid treatment [6]. Many of these patients indeed benefit from referral to a sarcoidosis centre.

The agents that appear to have the most significant benefit in pulmonary sarcoidosis with an acceptable side-effect profile are MTX, AZA, MMF and TNF antagonists [7]. Notably, these agents all carry a risk for myelosuppression, hepatotoxicity and opportunistic infection and thus the decision is guided by the patient's history of medication-related adverse effects, clinician experience with the agents, and patient preference.

The cytokine TNF-α is believed to accelerate the inflammatory process of sarcoidosis *via* its role in the maintenance of granuloma formation, therefore using agents that block these effects of TNF-α is an effective treatment option of sarcoidosis [7]. TNF antagonists used include infliximab, adalimumab and etanercept. The European Respiratory Society guideline [28] supports the addition of infliximab to improve and/or preserve FVC and quality of life for patients with symptomatic pulmonary sarcoidosis believed to be at higher risk of future mortality from sarcoidosis who have been treated with glucocorticoids or other immunosuppressive agents and have continued disease. FVC was the primary endpoint in two phase III randomised trials with secondary endpoints including chest imaging and quality of life assessments [28].

Insufficient data exists to determine whether MTX should be used alongside TNF-α antagonist therapy. Although combination therapy has been used in rheumatoid arthritis to both improve efficacy and reduce the risk of development of antibodies to the TNF-α inhibitor, it has not been formally evaluated in sarcoidosis and may also carry an increased risk of opportunistic infection and malignancy [29].

The response to adalimumab therapy in this case will again continue to be evaluated in the same manner as that which is described for initial therapy of sarcoidosis, with ongoing evaluation of symptoms, spirometry and radiographic abnormalities.

Conclusion

Sarcoidosis is a multisystem inflammatory granulomatous disorder with a variable clinical presentation and disease course, depending on the organs involved. In this case of pulmonary and cutaneous sarcoidosis, many classic features were displayed with lupus pernio, airway nodularity evident on bronchoscopy, restrictive spirometry along with hilar adenopathy and upper lobe predominant peribronchial nodules on radiographic imaging. The case demonstrates refractory cutaneous and pulmonary sarcoidosis despite oral corticosteroids and low-dose hydroxychloroquine treatment that responded to the addition of a third-line treatment with a TNF inhibitor upon review at our specialist centre.

Answer 1

- Lupus pernio
- Acute cutaneous lupus erythematosus
- Chronic cutaneous lupus (*e.g.* Discoid lupus, lupus profundus, chilblain lupus erythematosus)
- Lupus vulgaris
- Benign or malignant lymphocytic infiltrates [1]

<< Go to Task 1

Answer 2

a) Nodularity, cobblestoning, plaques, airway thickening, increased vascularity and granulomas.
b) 40–50%

<< Go to Task 2

Answer 3

a) High-dose prednisolone at 40 mg per day was not superior to a lower dose of 20 mg·day^{-1} in improving outcomes or quality of life in sarcoidosis and was associated with similar adverse effects.
b) Steroid sparing agents for example methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF) and tumour necrosis factor (TNF)-α antagonists.

<< Go to Task 3

Conflict of interest: The authors have nothing to disclose.

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