CASE REPORT

REFRACTORY SARCOIDOSIS

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A multi-organ granulomatous disease with characteristic lung manifestations, sarcoidosis generally responds well to glucocorticoid therapy but 10% of cases are refractory necessitating immunosuppressive therapy. A 58-year-old lady presented with a dry cough and progressively worsening shortness of breath for the last 12 months. On investigation, her ESR was raised but cultures, malignancy screen and TB quantiferon were negative. HRCT chest demonstrated multiple pulmonary nodules with hilar lymphadenopathy and CT guided biopsy revealed non-caseating granuloma. She was diagnosed with Pulmonary Sarcoidosis and started on oral steroids with minimal improvement. Azathioprine was added but due to gastric intolerance switched to methotrexate. Her disease however continued to worsen and infliximab was started but she developed a severe allergic reaction. She was then started on mycophenolate mofetil but her chest imaging continued to worsen. After failing prednisone, azathioprine, methotrexate, infliximab and mycophenolate mofetil, the patient was started on rituximab.

Keywords: Sarcoidosis; Non-caseating granulomas; Rituximab; Infliximab; Mycophenolate Mofetil; Methotrexate; Azathioprine

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INTRODUCTION

Sarcoidosis is a multi-organ granulomatous disease in the majority of the patients having characteristic lung manifestations including non-caseating granulomas on biopsy, hilar lymphadenopathy and lung reticulo-nodular opacities which aid in staging the disease (Table-1).[1] Sarcoidosis generally responds well to glucocorticoid therapy but up to 10% of cases are refractory necessitating other immunosuppressive therapy.[2] However consensual definition for refractory sarcoidosis is not provided in the literature or guidelines. According to STAT cohort[3] refractory sarcoidosis was defined when second-line immunosuppressive therapy was insufficient to provide satisfactory disease control. Korsten et al.[4] defined refractory case as sarcoidosis when oral prednisolone cannot be tapered to less than 10 mg per day. Similarly, Sweiss *et al*.[5] labelled refractory cases as symptomatic sarcoidosis while the patient is taking prednisolone $\geq$10 mg daily or any other immunosuppressive drug. Jammal *et al*.[6] defined refractory sarcoidosis as a condition where steroids and second-line immune-suppressive therapy (azathioprine, methotrexate, mycophenolate) fail to achieve remission clinically.

Table-1: Stages of Pulmonary Sarcoidosis

Stage	Radiographic Findings	Prevalence
Stage 0	No Abnormalities	5–10%
Stage 1	Hilar Lymphadenopathy	50%
Stage 2	Hilar Lymphadenopathy plus Pulmonary Infiltration	25–30%
Stage 3	Pulmonary Infiltration	10–12%
Stage 4	Pulmonary Fibrosis	5%

CASE REPORT

We present the case of a 58-year-old hypertensive lady who presented with a dry cough and progressively worsening shortness of breath for the last 12 months. She had consulted a local GP previously who had diagnosed her with pulmonary tuberculosis when her chest X-ray showed hilar lymphadenopathy and pulmonary nodules. She had completed a 6-month course of anti-tuberculosis therapy with no improvement in her symptoms. She did not smoke or use illicit drugs. On investigation, her ESR was raised but cultures and malignancy screen were negative. Her TB quantiferon had been checked numerous times and was always negative. Spirometry was normal for lung volumes and flow-volume loop but the diffusion capacity of lung for

carbon monoxide (DLCO) was reduced. Bronchoalveolar lavage (BAL) showed lymphocytes 37% and CD4:CD8 ratio 4.32. Autoimmune workup showed elevated serum ACE level but negative ANA and ANCAs. HRCT chest demonstrated multiple pulmonary nodules with hilar lymphadenopathy, however, there was no evidence of pulmonary fibrosis. A CT-guided biopsy of pulmonary nodules revealed non-caseating granuloma. Her echocardiography was within normal parameters.

She was diagnosed with Pulmonary Sarcoidosis and started on oral prednisolone 10mg per day with minimal improvement in symptoms and repeat imaging showing worsening consolidation and opacities. Azathioprine was added but she had gastric intolerance (nausea and vomiting) and was switched to methotrexate. Her disease however continued to worsen with increasing oxygen requirement and worsening bilateral nodules and large cavitation was seen in the left upper lobe. Infliximab was added but during the infusion, she developed a severe allergic reaction and thereby she was started on mycophenolate mofetil. She had multiple admissions during the course of the treatment and chest imaging continued to worsen. After failing prednisone, azathioprine, methotrexate, infliximab and mycophenolate mofetil therapy, the patient was started on rituximab. Her disease process and oxygen requirement are currently stable on rituximab.

DISCUSSION

Sarcoidosis, a granulomatous disease of undetermined aetiology, has a variable global prevalence. It typically affects the lungs but it may involve any organ and has an unpredictable course clinically. Signs and symptoms of pulmonary Sarcoidosis vary from asymptomatic patients having incidental radiographic abnormalities to chronic progressive respiratory disease refractory to therapy. Respiratory failure is the commonest cause of death in Sarcoidosis.[7] Poor prognostic factors in Sarcoidosis include pulmonary hypertension, lung fibrosis, severe disease on HRCT chest and deranged pulmonary function.[8] Corticosteroids are the first-line treatment but their prolonged use is linked with marked adverse effects. Steroid-sparing immunosuppressive therapies are used as second-line and include azathioprine, methotrexate and mycophenolate mofetil.[9]

Refractory Sarcoidosis, seen in up to 10% of cases and linked with raised morbidity and mortality, is defined as a condition where clinical remission is not achieved with corticosteroids and immunosuppressive therapy.[2] In spite of limited evidence for effect on extra-pulmonary involvement, cyclophosphamide has been used successfully in refractory neurologic and cardiac manifestations but the use of cyclophosphamide is limited by its toxic and teratogenic adverse effects.[10] Biologics that target tumour-necrosis factor (TNF) including infliximab and adalimumab may be used as third-line therapy and have been shown to be efficacious in refractory Sarcoidosis.[11] However, TNF inhibitors used in Sarcoidosis were less tolerated by patients suffering from increased risk of infection and malignancy.[12] There is a deficiency of treatment options for patients that are refractory or intolerant to TNF inhibitors. In sarcoid patients' refractory to TNF inhibitors, fourth-line therapies have been proposed recently which include JAK inhibitors and other biologics (rituximab and tocilizumab).[13,14] In the case series by Cinetto *et al.*[13] patients of multi-organ sarcoidosis responded well to rituximab after failing to achieve remission with corticosteroids, azathioprine, methotrexate and cyclophosphamide. Zella *et al*.[14] reported 3 cases of neurosarcoidosis that were successfully treated with rituximab. The findings of these studies are similar to our patient who after failing therapy with prednisone, azathioprine, methotrexate, infliximab and mycophenolate mofetil was started on rituximab. Her disease process and oxygen requirement currently remain stable on rituximab.

In conclusion, Sarcoidosis generally responds well to steroids which are first-line treatments. Poor response to steroids should prompt investigation to rule out other causes, non-adherence to medications and evaluation of lesions because fibrotic lesions may be irreversible. Immunosuppressive therapy is given as second-line but data to establish their usefulness is limited. When steroids and other immunosuppressive therapy treatments fail to improve the disease, it is considered refractory sarcoidosis. The pathophysiology of refractory sarcoidosis remains poorly understood and presents a challenge for treating physicians. Identification of molecular targets in refractory Sarcoidosis treatment is a priority and data from various perspective ongoing trials would help to provide further information on treatment agents in refractory sarcoidosis.

Consent: Informed consent was taken from the patient.

Conflict of Interest: None declared.

AUTHORS' CONTRIBUTION

This study was conceived and designed by NIB and RY. FA and KM did the initial literature research. FA and KM did the data collection, assembly and patient assessment. NIB and RY were involved in manuscript writing. KM and FA did the final critical

review and corrections. NIB is the corresponding author on behalf of all other authors.

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