The Cobblestone Heart

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SUMMARY

Sarcoidosis is a chronic, multisystem disorder. A 38 years old lady presented at Hospital Raja Perempuan Zainab II, Kota Bharu ,Malaysia with cough and breathless for 2 months and constitutional symptoms of weight loss and loss of appetite. She was initially treated as smear negative pulmonary tuberculosis for 5 months. However, her clinical condition deteriorated with worsening New York Heart Association (NYHA) class 1 to class 3. Subsequently, workout of computed tomography(CT) thorax showed multiple perilymphatic distribution of nodules and multiple mediastinal lymphadenopathy coupled with pleura biopsy showed non caseating granuloma and cardiac magnetic resonance imaging (MRI) with positive late gadolinium enhancement revised the diagnosis of pulmonary sarcoidosis with cardiac involvement. Patient's functional status and cough improved with immunosuppresant was given in tapering dose fashion

INTRODUCTION

Sarcoidosis is a chronic, multisystem disorder. Although clinical evidence of myocardial involvement is present in only 5% of patients with sarcoidosis, subclinical cardiac involvement as proven by autopsy is present in 20 to 30% of cases.[1] Myocardial involvement of sarcoidosis has been proven to occur much more commonly in patients presenting with cardiac symptoms compared with those who do not have cardiac symptomatology (84 vs 4%) with morbidity up to 90 % and mortality of 30%.[2]

CASE REPORT

We describe here a case of 38 years old lady who presented at the Hospital Raja Perempuan Zainab II .with breathlessness and cough for 2 months, no loss of appetite and weight and denied any failure symptoms. Chest radiograph revealed multiple nodular opacity over right upper and middle lobe of lungs. She was empirically treated as smear negative pulmonary tuberculosis with negative sputum acid fast bacilli (AFB) initially and subsequent sputum mycobacterium (MTB) culture yielded no growth. Persistent symptoms of cough and weight loss with non-improving serial chest radiograph were observed during follow up day 14, 1 month of anti tuberculous medication. We noticed the patient had new onset of heart failure symptoms i.e. orthopnoea and bilateral leg swelling after 2 months of treatment with chest radiograph with worsening consolidation of right upper and middle lobe and right pleural effusion. Urgent computed tomograph (CT) thorax showed multiple mediastinum matted lymph node enlargement with multiple peribronchovascular distribution of nodular opacity with coalesce consolidation over the right middle lobe and right pleural effusion. She underwent pleuroscopy after the new onset of exudative right pleural effusion revealed multiple well form coalescing non granulomatous inflammation over parietal pleura. Blood was unremarkable with normal calcium level, angiotensin converting enzyme level and normal erythrocyte sediment rate (ESR) of 20mm/hr. With the new onset of cardiac symptoms reduced effort tolerance and worsening NYHA status and abnormal electrocardiogram (ECG) of multiple premature ventricular ectopics (PVCs), right bundle branch block and poor R wave progression over precordial leads, we ordered urgent echocardiogram (ECHO) which showed dilated cardiomyopathy with global hypokinesia and with reduced left ventricular ejection fraction (LVEF) of 33%. With highly suspicions of cardiac sarcoidosis, as recommended in the American Thoracic Society (ATS) guidelines 2020, we proceeded with cardiac MRI showed extensive and variable pattern of myocardial inflammation and fibrosis with positive late gadolinium enhancement predominant at basal left ventricle (LV) segment. the patient fulfilled >2 major criteria -3 major (1, basal interventricular septal thinning, gadolinium enhanced MRI of myocardium, depressed LVEF <50% and 1 minor criteria of multifocal arrhythmia-premature ventricular contraction in 2017 Japanese Ministry of Health and Welfare Criteria for diagnosis of cardiac sarcoidosis. Eventually, 0.5mg/kg corticosteroid with weekly incremental dosage of methotrexate from 7.5mg /week up to 20mg/week planned for 6 months were initiated. Besides, anti-heart failure medication T perindropil 8mg and bisoprolol 2.5mg OD and spironolactone 25mg OD were given under cardiology care. Her repeated computed tomograph thorax after 3 months of treatment showed significant improvement of resolving nodules and consolidations (arrow) and reducing sizes of mediastinum lymphadenopathy (arrowhead). However, there was residual right pleural effusion which we attributed it to pleural sarcoidosis and heart failure in combination. Repeated ECHO after 3 months of treatment revealed static ejection fraction of 30 % with dilated cardiomyopathy. Otherwise, she clinically remained well with no reported failure symptom with low dose 10mg steroid daily and 20mg /week methotrexate. We planned to follow up every 3monthly with close monitoring of her heart and lung function by doing chest radiograph, cardiac positron emission tomography PET scan imaging to assess the cardiac disease activity and blood investigations to monitor for methotrexate MTX toxicity.

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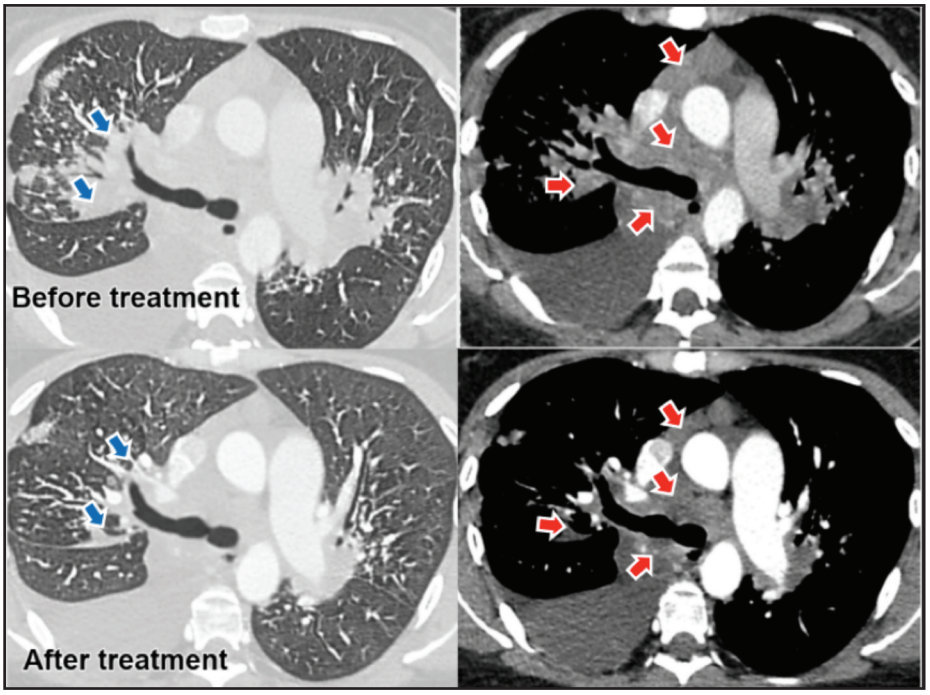

Fig. 1: Pre and post treatment CT thorax image showing resolving peribronchovascular nodules and consolidation (blue arrow) and reducing sizes of station 3A, 4L ,4R ,7 and 10R and mediastinum lymph nodes (red arrow).

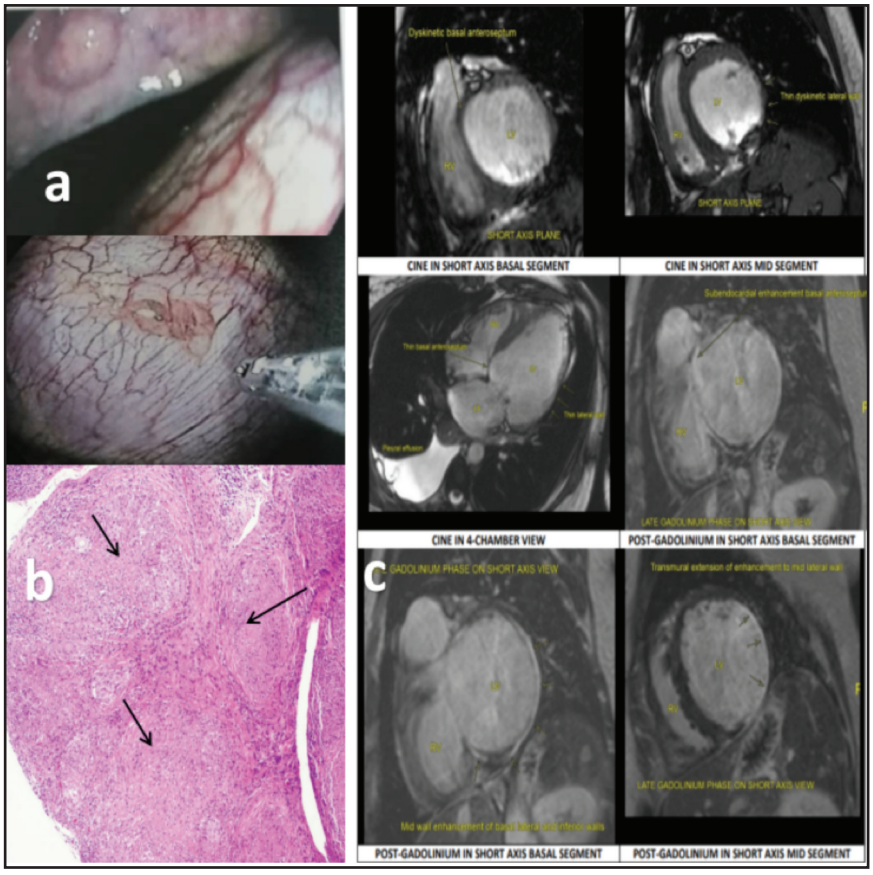

Fig. 2: (a):Pleuroscopy revealed parietal pleura nodule.
(b):Pleural biopsy histology showed multiple coalescing granuloma (arrow).
(c):Cardiac MRI showed late gadolinium enhancement at basal left ventricular segment.

DISCUSSION

Sarcoidosis is a disease with multiorgan inflammatory disorder and no definite criteria to diagnose. The cause is usually idiopathic, and clinical presentation and prognosis is variable. The diagnosis of sarcoidosis is not standardized, but is based on three major criteria: a compatible clinical presentation, the finding of non-necrotizing granulomatous inflammation in one or more tissue samples (not always required, as discussed subsequently below), and the exclusion of alternative causes of granulomatous disease.[1] Sarcoidosis exhibits myriads of spectrum of manifestations ranging from asymptomatic to progressive and relapsing disease. This disease is now much more prevalent than previously estimated and mortality is higher than reported earlier. Certain clinical features are pathognomic for the condition which include Lofgren's syndrome, Lupus Pernio and Heerfordt's syndrome.[5] With nonspecific clinical features of sarcoidosis, histological evaluation of detecting tissue granulomas is imperative in establishing the final diagnosis. Typical histological features are sarcoidosis granuloma include well-formed concentrically arranged layers of immune cells with most prominent central core of macrophage aggregates and multinucleated giant cells.[5] Sarcoidosis granulomas are most often non-necrotic. However, some variants of mixture necrotic and nonnecrotic granulomas can be present in particularly nodular pulmonary sarcoidosis. Differential diagnoses and alternative condition must be excluded in the evaluation of sarcoidosis. CT thorax of the patient revealed mutiple nodular opacity with peribronchovascular distribution and multiple mediastinal lymphadenopathy (Figure 1). As tuberculosis is endemic in Malaysia ,both tuberculosis and atypical mycobacterial infections have to be excluded . In relation to our case, sputum and pleural tissue for mycobacterium culture were both negative and patient did not respond to standard antitubercular medications, which was an important clinical vignettes to find alternative diagnosis to tuberculosis .Patient denied of occupational history and environmental exposure to birds or metals to exclude hypersensitive pneumonitis and chronic beryllium disease which might mimic sarcoidosis.[5]

Cardiac sarcoidosis has been described only in less than 5 % of patients with systemic involvement.[3] Diagnosis of cardiac sarcoidosis is often challenging and there is no definite guidelines of the treatment and disease monitoring. Cardiac sarcoidosis diagnosis usually is inferred when there is diagnosis of histology proven extracardiac sarcoidosis with deteriorating heart function.[2] We did pleuroscopy for our patient and found nodules in parietal pleura in which the histology and cardiac MRI as shown in Figure 2. Histopathological examination revealed multiple non-caseating coalescing granulomatous inflammation and negative for mycobacterium culture. The cardiac MRI showed-severely dilated left ventricle with reduced ejection fraction, LVEF 30%, myocardial inflammation of basal septum and basal inferior LV and RV walls. Extensive mid wall fibrosis of basal lateral, inferior and inferoseptal walls with transmural extension into the mid to apical lateral walls, mid inferior wall and the apex of the LV, Subendocardial fbrosis/infarction of basal anteroseptal LV wall and subepicardial fibrosis of part of basal inferior right ventricle wall. With regards to diagnosis of cardiac sarcoidosis based on the Japanese Ministry of Health and Welfare Criteria, most of the cases fall into the category of clinically diagnosis group in view of endomyocardial biopsy rarely been performed.[2] Major criteria include 1)Advanced atrioventricular block 2) Interventricular septum basal thinning 3)Positive Gallium -67 uptake in heart 4)Depressed left ventricular ejection fraction<50%. Minor criteria include 1)Abnormal ECG findings: Ventricular arrhythmia, axis deviation,complete right bundle branch block or abnormal Q wave 2)Abnormal ECHO: wall motion abnormality 3)Perfusion defect in nuclear imaging 4)Delayed gadolinium enhancement on cardiac MRI 5)Interstitial fibrosis or monocyte infiltration on cardiac biopsy.Clinical diagnosis of cardiac sarcoidosis fulfilled when 2 or more major criteria or 1 major and 2 or more minor criteria are satisfied. Glucocorticoids are a therapeutic choice when it comes to sarcoidosis.

However, there is scarcity of data in regards to their implication in the treatment of cardiac sarcoidosis with no randomised controlled trial (RCT) data. Based on recommendations of the American College of Cardiology (ACC), American Heart Association, and the Heart Rhythm Society, steroid sparing therapy such as methotrexate in our case is important to control the inflammation over the myocardial tissue while optimization of heart failure medication are the cornerstone in treating cardiac sarcoidosis.[2] Other suggested steroid sparing agents in ACC recommendation in low level evidence level depicted in case reports are infliximab, azathioprine, cyclosporine.[2] There are no guidelines available on follow ups for cardiac sarcoidosis. Edward et al suggested that for serial PET cardiac scan 3- 6 months to assess the cardiac activity and monitor treatment response. However, further randomized clinical trial are needed in this in this new field.[2]

Anecdotal data from an observational survey based on a study of 104 cases demonstrated increased survival. Another retrospective observational study from Japan by Yazaki et al. demonstrated a 75% survival at five years in the glucocorticoid arm versus 10% in non-steroid treated patients.[3] The optimal dose of prednisolone and duration of therapy has not been established. Yazaki et al. suggested that an initial dose as low as 30 mg per day may be effective, followed by a slow tapering over 6-12 months once symptomatic improvement has been achieved.[4] Other reports suggested that treatment with prednisolone is effective in preventing progressive pump failure, scar formation and sudden death.[4,5]

Currently, the role of glucocorticoids in the management and treatment of patients with cardiac sarcoidosis remains unclear. Cardiac sarcoidosis usually present in the form of supraventricular and more commonly ventricular arrhythmia, conduction abnormalities such as first-degree heart block progressing to complete heart block, valvular dysfunction such as mitral incompetence, cor pulmonale with advanced fibrotic pulmonary sarcoidosis, pericarditis, or heart failure.[5] Progressive heart failure has accounted for about 25 to 75% deaths in sarcoidosis. The prognosis of symptomatic cardiac sarcoidosis is not well defined. A

previous autopsy series of 113 patients concluded that survival in most patients are limited to approximately 2 years after development of cardiac symptoms.[5]

Sudden cardiac death due to ventricular tachyarrhythmia or conduction block accounts for 30 to 65% of the deaths. Implantable cardiac defibrillator ,ICD implantation should be strongly considered in patients with known cardiac sarcoidosis, LVEF less than 35%, NYHA class III-IV or those with history of spontaneous sustained ventricular tachycardia or ventricular fibrillation. For those patients who progressed, heart transplant remains the last resort for the treatment of refractory cardiac sarcoidosis.[5]

CONCLUSION

One of the main challenges in the assessment of patients with systemic sarcoidosis is determining when and how to evaluate cardiac involvement. Cardiac sarcoidosis should be suspected by all clinicians when an otherwise healthy young or middle-aged patient develops cardiac symptoms or in a patient with known sarcoidosis who develops arrhythmia. Unfortunately, there is no randomized clinical trial for the treatment of cardiac sarcoidosis, further research is necessary for cardiac sarcoidosis to fully understand the impact this treatment regimen will have on patients with cardiac sarcoidosis.

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CONSENT

Written informed consent was obtained from the patient for publication of this case report and all accompanying images.

CONFLICT OF INTEREST

The authors declare that there was no potential conflict of interest relevant to this article was reported.

REFERENCES

1. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 1999; 160(2): 736-55.
2. Hulten E, Aslam S, Osborne M, Abbasi S, Bittencourt MS, Blankstein R. Cardiac sarcoidosis-state of the art review. Cardiovasc Diagn Ther 2016; 6(1): 50-63.
3. Yazaki Y, Isobe M, Hiroe M, Morimoto S-I, Hiramitsu S, Nakano T, et al. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. The American Journal of Cardiology 2001; 88: 1006-10.
4. Kato Y, Morimoto S, Uemura A, Hiramitsu S, Ito T, Hishida H. Efficacy of corticosteroids in sarcoidosis presenting with atrioventricular block. Sarcoidosis Vasc Diffuse Lung Dis 2003; 20: 133-7.
5. Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, Abston E et al. Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med 2020; 201(8): e26-e51.