

Tubercular Neuro-Osseous-Pulmonary Sarcoidosis- A Challenging Combination

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Abstract: *Neuro-Osseo-sarcoidosis is a rare presentation and tubercular etiology for sarcoidosis is always debatable. We had a middle-aged woman who presented with symptoms and signs suggestive of chronic meningitis including arachnoiditis and was further investigated for probable etiologies with CSF study being equivocal with high proteins and normal cell counts. She had contact family history of tuberculosis. On imaging studies, MRI and MRI lumbosacral spine revealed lesions consistent with neuro-osseo-sarcoidosis following which biopsy taken from bony lesions was inconclusive. CT-chest done to see pulmonary involvement suggested typical features of sarcoidosis. She was started with corticosteroids and she had improvement in her symptoms and regain of appetite suggesting response to treatment and confirms diagnosis of disseminated sarcoidosis. On follow-up after 1 month, there was deterioration further in general condition with appearance of new onset focal seizures and neuroimaging suggested multiple ring lesions consistent with tuberculoma along with chest CT imaging showing cavitary lesions in left lung. However, there were partial/complete regressions of all previous lesions in brain and chest. Bronchoalveolar lavage suggested positive acid-fast bacilli and CBNAAT confirmed rifampicin sensitive Mycobacterium tuberculosis. Hence coexistence of tuberculosis and sarcoidosis, reactivation of tuberculosis, or tuberculosis as probable etiology for sarcoidosis could not be ruled out.*

Keywords: Antitubercular therapy, Disseminated tuberculosis, Granulomatous disease, Osseous sarcoidosis

1. Introduction

Sarcoidosis is a systemic disease with heterogeneous manifestations which sometime becomes diagnostic challenge in resource limited setting. Though many etiological associations and pathophysiological mechanisms have been described in literature, a precise causative agent is yet to be identified.

Most common manifestations of the disease (cutaneous/pulmonary/ocular) are ascribed to the hypothesis that an outside/environmental agent is responsible for dysregulated Th1 immune response leading to formation of non-caseating granulomas and organ dysfunction. Though isolated internal organ involvement is rare such cases has been previously reported. Neurosarcoidosis affects almost all components of central as well as peripheral nervous system. The spectrum of CNS disease include Cranial neuropathies of which facial nerve involvement is most common, meningeal disease, inflammatory spinal cord disease which may result from leptomeningeal infiltration and or parenchymal involvement leading to myelitis, peripheral neuropathy presenting as asymmetrical polyradiculoneuropathy to neuromyelitis multiplexa to phenotypic presentation as GBS, hypothalamic-pituitary axis dysfunction presenting as diabetes insipidus and other hormonal irregularities[1].

Bone involvement is seen in 1-15% patients of sarcoidosis and is usually accompanied with skin lesions [2]. Usually, involvement of small bones is seen with lesions being cystic and sclerotic types based on radiological imaging. Long bone involvement is rare but any bone can be involved in sarcoidosis. Long bone lesions usually present as purely lytic, purely sclerotic or mixture of two types [2][3].

Here we present a challenging case of neurosarcoidosis with osseous and pulmonary involvement and later confirms to be tubercular origin.

2. Case Presentation

A 41-year-old woman presented with low grade intermittent fever associated with chills and evening rise of temperature for 6-months. She had consulted various doctors and had taken cocktail treatments of antibiotics (cefoperazone), steroids (prednisolone 10mg for initial 2 months), and antipyretics. Her symptoms were persistent and she developed high grade fever for the last 2-months. For the last 4-weeks she had low back ache that was more with lifting objects and long periods of standing and frontal headache, associated with nausea and non-projectile vomiting. Three days before presentation to us she started talking irrelevantly and became drowsy. She had neither any seizure episodes nor history of focal limb weakness. She also complained of apparent weight loss for past 6-months evident by loosening of clothes. In past history she had a history of contact with tuberculosis with family members.

Her general physical examination was normal except febrile. Abdominal examination revealed traube's space dullness and CNS examination showed neck rigidity with positive Kernig's sign. Rest of systemic examination was unremarkable. A differential of chronic meningitis (tubercular v/s autoimmune v/s carcinomatous) was kept in mind and evaluation started.

Her hemogram showed mild normocytic normochromic anaemia with normal platelet and leukocyte count with shift to left (N80.5L6.3M12.8). Her serum calcium was normal on serial occasions with normal liver function tests except ALP (181 IU/L; Normal: 44-147 IU/L) and GGT (107U/L; Normal: 9-48 IU/L). Urgent CT-head showed ill-defined hypodensity in left frontal lobe. Her CSF analysis suggested protein (128mg/dL), glucose (14mg/dL; serum glucose - 108mg/dL), cells (10), and normal ADA (1U/L). CSF staining and culture were normal. Urine and blood cultures didn't grow any organism. Other tests for common

infections were non-reactive. Ultrasonography-abdomen showed hepatosplenomegaly. Contrast-MRI brain was done that showed diffuse pachymeningeal and leptomeningeal enhancement with multiple ring enhancing lesions with calvarial lesions s/o neurosarcoidosis and right ACA territory early subacute infarct. Ophthalmology evaluation demonstrated no evidence of ocular sarcoidosis. Due to alarming backache, MRI lumbosacral spine and pelvis was done that showed multiple discrete foci of inhomogeneous enhancement with peripheral brush border appearance and few lesions showing intra and perilesional fat and inhomogeneous enhancement in pelvic bones, lumbosacral vertebra, and bilateral proximal femur. This suggested possibility of either osseous sarcoidosis or metastasis from unknown primary. CT guided biopsy of bone lesion was done however that was inconclusive. To see usual site of involvement of sarcoidosis, CT-thorax was done that showed multiple small sized nodules in peri lymphatic distribution along with multiple enlarged lymphadenopathies at station 6, 7 and 10. Biopsy of these lesions could not be possible. BAL for lymphocyte profile could not be done. Serum ACE level came to be 60 U/L (Normal: 8-53 U/L).

Considering brain, chest, and bone images and chronic symptomatology disseminated neurosarcoidosis was diagnosed. She was started on high dose corticosteroids (prednisolone 40mg). Her fever intensity decreased and sensorium started improving. She was discharged on advice to follow up.

After 15 days of discharge she followed up in OPD with clinical improvements. But in next visit 1-month later, she presented to the emergency with complaint of jerky movement of her left hand followed by loss of consciousness and altered sensorium for 3 days duration. She also had multiple episodes of vomiting during this period. Her GCS at presentation was E2V2M3. She had neck rigidity, positive Kernig's sign, and myoclonic jerks in left upper limb. Chest examination had diffuse wheeze bilaterally.

On investigation, she was found to have neutrophilic leucocytosis and anaemia. Her repeat CSF examination showed protein (182mg/dL), glucose (54mg/dL with corresponding serum RBS of 132mg/dL), and cell counts (WBC 150 with L43%N57%). Her CSF stains and cultures were negative again. Repeat CE-MRI brain showed appearance of new non-enhancing lesions s/o acute infarcts. New onset non-obstructive hydrocephalus was also seen, however, compared to previous MRI there was a marked reduction in thickness and extent of enhancements. Repeat CT thorax showed small cavitary lesions in left lung and regression of all previous lesions. Bronchoalveolar lavage was performed that showed acid fast bacilli and CB-NAAT detected Mycobacterium tuberculosis without rifampicin resistance. Her lavage fluid culture showed pseudomonas and klebsiella and antibiotics were added according to sensitivity profile. On starting ATT, her GCS improved to E4V2M5. During hospital stay she developed grade-2 bedsores and culture from bed sore grew klebsiella and Acinetobacter. She was managed with antibiotics according to sensitivity profile and later on discharged in partial recovery state (modified Rankin score-4) with a final diagnosis of

disseminated tuberculosis (brain and lungs), neuro-osseous-pulmonary sarcoidosis (on recovery trend), and hospital acquired-pneumonia and bed sore (klebsiella, pseudomonas, and Acinetobacter). She is in regular OPD follow up and has been afebrile with stable vitals but with neuro disability stage (modified Rankin score-3).

3. Discussion

The patient presents with symptoms and signs suggestive of chronic meningitis and arachnoiditis and imaging studies reveal neuro-osseo-pulmonary sarcoidosis. Despite response to steroid on follow up there is deterioration and further imaging and molecular test consistent with disseminated tuberculosis. Given the history of tubercular contact and prevalence of tuberculosis in our society, reactivation of latent tuberculosis can be suggested but possibility of coexistence of both sarcoidosis and tuberculosis or tuberculosis as the cause of sarcoidosis cannot be ruled out.

Neurological manifestations of sarcoidosis occur in about 5-10% of patients. Meningitis is one of the common presentations of neurosarcoidosis. Another two lines from CNS manifestation. In general, sarcoidosis can involve any bone of the body. Usually bilateral involvement of bones of hands and feet, especially phalanges, are most common. Here discuss clinical presentations of neuro-osseo-pulmo sarcoidosis, very few cases have been reported with concurrent osseous and neuro-sarcoidosis.

On MRI the involved bones show hypointense lesions on T1 weighted images and hyperintense on T2 weighted images. Cases have been reported with long bones, vertebral, and pelvic involvement. In our case similar discrete lesions were found in vertebrae, pelvic, and femur bone with the background of features of probable neuro-pulmonary-sarcoidosis on imaging and less possibility of any other alternative diagnosis. The diagnosis of sarcoidosis was primarily radiological since we could not demonstrate sarcoid granulomas in any organ system. However, serum ACE levels were within normal limits (just above upper limit) which is commonly found during active sarcoidosis. Due to lack of laboratory facility, we didn't do CSF ACE levels that could have provided more weightage to our initial diagnosis. CSF ACE levels have been reported by various authors to be more specific than serum ACE levels though it has poor sensitivity [4].

Sarcoidosis is a multiorgan disease with poorly understood etiology with probable pathogenesis well postulated. Clinical features are often generalised and nonspecific for disease with a considerable overlap with diseases such as tuberculosis, especially in endemic countries like India [5][6]. While some patients present with clinical features weighing more towards sarcoidosis, there is a considerable portion of patients which lie in the grey zone of tuberculosis and sarcoidosis and the same has been classified as tuberculous sarcoidosis, which represent stage of transition between the two [7][8]. The main differentiating feature lies based on biopsy of involved organ system and characteristic lesions showing granulomas specific to both diseases. The difference in clinical features and lab parameters between the two is summarised in table 1 and table 2 respectively [5].

Table 1

Predominant feature	Sarcoidosis	TB
Constitutional	Fatigue, myalgia Fever (less common)	Fever, weight loss
Respiratory	Dry cough Dyspnea	Productive cough, hemoptysis
Extra-thoracic	Parotid enlargement, Bell's palsy, arrhythmias, lupus pernio, and erythema nodosum	Cervical adenopathy, cutaneous sinus, joint pain and swelling, neck stiffness

Table 2

Laboratory investigations	Sarcoidosis	TB
Biopsy	Non-necrotizing lymphocyte poor ("naked") granulomas	Lymphocyte dense necrotizing granulomas
Acid-fast bacilli (AFB) positive and/or culture-positive	May be rarely seen in coexistent cases	Diagnostic
Tuberculin skin test (TST)	Usually negative	Positive, specificity of >85%
IGRA using QuantiFERON-TB-Gold In Tube assay (QFT) in blood ^[11]	Positive in upto 34%	Higher sensitivity and specificity for MTB detection.
Serum angiotensin-converting enzyme (ACE)	More than twice elevation in 60% to 80% cases	Variable
Hypercalcemia	Fairly characteristic	Not seen
Urine analysis-Hypercalciuria	Fairly characteristic	Not seen
Neutrophil/lymphocyte ratio in blood ^[17]	<2.55	≥2.55

In our case on initial presentation in history the clinical features were more consistent with that of tuberculosis and treated with 2-months of ATT in outside hospital with steroid but stopped treatment and on subsequent presentations, investigations were not suggestive of tuberculosis. Based on imaging probable sarcoidosis was diagnosed and treated with steroid. Then during subsequent admission, we found AFB in bronchoalveolar lavage that became the turning point of patient management. Hence, we hypothesize the disseminated sarcoidosis (responded to steroid effectively) had etiology as tuberculosis but latent and with immunosuppression, it became evident. It could have prevented if anti-tubercular treatment would have re-started along with steroids.

The main limitations in this case was lack of tissue diagnosis in initial presentation and lung biopsy (not available in our setting) of pulmonary lesions should have been done that could have yielded more information regarding diagnosis. More over such single case-based study cannot clearly establish a strong evidence for cause-effect relation between the two differentials (tuberculosis and sarcoidosis). Although many other case reports have already established that tuberculosis can precede, coexist, or reactivate during therapy with sarcoidosis.

4. Conclusion

High index of suspicion is required for diagnosing sarcoidosis with uncommon presentations and detailed imaging help. A rule out approach should be considered for diagnosing sarcoidosis with rare organ involvement.

Patient should be monitored after initiating steroids for the risk of reactivation of TB specially in high TB burden countries. For the benefit of doubt, empirical ATT may be started in probable sarcoidosis cases (not supported with biopsy) along with treatment for same.

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