Case report

Case series of concurrent occurrence of sarcoidosis and breast cancer – A diagnostic dilemma☆

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ABSTRACT

Sarcoidosis is a multi-system granulomatous disorder characterized by involvement of multiple systems with or without lymphadenitis. Pulmonary complications are common and may lead to morbidity. Breast cancer is one of the commonest malignancy among women across the world. There is an increased risk of malignancies in sarcoidosis. This association with cancer creates a diagnostic dilemma due to the predominant involvement of nodes and organ systems in both conditions. Here we report three cases of sarcoidosis with breast cancer diagnosed over one year.

1. Introduction

Sarcoidosis is a granulomatous inflammatory disease with its characteristic pathologic hallmark of systemic non-caseating granulomas [1]. Sarcoidosis may affect any organ and sometimes multiple organs at a time. It has an unclear aetiology however available evidence points towards an aberrant immune response as the pathogenic mechanism [2]. Association of cancer and sarcoidosis has been previously described, and this creates a diagnostic dilemma [3]. As early as 1970’s studies have attempted to decipher a cause and effect relationship between sarcoidosis and cancer, but results are conflicting at best [4]. A systematic review involving more than 25,000 patients reported a significant, though moderate, association between sarcoidosis and malignancy. The reported increased risk of malignant involvement included skin (Relative risk (RR) 2), hematopoietic system (RR 1.92), hepatic (RR 1.79), upper digestive tract (RR 1.73), renal (RR 1.55), and colorectal cancer (RR 1.33) [5]. There are no prospective studies looking at the causative association between these two entities.

2. Case series

We report three cases of breast cancer associated with sarcoidosis all of them diagnosed within one year, suggesting that it is, after all, not such a rare entity. In all probability, they are misdiagnosed. Among these three cases, two patients were diagnosed after the
diagnosis of malignancy, and one had a pre-existing diagnosis.

2.1. Case 1

A 46-year old woman was evaluated for right breast lump and diagnosed as clinically stage II, invasive mammary carcinoma – not otherwise specified (NOS), Luminal B subtype. The post-mastectomy staging PET scan (positron emission tomography) revealed Fluorodeoxyglucose (FDG) avid prevascular, right upper paratracheal, mediastinal para-aortic, bilateral lower paratracheal, subcarinal, bilateral hilar and paraesophageal nodes (Fig. 1a). She was subjected to endoscopic bronchial ultrasound (EBUS) and transbronchial needle aspiration (TBNA) to assess the nature of nodes. EBUS TBNA from station 7 node was reported as granulomatous lymphadenitis. GeneXpert and acid fast bacilli (AFB) culture were negative. Tuberculin skin test was found to be positive with 10mm induration. The case was discussed in multidisciplinary tumor board. As she was planned for chemotherapy and there was chance of dissemination of tuberculosis (TB) if the granulomatous lesions were due to TB, she was initiated on empirical anti TB drugs. She received anti-tuberculosis drug therapy for six months. Concurrently she received adjuvant chemotherapy for her breast cancer. She had a reassessment PET computed tomography (CT) after completion of chemotherapy which showed persistence of FDG avid mediastinal lymph nodes with no change in avidity or size (Fig. 1b). Suspecting sarcoidosis her serum angiotensin-converting enzyme (ACE) level was done and found to be 32 U/L. She was subjected to video-assisted thoracoscopic guided biopsy from the subcarinal lymph node to rule out metastasis from breast cancer. The lymph node biopsy histopathology was consistent with non-necrotising granulomatous inflammation, and mycobacterium tuberculosis (MTB) culture was negative. The final diagnosis of granulomatous disease due to sarcoidosis was made. After completion of chemotherapy, she was started on hormonal therapy. For sarcoidosis, it was decided to keep her under follow up as she was asymptomatic. She continues to be asymptomatic.

2.2. Case 2

A 55-year-old lady presented with a right breast lump of two months duration. Clinically she had a contralateral supraclavicular node. USG guided tru-cut biopsy reported Luminal A (ER, PR positive, Her2 negative) invasive mammary carcinoma. Staging PET-CT (Fig. 2) showed FDG avid axillary, left supraclavicular, bilateral upper paratracheal, subcarinal and mediastinal lymphadenopathy.
involving prevascular and bilateral hilar nodes and abdominal nodes with SUV of 3.4–22.8. Since the involved nodal distribution was unusual for a right-sided breast cancer metastasis, she was subjected to a right MRM and left supraclavicular node biopsy. Node biopsy was reported to be non-necrotising granulomatous inflammation. Quantiferon TB Gold and Mantoux test were negative. The ACE level was 130 u/ml. A diagnosis of thoracic sarcoidosis with right-sided carcinoma breast was made. Due to her asymptomatic status, she was kept under observation for the sarcoidosis. She was started on endocrine therapy for breast cancer as she had receptor-positive early-stage disease. She is doing well.

2.3. Case: 3

A 65-years-old lady was evaluated for a self detected left-sided breast lump. She was suffering from sarcoidosis since 2005 and had been previously treated with steroids for one year. Mammogram reported a locally advanced left breast neoplasm with at least 9 abnormal lymph nodes involving all 3 axillary levels. USG guided biopsy of the left breast was suggestive of triple-negative (estrogen receptor (ER), progesterone receptor(PR), human epidermal growth factor receptor (Her2)negative) invasive mammary carcinoma. PET-CT showed metabolically active primary left breast malignancy and FDG non-avid bilateral level IV cervical, bilateral supraclavicular, paraaortic, subaortic, bilateral internal mammary, subcarinal, bilateral hilar, portocaval, left paraaortic lymph nodes, FDG avid and non-avid multiple soft tissue nodules involving bilateral parenchyma, left adrenal and liver lesions. D1, D2, D4, D11, L5 vertebrae, bilateral iliac, right ischium and proximal shaft of the femur showed FDG avid mixed lytic, sclerotic lesions. Serum ACE level was 152 u/L. She received palliative chemotherapy and is currently on follow up. She was not treated for sarcoidosis as she was asymptomatic.

3. Discussion

Prevalence of sarcoidosis in the world is around 11.5/100,000 population [6]. The actual burden of Sarcoidosis in India is unknown, but estimations from hospital-based data in the last decade showed 61.2/100,000 new cases, which is significantly higher than the world average [7,8]. The evaluation of sarcoidosis in the Indian population is still in nascent stages. It is only recently that diagnostic modalities have come to fore but still lacks universal availability and expertise [9]. Endobronchial ultrasound guided TBNA is less
invasive modality for the diagnosis of sarcoidosis [10]. EBUS can be combined with endobronchial biopsy or transbronchial lung biopsy for increasing the yield as shown in previously published studies [10,11]. With the endemic presence of other granulomatous diseases like tuberculosis, and co-occurrence with malignancies makes the diagnosis complex. In the absence of sufficient diagnostic capabilities, some of these patients get unwarranted/inappropriate treatment.

We reported 3 cases of breast cancer that had a concurrent diagnosis of sarcoidosis (Table 1). One of the patients had prior history sarcoidosis while 2 had a concurrent diagnosis of sarcoidosis with carcinoma breast. The radiological features observed in these patients were similar to those in “idiopathic” sarcoidosis. In a large retrospective case series reporting 1000 odd sarcoidosis patients, 43% (429/1000) were females of which 4.6% (20/429) had associated breast cancer [12]. In most of them, the diagnosis of sarcoidosis preceded breast cancer diagnosis by 52–200 months. A smaller proportion was diagnosed concurrently. Both sarcoidosis and breast cancer has a female preponderance.

The co-existence of sarcoidosis and breast involvement has significant clinical implications. A woman of younger age with a prior diagnosis of sarcoidosis, who develops breast lesion in the course of time, should be mandatorily evaluated for breast malignancy as breast involvement with sarcoidosis is rare (<1%) [13]. On the other hand, if an older woman diagnosed with carcinoma breast, develops new pulmonary infiltrates and mediastinal/hilar lymphadenopathy, sarcoidosis should be ruled out. Sarcoidosis may be discovered shortly after breast cancer diagnosis and treatment. It has classical chest involvement but occurs in older women as seen in the current series. It is mandatory to get a histological diagnosis in such cases. Due to availability of less invasive procedures like EBUS guided lymph node biopsy it has become easier compared to a decade ago when mediastinoscopy or video assisted thoracoscopy (VATS) guided biopsy were the only ways to diagnose these cases. EBUS has a diagnostic accuracy of up to 90%, for both malignant and benign conditions [14]. When sarcoidosis is suspected, and scans reveal mediastinal/hilar adenopathy, lymph node sampling is the procedure of choice [15]. Two out of three patients had early-stage cancer with ER positivity and a favourable long-term survival. Bassler et al. postulated that triggering of oligoclonal T cell hyperactivity towards granulomatous disease by tumour antigen(s) could be the reason behind co-existence of sarcoidosis and the malignancy [16]. Such antigens could theoretically be implicated in chemo-naive patients where there is a concomitant presentation of sarcoidosis and cancer. The short interval between the diagnosis of breast cancer and sarcoidosis could support the above hypotheses. Another theory is that sarcoidosis could be an effect of malignancy rather than just a coincidence. A Danish study reports the incidence of sarcoidosis to be higher in inpatient subgroups of lymphoma and breast cancer than the general population. They discovered that the patients developed sarcoidosis after a diagnosis of malignancy on sequential CT-PET scans [17]. Patients in the previous series have done well both on the front of malignancy and sarcoidosis. An Australian and a Danish study also suggests that the presence of sarcoidosis maybe associated with a good prognosis [18, 19]. Data from early-stage lung cancer patients who underwent definitive surgical resection and were found to have the presence of ‘sarcoid like’ reactions in regional lymphnodes had a lower rate of recurrence [20]. Similar reports are also available for other malignancies including Hodgkin’s disease. Since sarcoid-like granulomas are histologically identical to sarcoidosis, the diagnosis of sarcoid-like

### Table 1

| Characteristic | Patient number |
|---------------|----------------|
| Age at diagnosis, years | 46 | 55 | 65 |
| Breast cancer | Right | Right | Left |
| Side | Invasive mammary | Invasive mammary carcinoma | Invasive mammary carcinoma, Grade III |
| Type | pt2N1aM0 | pt2N0M0 | Stage IV |
| Stage at time of diagnosis | MRM + Adj chemo | MRM + Endocrine treatment | Palliative chemo |
| ER | Positive: 70% | Positive 70% | Negative |
| PR | Positive: 20–30% | Negative | Negative |
| Her2nu | Negative | Negative | Negative |
| Time of diagnosis of sarcoidosis since the time of diagnosis of breast cancer | At the same time | At the same time | 14 years before |
| Sites involved by sarcoid | Thoracic | Thoracic and ocular | Thoracic |
| ACE level U/L | 32U/L | 122 | 152# |
| Calcium level mg/dL | 9.02 | 9.5 | 9.88 |
| Mantoux test | 10 mm induration | negative | NA |
| Lymphnode location | Bilateral lower paratracheal, subcarinal, prevascular and bilateral hilar | Left supraclavicular, right paratracheal, prevascular, subcarinal, bilateral hilar | right supraclavicular, para-aortic, right upper paratracheal, bilateral hilar, left axillary, aorto caval, portocaval lymph nodes |
| Confirmation of diagnosis done through | EBUS TBA followed by VATS biopsy: Granulomatous inflammation | Biopsy of supraclavicular lymph node: Granulomatous inflammation | Cervical lymph node biopsy |
| History of anti TB drugs | Given ATT during course of illness | Nil | Nil |
| Treatment given for sarcoidosis | Observation | Observation | Observation |
| Outcome | Doing well, CRa | Doing well, CRa | Under follow up. |

*Clinical Remission, # at time of diagnosis, MRM-modified radical mastectomy, ATT-anti tuberculous treatment, ER: Estrogen receptor, PR: Progesterone receptor, Her2: human epidermal growth factor receptor 2, VATS: Video assisted thoracoscopy, EBUS: endo-bronchial ultrasound.*
reaction should be based on the absence of other features of sarcoidosis [17]. The high rate of sarcoid-like reaction among breast cancer patients in the literature highlights the importance of a thorough clinical investigation when sarcoid-like granulomas are found in the context of known breast cancer to detect the possible presence of sarcoidosis. Furthermore, attention also needs to be paid since sarcoid-like reaction in regional lymph nodes can conceal a metastasis and should be carefully evaluated [19]. The higher frequency of sarcoidosis after specific cancers like lymphoma, breast cancer, suggests a causative association between malignancy or the treatment thereof, and development of sarcoidosis.

As seen in our series, sarcoidosis following malignancy is no different from the “idiopathic” form of the disease. Patterns of lung parenchymal disease and particularly of lymph node involvement in our series, with predominantly subcarinal, paratracheal, and bilateral hilar lymphadenopathy, were similar to previously published series of patients with a breast and sarcoidosis. (21) The availability and routine use of CT and PET-CT scan at diagnosis and during follow-up surveillance of oncology patients may result in an earlier diagnosis of subclinical disease. (21) Our patients were mainly asymptomatic.

4. Conclusion

This is the first case series of patients with co-existent sarcoidosis and breast cancer from the Indian subcontinent. The women belonged to later than usual age and were asymptomatic for sarcoidosis which was primarily intrathoracic in location. Oncologists and pulmonologists should be aware of the co-occurrence of sarcoidosis and malignancy. They should pursue a histological diagnosis instead of assuming it to be malignant or otherwise, which may lead to inappropriate treatment.

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Nil.

Authors’ contribution

Conceived and designed: Mehta AA, K Pavithran.

Data collection and analysis: Mehta AA, K Pavithran.

Writing of the paper: Mehta AA, Wesley M, Vallonthaiel AG, George R, Nidhi S.

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