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Case Report

Coexistence of IgG4-related disease and tubercular lymphadenopathy in a rheumatoid arthritis patient

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ABSTRACT

Extrapulmonary tuberculosis is a very common cause of generalised lymphadenopathy especially in tuberculosis endemic regions like India. A 33-year-old lady who had been diagnosed with rheumatoid arthritis 5 years back and had received treatment with biologicals including adalimumab presented with a 3 week history of persistent fever associated with significant weight loss and abdominal fullness. Investigations pointed towards a picture of tubercular aetiology although, a definite microbiological diagnosis was not possible at this stage. Patient also had an underlying subacute thyroiditis with diffusely increased uptake in Tc99 scan. Considering the background risk factor of use of biologicals and typical clinical presentation resembling tuberculosis, a decision to start antitubercular therapy was taken. The fever resolved but it recurred after 2 weeks and then after an extensive workup, the diagnosis of coexistent IgG4-related disease along with microbiological diagnosis of tuberculosis was established. This case highlights the importance of an active search for coexistent pathologies in cases of lymphadenopathy with insufficient response to standard therapy.

1. Introduction

Tuberculosis has always been a difficult disease to tackle given its multifaceted presentations and variable response to treatment. India, being a tuberculosis endemic nation, has been faced by a number of challenges in TB control. Since there is no end to the number of ways that tuberculosis can manifest itself in the clinical scenario, Indian clinicians are always on the watch out for this dangerous infection. TB lymphadenopathy is one of the most common causes of clinically significant lymphadenopathy in India. Therefore, in patients presenting with lymphadenopathy associated with a clinical profile which matches with TB infection, a tubercular aetiology is often an undoubted main differential. Another problem in obtaining a definitive diagnosis of tubercular lymphadenopathy is the low yield of the bacillus from biopsy specimens. Hence the clinician often has to rely on the histology of the affected tissue to come to a clinical diagnosis and often there is a requirement to start antitubercular therapy without microbiological evidence. This becomes a difficult call to make but sometimes it is unavoidable because the risk of not initiating ATT in a potential TB patients can be catastrophic. In this background, it is important to note that there can be some other differentials of lymphadenopathy and multi-system involvement which have a histologic picture which is not very different from tuberculosis. Such an entity is IgG4-related disease. This present case report is one where there was coexistence of two differentials of lymphadenopathy, tuberculosis and IgG4-related disease.

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2. Case Presentation

Our patient, a 33-year-old lady from Eastern India who was a diagnosed case of rheumatoid arthritis and was under treatment for 5 years, presented with a history of high grade fever for almost 3 weeks associated with chills and rigor. She had been treated with both conventional DMARDs (Disease-modifying anti-rheumatic drugs) and biologicals including adalimumab. The febrile episodes were associated with persistent flu like symptoms including myalgia, fatigue, decreased appetite. Significant weight loss was also present. She also complained of a tense feeling in her abdomen with occasional mild diffuse pain. Her initial workup was aimed at ruling out common persistent infections including tuberculosis, especially since she had an additional risk factor of TB activation after use of biologicals. Tests to detect an underlying sensitisation to the TB bacilli and existence of latent TB was performed. Mantoux test was positive. She tested negative for most other infections but interestingly enough, her blood panel revealed suppressed TSH and increased thyroglobulins for which she was evaluated alongside the workup for her main pathology. Since the initial investigations did not point at any evidence of pulmonary tuberculosis, a search for extra-pulmonary foci was commenced. A CT scan of her abdomen was done keeping in mind about her background in abdominal symptoms. It showed hepatomegaly with fatty changes, mild ascites and omental thickening with solitary aortocaval lymph node thereby pointing towards a picture resembling abdominal tuberculosis and tubercular lymphadenopathy. With the intention of obtaining a microbiological and histological diagnosis, an omental biopsy was arranged. Tissue section from omental biopsy showed omental fibrofatty tissue with multiple caseating and coalescing epithelioid cell granulomata, Langhan's giant cell and moderate chronic inflammation. There was no evidence of any atypia or malignancy. Ziehl - Neelsen staining and CBNAAT (cartridge based nucleic acid amplification test) of tissue specimen failed to reveal any evidence of the bacillus. This point in the patient's workup was crucial since the treating physicians had to make the tough call whether to label the condition as tuberculosis based on the histopathological features and initiate antitubercular therapy or whether to search for alternative diagnoses. This histology is of particular interest since a similar picture is found in some other multisystem diseases which are fairly rare including IgG4-related disease and multicentric Castleman's disease. Especially in the Indian scenario with tuberculosis being the predominant explanation for most such findings it is common to halt the workup at this stage and start antitubercular therapy.

In this particular case, side-by-side workup for her thyroid abnormality showed bilateral sub-centrimetric thyroid nodules in thyroid ultrasound. The next line workup being a Tc99 thyroid scan revealed diffusely increased uptake suggestive of toxic goitre.

Before initiating on antitubercular therapy, a FDG PET scan was done to look for any other foci which might be coexistent and in a latent state. It showed FDG avid lymph nodes in the bilateral supraclavicular, mediastinal, upper retroperitoneal and upper portocaval region. Although, tubercular lymphadenopathy can affect such wide domains, other diseases which can explain this presentation were searched for especially keeping her thyroiditis in mind. IgG-related disease and multicentric Castleman's disease were two such entities. However, keeping the most predominant and treatable differential in mind, decision was taken by the multidisciplinary team to initiate Anti-tubercular therapy. The patient improved symptomatically. Hence, she was advised to continue her ATT and follow-up visits were scheduled.

But 2 weeks later, she needed to be readmitted with a week-long high grade fever associated with cough and GI symptoms like vomiting and diarrhoea. This time her blood reports revealed eosinophilia, persistent hyperthyroidism, raised inflammatory markers and positivity for *Salmonella typhi* infection. Serum IgG4 levels were found to be elevated. As the suspicion of other pathology increased, a repeat biopsy from a thoracic node was planned. Vascular surgery team was consulted and biopsy of left internal mammary lymph node was performed. Notably enough, this time CBNAAT of lymph node biopsy sample was positive for TB. Histopathological examination report showed similar findings of omental biopsy, that being multiple caseating and coalescing epitheliod cell granulomata, Langhan's giant cell, foreign body type of giant cells. However, this time an excess of plasma cells was noted which stained positive for IgG4. (Figure 1)[1] A multidisciplinary team meeting with departments of pathology, haematology, endocrinology and internal medicine was arranged and after discussion of the case details and existing literature the collective decision of the diagnosis was established as coexistent tuberculosis and IgG4-related disease. She was started on IV steroids as induction therapy and maintained on oral steroids alongside the continuation of NTEP (national tuberculosis elimination programme) recommended dose of drug sensitive extrapulmonary tuberculosis consisting of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol. Her condition improved and clinical, biochemical and radiological remission was obtained on follow-up visits and tests.

3. Discussion

The clinical picture which this patient presented with, matches well with the commonly encountered scenario of extra-pulmonary tuberculosis. But the coexistence of thyroiditis in this patient led the internal medicine team to look for other rare differentials which could have

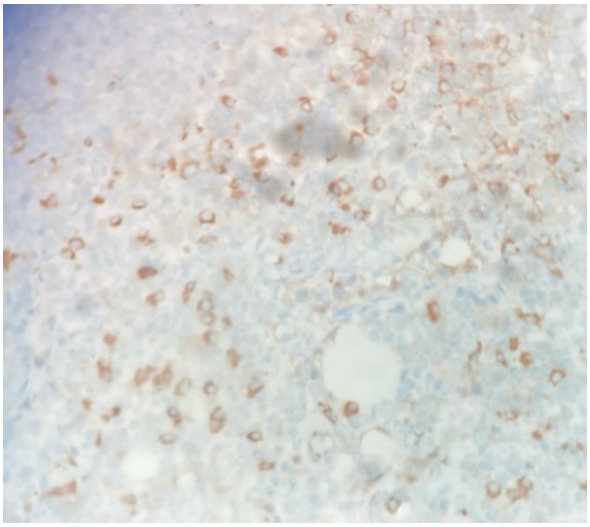

Figure 1

explained the entire picture rather than assuming that both these findings were separate disease entities. The suspicion became more relevant when the patient had another flare of her symptoms even after initiation of antitubercular therapy. The main differentials of this clinical picture of multisystem involvement with widespread lymphadenopathy include infections like tuberculosis, sarcoidosis, IgG4-related disease, lymphoma and idiopathic multicentric Castleman's disease. The probability of a malignancy was ruled out by absence of neoplastic features on histopathology.

IgG4-related disease (IgG4RD) is a multisystem, fibroinflammatory condition which can affect virtually any organ. The multifarious presentation of IgG4RD coupled with its rarity makes its diagnosis quite challenging.[2] IgG4 related thyroiditis, previously described as Riedel's thyroiditis could potentially explain the entire clinical picture.[3] The presence of IgG4 related disease was confirmed by the elevated levels of IgG4, high IgG4/IgG ratio and presence of plasma cells which stained positive for IgG4.

Another disease entity with a close similarity in cellular architecture with IgG4-RD is a rare lymphoproliferative disorder, that is Castleman's Disease.[4] To distinguish between the two, the role of IHC (Immunohistochemistry) is extremely important along with histopathologic examination and biochemical markers like IL6, CRP etc. IgG4 levels may be raised in multicentric Castleman's disease as well.[5] IL6 being an marker of inflammation, rises in many inflammatory conditions such as rheumatoid arthritis, multicentric Castleman's disease, Crohn's disease and COVID-19. CRP also rises on various conditions. In this particular case, serum IL6 levels could not be done due to financial constraints but raised serum IgG4 levels and serum IgG4/IgG ratio were supportive of IgG4-RD. Presence of eosinophilia in this patient also supported IgG4-RD since eosinophilia is a common association of it.[6] Systemic IgG4-RD has very close similarity with a few conditions which have even been described as IgG4-RD mimickers. The list includes conditions like Sjögren syndrome, granulomatosis with polyangiitis, and multicentric Castleman disease.[7] The list widens significantly if region-specific phenotype is considered. Tuberculosis is usually not considered as a close differential of IgG4-RD but coexistence of Tuberculosis and IgG4-RD has been observed in a number of cases.[8] Whether tuberculosis is a probable risk factor for development of IgG4-RD still remains to be investigated.

4. Conclusion

The art of diagnosis involves suspecting common diseases first and going to the rarer ones only when the former does not explain the clinical picture sufficiently well. This approach was followed initially in this case. Since tuberculosis is such a predominant and widespread health problem in India, it was first thought of, and since the clinical picture matched very well, the patient was managed accordingly. Coexistence of a thyroid problem and recurrence of symptoms even after initiation of ATT led to a search for alternate explanations or a coexistent separate pathology. Hence, this case illustrates the importance of keeping a wide outlook for all other differentials and possibility of coexistence of pathologies in all scenarios. Missing a coexistent disease can lead to unachieved remissions, chronic problems and improper and insufficient treatment. This case highlights the importance of evaluation for IgG4-RD in patients of tubercular lymphadenitis and other extra-pulmonary tuberculosis patients who are not responding to ATT sufficiently. Active search and a low threshold of suspicion of IgG4-RD in such patients can potentially lead to an increase in the number of IgG4-RD diagnosis and subsequent successful management.

5. Patient's Consent

Patient's consent for publication of this case was taken.

6. Source of Funding

This case report received no external funding.

7. Conflict of Interest

The authors declare no conflicts of interest.

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