CASE PRESENTATION:

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CASE HISTORY

A 40 year old Native American male with a 1 year history of untreated HIV infection presented with shortness of breath, productive cough and fever of 6 weeks duration. He was noted to have cervical and axillary lymphadenopathy on exam. The chest radiograph showed densities compatible with interstitial pneumonitis and his sputum was acid fast bacilli (AFB) smear and culture positive for *M. tuberculosis* which was susceptible in vitro to all first line antituberculosis medications. An axillary lymph node biopsy showed caseating granulomas with numerous acid fast bacilli consistent with TB lymphadenitis. The CD4 count was 131 cells/ul. Following initiation of treatment with standard antituberculosis therapy, INH, rifampin, ethambutol, and PZA daily, his symptoms progressively improved. Two weeks after starting TB medications, Atripla (combination tablet consisting of efavirenz, emtricitabine, and tenofovir) was added.

The treatment course was complicated by the development of immune reconstitution inflammatory syndrome (IRIS) reaction which was manifested by recurrent fevers, abdominal pain, respiratory failure and renal failure which necessitated discontinuation of the Atripla for about 2 months. The patient attributed these new symptoms to INH and was unwilling to take further INH. His antituberculosis regimen was changed to moxifloxacin, ethionamide, rifampin, ethambutol and PZA. Moxifloxacin and ethionamide were discontinued when drug susceptibility results became available.

After 3 months of treatment, a skin biopsy of a small thigh lesion revealed Kaposi sarcoma, while a cervical lymph node biopsy revealed necrotization with acid fast bacilli, but was culture negative. The patient subsequently received a further 9 months of therapy with daily rifampin, ethambutol and PZA. Treatment was self administered and the patient was confirmed to be adherent by pharmacy pill count and multiple physician visits. The patient tolerated the treatment well with significant clinical improvement. Sputum cultures converted to AFB negative by the third month. After 1 year of antituberculosis therapy, the pulmonary infiltrates had resolved and his CD4 count rose to > 400 cells.

Despite the good radiographic, bacteriologic, and clinical response to treatment, the patient had persistent lymphadenopathy. At the completion of 12 months of Rifampin, Ethambutol, and PZA, two tender, erythematous and fluctuant cervical nodes were still present. Aspiration of the larger node obtained about 1 cc of purulent fluid which was AFB smear positive and PCR positive for M. tuberculosis, but culture negative. Treatment was stopped and the patient remains asymptomatic. The lymph nodes have slowly regressed in size during the 3 months after discontinuation of antituberculosis treatment.

Treatment was extended to 12 months in this patient due to the slow conversion of sputum cultures to negative, disseminated disease and HIV infection, and the non standard treatment regimen.

PATHOPHYSIOLOGY

Mycobacterium tuberculosis is most commonly spread via the respiratory route by inhalation of infected aerosols. These aerosols contain small droplets, termed infectious droplet nuclei, which contain viable *M. tuberculosis* organisms. After inhalation of *M. tuberculosis* into the lungs, a short period of replication occurs prior to mobilization of a lymphocyte-mediated immune response. During this initial phase of infection, the tuberculosis bacilli disseminate to extrapulmonary sites via lymphohematogenous spread. This process results in the influx of lymphocytes and macrophages into infected lymph nodes producing granulomatous inflammatory responses and granuloma formation.

EPIDEMIOLOGY

Ninety-five percent of mycobacterial cervical lymph node infections in adults are caused by *M.tuberculosis*. Tuberculous lymphadenitis accounts for 5% of all tuberculosis cases in the immunocompetent adult population and is the most commonly diagnosed form of extrapulmonary TB in the US and globally (5,8,19,22). In 2009, 44.9 % of all extrapulmonary TB cases in the United States were lymphatic (4). Cervical lymph node involvement, previously termed "scrofula", is the most common site. In a study of 100 adult immunocompotent patients with TB lymphadenitis, 92% had cervical or supraclavicular lymphadenitis (2).

CLINICAL PRESENTATION

In most cases tuberculous lymphadenopathy is associated with progressive primary tuberculosis. Patients note painless masses which are persistent and tend to enlarge. The infected lymph nodes are initially firm and have a rubbery consistency. They generally become firmer as the disease progresses. In the majority of cases there are no general or systemic symptoms, however malaise and weight loss have been noted in 20 - 43% of patients (10). Two thirds of patients present with multiple lymph nodes and one third have bilateral lymph node involvement. In some instances the nodes become fluctuant and may rupture resulting in a draining fistula or ulcer.

HIV infected patients usually present with systemic symptoms(malaise, weight loss fever). Initially the nodes of HIV infected patients tend to be firm, discrete and painless. If left unchecked the nodes become fluctuant and drain spontaneously with a sinus tract formation. According to a 1994 study conducted by the Tanzanian National Institute of Medical Research, which compared the clinical features of HIV seropositive and HIV seronegative patients with tuberculous lymphadenitis, the lymph nodes of HIV seropositive patients were significantly less enlarged than in HIV seronegative patients (1). Half of the HIV infected patients had lymph nodes smaller than 2.5 cm(1). According to a study conducted by the Bamrasnaradura Infectious Diseases Institute in Thailand Paradoxical re-enlargement of involved lymph nodes along with fever are also the most common clinical features of Immune reconstitution inflammatory syndrome(3).

DIAGNOSIS

Diagnosis can be made by a positive sputum culture for M. tuberculosis in a patient with pulmonary disease and enlarged nodes. When respiratory samples are smear and culture negative, either a fine needle aspiration (FNA) for cytology and culture or an excisional biopsy for smear, culture, and pathological examination should be done. The smear is often negative in tissue specimens due to the low number of organisms, but culture may be positive in up to 80 percent of persons. (24) The presence of non caseating granulomas in an individual with risk factors for tuberculosis, especially if the individual has a positive tuberculin skin test (Mantoux) and/or interferon gamma release assay (IGRAs), supports a clinical diagnosis of tuberculous lymphadenopathy. However the pathology alone does not differentiate tuberculous adenopathy from other granulomatous infections. Recently PCR has been used by some clinicians but results have been variable.

TREATMENT

Effective treatment of TB lymphadenopathy caused by drug susceptible *M. tuberculosis* can usually be accomplished with the 6 month standard short course therapy regimen. A 1986 study by the British Thoracic Society noted similar results when a 6 month regimen of INH and rifampin, supplemented by PZA was given compared to 9 months of INH and rifampin. Nine patients out of the initial 199 were diagnosed with clinical relapse but all 5 of the nine who had specimens cultured were negative (17).   Paradoxical enlargement of involved lymph nodes or even the appearance of newly enlarged lymph nodes can occur while patients are receiving appropriate therapy. As occurred in the case described above, these paradoxical reactions rarely indicate treatment failure. However they often necessitate a repeat lymph node aspirate or biopsy to exclude disease progression or emergence of drug resistance. A report by the Lancashire Postgraduate School of Medicine and Health of the clinical outcomes of 100 cases of TB lymphadenitis studied prospectively in Preston, UK found; despite the paradoxical enlargement of lymph nodes during treatment, 6 month treatment is sufficient unless bacteriologically confirmed relapse occurs. Treatment, either surgical or medical, of residual lymph nodes at the end of therapy is not required unless the presence of viable TB bacilli is confirmed through culture.

TEACHING POINTS and KEY CONCEPTS

1. Lymph node disease is the most commonly diagnosed form of extrapulmonary TB.

2. The most common cause of cervical lymph node enlargement in developing countries is TB.

3. Six months is usually sufficient for the treatment of lymphatic TB unless there is drug resistance, bacteriologically confirmed delayed response, or treatment failure (positive culture at 4 months).

4. Treatment often needs to be extended in HIV infected individuals, especially in those with extensive or disseminated disease and in those with delayed sputum conversion (positive at two months of later).

5. A presumptive diagnosis of TB as the cause of enlarged lymph nodes is made when a positive culture for *M tuberculosis* is available from another site (usually respiratory). Patients without positive respiratory cultures should have either a FNA of the node for smear, culture, and cytology or an excisional biopsy for smear, culture, and pathological examination. Smears may be positive < 50% of the time but cultures are positive in up to 70% of individuals. A positive TST or IGRA may provide additional support for the diagnosis.

6. Lymphadenopathy as part of disseminated TB is much more prevalent in HIV infected patients.

7. Up to 16% of patients develop new nodes during the course of TB Treatment. This represents an immune response to killed mycobacteria. Residual lymphadenopathy at the conclusion of treatment is present in 23-41% of patients and does not require extension of therapy unless the culture is positive.

8. The enlargement of additional nodes during treatment is a common symptom of an IRIS reaction. Lymph node re-enlargement and fever are the most common symptoms of an IRIS reaction.

9. Lymph node aspirates which are smear or PCR positive are not an indication of treatment failure. In this clinical situation, the positive smear or PCR is usually due to the presence of non-viable organisms. A positive culture is usually needed to document treatment failure

10. Surgical excision is rarely required as a treatment for tuberculosis cervical lymphadenopathy. This patient's biopsies were done to exclude treatment failure and other disease processes.

11. TB lymphadenopathy in HIV negative individuals is usually not associated with constitutional symptoms (fever, malaise, weight loss, night sweats), however systemic symptoms are common in HIV infected individuals.
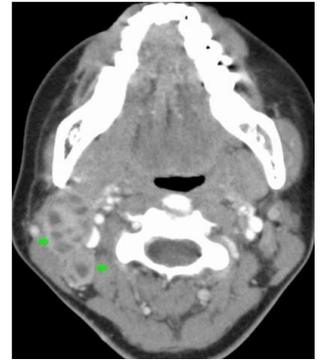
Pictures are intended to show examples of TB lymph node disease, they are not related to this specific case presentation

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