

# Treatment Failure of Tuberculosis due to Concomitant Pathology

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## Introduction

Tuberculosis is a worldwide problem. Nearly 3 million cases of tuberculosis occur per year in Southeast Asia alone.<sup>1</sup> Several factors contribute to treatment failure and significant morbidity and mortality. While the most common causes in the "Third World" include poor compliance, late presentation, improper therapy, and the development of drug resistance<sup>2</sup>, underdiagnosis of this disease is an important reason in the West.<sup>3</sup> We present two cases that demonstrate the importance of another factor, the impairment of the body's innate defense mechanism due to concomitant pathology, as a cause of treatment failure.

## Case Report

### Case 1

A 19-year-old male was referred to the Infectious Diseases clinic for the evaluation of a progressively increasing neck swelling associated with persistent fever and pain. He was given anti-tuberculous therapy (ATT) at another hospital for tuberculous cervical lymphadenitis and Pott's disease of the lumbar vertebrae, which had caused a compression fracture with spinal cord impingement. According to the patient and his family, compliance with the drug regimen was good.

Examination revealed a 15-centimeter firm, tender right cervical lymph node. Fine needle aspiration biopsy (FNAB) confirmed a chronic granulomatous process. A nine-month course of ATT (an initial 4-drug regimen consisting of isoniazid, rifampicin, ethambutol and pyrazinamide in doses appropriate for weight for 2 months, followed by a continuation phase of isoniazid and ethambutol) was completed with good compliance and symptomatic improvement, although he had several isolated recurrences of bacterial superinfection.

Three months after completing his ATT, the patient returned with symptoms of fever, weight loss, and recurrence of his neck swellings. A chest CT showed mediastinal and axillary adenopathy. Diagnosed as having a relapse of his TB, he was restarted on the same regimen of ATT. The patient's condition worsened on subsequent follow-ups, and MRI revealed progressive adenopathy and the development of cord compression. The patient underwent surgical decompression of the spinal cord with concurrent vertebral bone biopsy and an excisional lymph node biopsy. Bone histopathology revealed a chronic granulomatous process (Figure 1) while the lymph node biopsy showed an effaced architecture, infiltrative inflammatory cells with predominant lymphocytes, as well as atypical cells (Figure 2). Immunophenotyping confirmed a T-cell rich B-cell non-Hodgkin's lymphoma.

The final diagnosis was a stage IIIB non-Hodgkin's lymphoma with concomitant disseminated TB. The patient is currently continuing his ATT regimen and is receiving chemotherapy.

### Case 2

A 62-year-old male presented to the Emergency Department with complaints of progressive dyspnea, fever, malaise, and weight loss almost a year after completing, with good compliance, anti-tuberculous therapy (an initial intensive phase of isoniazid, rifampicin, pyrazinamide and ethambutol in weight-appropriate doses for two months, followed by a continuation phase of isoniazid and ethambutol) for culture-proven, drug-sensitive pulmonary tuberculosis. One and a half years earlier, he had suffered similar symptoms of dyspnea and dysphagia. A chest x-ray had revealed a cavitating apical lung lesion and mediastinal adenopathy. Fiberoptic bronchoscopy was performed. Culture of the bronchoalveolar lavage grew *Mycobacterium tuberculosis*, and the patient was treated with a 7-month course of anti-tuberculous therapy (an initial intensive phase of isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin, followed by a continuation phase of isoniazid, rifampicin, and ethambutol). Subjective clinical improvement in symptoms and radiological evidence of disease regression was documented.

A chest X-ray taken for his current complaints revealed relapse of mediastinal along with left-sided atelectasis secondary to left mainstem bronchial compression. In light of his past medical history, he was admitted with the provisional diagnosis of mediastinal TB lymphadenitis resistant to first-line therapy. During his hospital admission, he suffered a respiratory arrest secondary to tracheal compression. The patient was emergently intubated and transferred to the intensive-care unit. Once stabilized, an excision biopsy of the right supraclavicular node was undertaken. The histopathology showed diffuse small cleaved cell (mantle cell) non-Hodgkin's lymphoma. In addition, culture of the lymph node material grew *Mycobacterium tuberculosis*.

The patient's final diagnosis was non-Hodgkin's lymphoma with concurrent tuberculous lymphadenitis. He has to date received three courses of chemotherapy for his lymphoma and restarted ATT.

### **Discussion**

Tuberculosis is caused by *Mycobacterium tuberculosis*, an aerobic, non-spore-forming, acid-fast bacillus that is transmitted by aerosolized droplets. Within the body, these bacilli are ingested by macrophages and either die or proliferate. An effective immune response is only achieved after widespread blood or lymphatic spread has occurred.<sup>3</sup> The bacilli are walled off by granulomatous inflammation, and some bacilli persist in these granulomas. This stage is known as primary tuberculosis, and is often asymptomatic. Post-primary tuberculosis manifests as a systemic illness, and occurs due to reactivation of a primary focus, or exogenous reinfection<sup>4</sup>, either in the lung or in an extrapulmonary site. Central to the effective control of tuberculosis is the body's cell-mediated immune system, which aborts 90-95% of infections. Symptomatic tuberculosis occurs in only 5-10% of infected individuals.<sup>3</sup> Anti-tuberculous therapy acts to augment the host's immune response and does not, by itself, effect a cure.

Intact cell-mediated immunity can be demonstrated by a positive Mantoux skin test. Suppression of cell-mediated immunity would promote symptomatic disease, as is evidenced by the increasing incidence of tuberculosis in the 1980s, paralleling the rise in the incidence of HIV infection.<sup>5</sup> Alterations in cell-mediated immunity should always be considered as a cause of treatment failure.

A primary malignancy such as lymphoma may cause suppression of cell-mediated immunity. It is important to recognize that tuberculosis of the lymph node may occur as a result of this disturbance, with the concomitant presentation of both pathologies.<sup>6-8</sup> The

incidence of TB lymphadenitis in lymphoma patients is much higher than in the patients without a malignancy<sup>8</sup> and the presence of TB may be the main factor contributing to the death of the patient.<sup>9</sup> Some studies suggest that the chronic inflammation of TB lymphadenitis may actually precede and accelerate the onset of the lymphoma.<sup>6,7</sup> It is interesting to note that one study found the incidence of disseminated tuberculosis to be more common in non-Hodgkin's lymphoma as compared to Hodgkin's disease.<sup>8</sup> Both of our patients suffered from non-Hodgkin's lymphoma. Geographic location also appears to have an impact on the concurrent appearance of both pathologies<sup>10,11</sup>, the association being higher in high-prevalence areas of TB.

The prevalence of both individual diseases in Pakistan is high. According to one study, lymphoma ranks closely behind lung cancer as one of the most common malignancies encountered.<sup>12</sup> In contrast to the Western literature, the incidence of this malignancy is higher in males.<sup>12</sup> As mentioned before, tuberculosis is also endemic in Pakistan<sup>1</sup> and it is among the differential diagnoses of a variety of clinical presentations. The clinical presentation of the two diseases is similar, thus presenting a diagnostic challenge. The patient with either disease can complain of progressive lymphadenopathy with constitutional symptoms of low-grade fever and weight loss. The presence of both diseases at the same time could thus be masked by symptoms suggestive of one or the other. When the clinical presentation fails to differentiate between them, other noninvasive and invasive methods are of use.

Imaging modalities show some promise in helping to differentiate tuberculosis from lymphoma. Yang et al support the use of contrast-enhanced CT as being a viable option.<sup>13</sup> Their study shows that patients with tuberculosis (nondisseminated and disseminated) had mesenteric nodal involvement whereas those with Hodgkin's disease did not show this pattern. In addition, lower para-aortic nodes were more often involved in lymphoma than in nondisseminated tuberculosis. The anatomic involvement was not significant, however, in the comparison of patients with disseminated TB and non-Hodgkin's lymphoma. In patients with tuberculosis, peripheral enhancement of the involved nodes was the rule, whereas the majority of lymphoma patients showed a homogenous nodal enhancement.

A definitive diagnosis can only be achieved by positive cultures, with histopathology<sup>9,14</sup> providing supporting evidence. In obtaining biopsy specimens, pitfalls of FNAB must be realized, especially when a lymphoproliferative disorder is in the differential. Performing excisional or incisional lymph node biopsy is preferred when lymphoma is suspected, as the characteristic histopathologic features of both disease processes can be easily delineated by this method. In view of the delay in diagnosis of the concomitant pathologies in both of our cases, and because of the high prevalence of TB and lymphoma in Pakistan, we would recommend early evaluation of the lymph nodes by excision biopsy to obtain a tissue and microbiologic diagnosis and therefore allow optimum treatment. However, the significant morbidity associated with any invasive procedure, especially laparotomy for the retrieval of an abdominal node, lends further weight to trying to find a noninvasive method with sufficient sensitivity and specificity that may become a routine and cost-effective diagnostic tool.

These cases demonstrate that treatment failure of extrapulmonary TB in a previously healthy patient should prompt investigation into finding common as well as uncommon causes, including concurrent pathology. Both lymphoma and tuberculosis show a high

prevalence in Pakistan, with the published literature showing an association between the two. Reduction in morbidity and mortality can only be achieved if there is an awareness of this phenomenon and a low index of suspicion, leading to early diagnosis and simultaneous treatment of both pathologies.

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