# PROLONGED FEVER DURING THE TREATMENT OF PULMONARY TUBERCULOSIS

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**ABSTRACT**

**A study was carried out to investigate the causes of prolonged fever or onset of fever, after starting anti-tubercular treatment (ATT) in sputum smear positive, HIV negative patients admitted in a Tuberculosis (TB) Sanatorium for directly observed therapy (DOT). A total of 40 patients were studied. All were males with age ranging from 22-55 years (mean 43 years). There were 22 (55%) patients with radiological extensive disease, 12 (30%) of whom had toxemia of TB (any three of the following, <90% body weight, hypoalbuminemia, hyponatremia, severe normocytic anaemia, <5mm response on tuberculin testing). Radiologically, moderately extensive disease was seen in 9 (22.5%) cases, whereas focal disease was present in another 9 (22.5%) patients. There were 28 (70%) patients who had evidence of dissemination of disease to extra pulmonary organs. It was found that fever occurred because of direct complications of TB in 22.5%, TB hypersensitivity (cold abscess) in 12.5%, drug resistance in 10% and drug reactions in 22.5%. Other diseases were the cause of fever in 32.5%. These included superadded lung infections in 15%, malaria in 7.5% anaemia in 5%. Filariasis and amoebic liver abscess in another 2.5% each. It is concluded that such fevers require a systematic and detailed investigation rather than attributing fever to drug resistance orTB toxemia alone.**

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**KEY WORDS :Prolonged fever; Pulmonary tuberculosis; Treatment.**

## Introduction

Fever has been reported to occur in 60-85% of patients afflicted with pulmonary TB [1]. As a rule every case of active pulmonary TB exhibits some degree of pyrexia which is one of the important signs of TB activity [2]. Fever usually resolves by the second week of starting chemotherapy [3]. Modern day chemotherapy assures cure in virtually all compliant patients [4]. However, there are subsets of patients who remain febrile beyond a reasonable period of time or develop fever during treatment. These cases raise issues such as correct diagnosis, drug resistance or associated cryptic disease [5]. This study has been carried out to investigate the causes of fever that occur in such patients.

### Material & Methods

This study was carried out in a TB sanatorium where only male patients are admitted for directly observed therapy. Only fresh sputum positive cases were eligible for entry into the study, if they had fever for more than 2 weeks after starting chemotherapy or if they developed fresh fever for 7 days while on treatment. Fever was defined as elevation of mouth temperature >100°F recorded at least once in 24 hours. The study commenced on 1 December 99 and ended on 30 September 2000. All patients were administered standard chemotherapy (2SHRZ/2EHRZ+4HR) modified as recommended [6]. Patients above 40 years of age received ethambutol containing regimen whereas those below 40 years received the streptomycin regimen. All dosages were standardized for weight as recommended [7]. Once inducted into the study the patients were examined in detail at least 3 times per week for development of any fresh clinical findings and weight recorded once a week. Clinical examination included palpation of liver, spleen, all sites of lymph nodes, caecal area, spine, and funduscopy. A high calorie diet was provided (50 Kcal/Kg) along with high proteins (2g/Kg) and vitamin supplements. Sputum smears were obtained once a week. A serial review of chest X-rays was done. Laboratory tests as indicated in Table-1 were performed.

TABLE 1

**Protocol for investigation of cases of prolonged fever undergoing treatment for pulmonary tuberculosis**

| | |
|---|---|
| 1. | Complete blood counts done weekly |
| 2. | Peripheral smears for toxic granulation, type of anemia, haemoparasites, abnormal cells |
| 3. | Bone marrow studies* |
| 4. | Blood cultures |
| 5. | Urine pyogenic cultures and MTB cultures |
| 6. | Sputum studies |
| 7. | Tuberculin test (1 TU) |
| 8. | Serial review of CXR |
| 9. | Ultra sound chest wall and abdomen |
| 10. | Anti-nuclear antibodies* |
| 11. | Cerebrospinal fluid examination* |
| 12. | CT scan chest and / or abdomen* |
| 13. | Bronchoscopy, lavage, biopsy* |
| 14. | Eliminate suspect drug |
| 15. | Repeated detailed clinical examination |

* where indicated; MTB - mycobacterium tuberculosis

All patients were classified according to radiological extent of involvement on chest X-ray, evidence of exra pulmonary involvement and presence of toxaemia of TB as follows :

1. Radiological extent

(a) Focal disease minimal, where less than one zone involved

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on chest X-ray with non cavitary disease or severe if cavitation present

(b) Moderate disease where more than one zone but less than three zones involved with non cavitary disease.

(c) Extensive disease if cavitation involved more than one zone or non cavitary disease involving more than three zones.

2. Disseminated disease was defined as clinical, sonological, radiological, or laboratory evidence of involvement of extra pulmonary organs but excluding pleura.

3. Toxaemia was defined as patients having any three of the following (a) <90% of the body weight (b) serum albumin <3.5g/dl (c) serum sodium <130meq/l (d) tuberculin test (1 TU) <5mm (e) normocytic normochromic anaemia with haemoglobin <8.0g/dl.

## Results

A total of 40 patients were studied. All cases were male, sputum smear for acid fast bacilli positive, and HIV negative. The age ranged from 22-55 years with a mean age of 43 years. 4 patients had diabetes mellitus, 2 had cirrhosis of liver and 1 had dilated cardiomyopathy. There were 14 smokers and 3 known cases of alcohol abuse.

A total of 22 patients had radiologically extensive disease. 20 of these had dissemination to other organs. 12 had additional toxaemia. Radiologically moderate or focal disease was seen in 9 patients each. There was dissemination in 4 cases, in each of these groups. However, none of these had toxaemia (Table-2).

TABLE 2

**Classification of 40 patients of pulmonary tuberculosis having prolonged fever**

| Radiological extent | Not disseminated | Disseminated | Toxemia & dissemination | Total |
|---|---|---|---|---|
| Extensive | 2 | 8 | 12 | 22 |
| Moderate | 5 | 4 | 0 | 9 |
| Focal severe | 2 | 2 | 0 | 4 |
| Focal minimal | 3 | 2 | 0 | 5 |
| | 12 | 16 | 12 | 40 |

The causes of fever detected are given in Table-3. It was seen that there were 9 patients with direct complications of TB. In 4 cases no cause other than disseminated TB with toxaemia was detected. Asymptomatic Pott's disease of the spine with para spinal abscess was detected in 2 patients. Loculated empyemas hidden behind radiological shadows of extensive disease were found by ultra-sonography of chest in 2 patients. One patient had a minimally symptomatic TB arthritis of hip with peri articular abscess detected by CT scan. Cold abscess, presumably a hypersensitivity manifestation of TB, was seen in 5 patients. There were 2 mediastinal abscesses detected by CT scan and 2 in the retroperitoneal location by ultra-sound. A cold abscess was also seen in the retropectoral area by ultra sound. Drug resistance was seen in 4 cases, 3 had rise and fall phenomena and 1 had treatment failure. All these cases were found to have multi drug resistance on sputum culture.

Fever due to drug hypersensitivity was seen in 9 cases. Streptomycin associated fever was seen in 7 cases but there was no rash or eosinophilia. In 2 cases, isoniazid induced lupus was detected. There were 13 patients who had fever due to associated illness. Of these, 6 patients had super added pyogenic lung infection and 3 patients had malaria. Severe anaemia alone was the cause of fever in 2 cases, while filariasis and amoebic liver abscess was seen in one case each. After effective management all cases made a satisfactory recovery.

TABLE 3

**Causes of prolonged fever in 40 patients of pulmonary tuberculosis undergoing chemotherapy**

| | Etiology | Cases (no) |
|---|---|---|
| 1. | Due to direct complication of TB | 9 |
| | • Dissem TB with toxemia alone | 4 |
| | • Potts disease of spine with abscess | 2 |
| | • Loculated empyema | 2 |
| | • TB arthritis of hip with abscess | 1 |
| 2. | Due to tubercular hypersensitivity (cold abscess) | 5 |
| | • Mediastinal | 2 |
| | • Retroperitoneal | 2 |
| | • Retro pectoral | 1 |
| 3. | Due to drug resistance | 4 |
| | • Fall and rise phenomenon | 4 |
| | • Initial drug resistance | 1 |
| 4. | Due to drug reactions | 9 |
| | • Streptomycin induced | 7 |
| | • INH induced lupus | 2 |
| 5. | Due to other illnesses | 13 |
| | • Pyogenic lung infection | 6 |
| | • Malaria | 3 |
| | • Anemia | 2 |
| | • Filariasis | 1 |
| | • Amebic liver abscess | 1 |

## Discussion

The febrile response confers an evolutionary benefit to humans in order to combat infecting microbes. This response is generated by the release of cytokines notably interleukin - 1 alpha and tumour necrosis factor. The same cytokines are released in large amounts in mycobacterial infections. Although short term fevers may be beneficial, prolonged fevers tend to extract a metabolic cost with depletion of muscle mass and essential nutrients leading to malnutrition that ultimately weakens the immune system [8]. Thus, it is necessary to correctly identify the underlying cause of fever and treat it effectively. In this study, only sputum positives were taken up for study to eliminate the doubt of incorrect diagnosis. Our laboratory does not have the facilities to monitor HIV positive patients hence they could not be included in this study.

When a patient of pulmonary TB continues to have fever despite DOT, the tendency is to consider drug resistance and add second line drugs. Alternatively, excessive hypersensitivity is thought to be producing fever and glucocorticoids are added. This study shows that both the above may be inappropriate as only 10% of the cases were due to drug resistance and 12.5%

due to excessive hypersensitivity leading to cold abscess. The most common cause of these fevers were associated diseases (32.5%), of which superadded lung infection formed the major part (15%). Such infections may be difficult to diagnose as fresh shadows on chest X-ray are difficult to identify in the presence of pre-existing radiological disease. In such situations reliance has to be placed on naked eye examination of sputum as well as sputum studies. The other associated diseases reflect their local prevalence to which cases of TB are also exposed. Severe nutritional anaemia produced fever in 5% of cases and resolved on its correction. Drugs were a cause of fever in 22.5% of the cases. The most common offender was streptomycin which produced fever in 17.5% of the cases. However, there was no rash or eosinophilia noted as reported by others [9]. The fever resolved after withdrawal of the drug. In 2 patients (5%) there was development of isoniazid induced lupus. These patients had increasing anaemia, hepatosplenomegaly and worsening shadows on chest X-ray. Both patients were sputum negative at this stage and strongly positive for anti-nuclear antibodies. There was marked improvement after withdrawal of the drug. This phenomenon should be borne in mind as it might be confused with drug resistance [10].

There were 22.5% cases due to direct complications of TB. In 10% cases, no cause other than toxaemia of TB was found and the fever resolved gradually at an average of 92 days. But in 5% cases, a loculated empyema requiring drainage was detected by chest sonography. This was obscured by confluence of shadows on chest X-ray. Due to debility, patients with toxaemia did not have signs of localization of TB in other organs. For instance Pott's disease of the spine with paraspinal abscess (5%) and TB arthritis of hip with periarticular abcess (2.5%) was present with minimal symptoms. These were detected by CT scan. Ultrasound was useful in detecting cold abscesses in mediastinum, retroperitoneal and retropectoral areas in 12.5% of the cases.

This study shows that fevers developing or persisting in patients undergoing treatment for pulmonary TB are a complex problem requiring careful repeated clinical examination and detailed investigation. Such fevers should not be attributed to TB alone, or drug resistance until extensive evaluation has excluded other causes or proof of resistance is obtained. Locally prevalent associated disease causing fever should be ruled out. Liberal use of ultrasonogram should be made to detect pus collections in the pleura, chest wall, mediastinum and retroperitoneal areas.

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