Endobronchial Involvement in Miliary Tuberculosis

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SUMMARY. Endobronchial tuberculosis (EBTB) is the tuberculous infection of the tracheobronchial tree. It has been reported in patients with parenchymal infiltrations and cavities in the lung and intrathoracic tuberculous lymphadenopathy. The occurrence of bronchial lesions in miliary tuberculosis is most likely to be a result of hematogenous dissemination of tubercle bacilli. We report six patients with endobronchial involvement in miliary tuberculosis. Bronchoscopic examination with histopathological evidence is essential to exclude or confirm endobronchial involvement in miliary tuberculosis. Chest computed tomography (CT) may be a useful diagnostic adjunct for evaluating bronchial stenosis, but does not show the mucosal changes of endobronchial inflammation if the lesions are superficial or mild. Local steroid injection appears to be useful for the treatment of superficial mucosal lesions involving less than one quarter of the bronchial lumen, but for advanced inflammatory lesions local treatment is ineffective. Local steroid injection for the treatment of bronchial narrowing is contraindicated by the finding of significant bronchial or segmental stenosis on CT scan. The evolution of airway involvement in miliary tuberculosis indicates that hematogenous dissemination of the bacilli is the primary mechanism for endobronchial tuberculosis. *Pneumon* 2010, 23(2):135-140.

INTRODUCTION

Endobronchial tuberculosis (EBTB) is defined as a specific inflammation of the tracheobronchial tree caused by the tubercle bacillus. It may occur in 10-40% of cases of active tuberculosis, and bronchial stenosis is a common complication despite the administration of effective treatment. Endobronchial involvement has been described as a feature of active tuberculosis in patients who have parenchymal infiltrations and cavities of the lung or mediastinal tuberculous lymphadenopathy. The exact pathogenesis of...
EBTB is not completely understood, but one of the suggested mechanisms is hematogenous dissemination of tubercle bacilli, which in miliary tuberculosis may be the primary route for endobronchial involvement.

A case series of six patients with EBTB in miliary tuberculosis, treated with local steroid injection is presented and the pathogenesis of endobronchial involvement is reviewed.

CASE REPORTS

A complete blood count, serum biochemistry and tuberculin test were performed on each of the six patients. Chest X-ray and computed tomography (CT) were the routine radiological examinations. Every patient underwent bronchoscopic examination with bronchial lavage for direct smear and culture of Mycobacterium tuberculosis and confirmation of endobronchial involvement by histopathological examination. Bronchoscopic reassessment was carried out to evaluate the bronchial lesions after administration of antituberculous treatment and local steroid injection. The clinical and radiological features of the patients are summarized in Table 1.

Patient 1

A 32 year-old previously healthy male presented with a one-month history of subfebrile fever (37.8°C) and malaise. The patient appeared well and had no abnormal physical findings. His hemoglobin level (Hb) was 14.3 g/dl, erythrocyte sedimentation rate (ESR) 48 mm/h and white blood cell count (WBC) 5.6 x10⁶/ml. The serum biochemistry was normal and the tuberculin test was negative. Chest X-ray showed diffuse miliary shadowing. On bronchoscopy the appearance was normal, but culture of bronchial lavage specimens grew M tuberculosis and histopathological examination of the transbronchial biopsy was consistent with caseating granuloma. The patient was started on quadruple therapy consisting of isoniazid, rifampicin, pyrazinamide and ethambutol. Spiral CT performed for the evaluation of a dry cough one month after the start of treatment revealed diffuse miliary nodules, with narrowing (50%) of the left lower lobe apical segment bronchus (Figure 1). At repeat bronchoscopy moderate to severe stenosis (50-60%) of the apical segment of the left lower lobe due to tumour-like lesions was seen. Local injection of 20 mg methylprednisolone was not successful in relieving bronchostenosis.

Patient 2

A 30 year-old male was admitted with a 3-week history of cough and night sweats. Physical examination was unremarkable. ESR was 52 mm/h and complete blood count and serum biochemistry results were within normal limits. The tuberculin test gave a response 14

<table>
<thead>
<tr>
<th>Patient</th>
<th>Symptoms</th>
<th>X-ray or CT of the chest</th>
<th>Bronchoscopy on admission</th>
<th>Lavage culture/TB histology</th>
<th>Bronchial stenosis</th>
<th>Local response to steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fever</td>
<td>Diffuse miliary shadowing</td>
<td>Normal</td>
<td>(+)/(+)/(+)</td>
<td>60% stenosis of the apical segment of the left lower lobe</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Cough and night sweats</td>
<td>Diffuse miliary shadowing</td>
<td>Normal</td>
<td>(+)/(+)/(+)</td>
<td>40% stenosis of bronchus intermedius</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Fever and malaise</td>
<td>Diffuse miliary shadowing</td>
<td>Normal</td>
<td>(+)/(+)/(+)</td>
<td>60-75% stenosis of the apical segment orifice of the left lower lobe</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Malaise, loss of appetite, weight loss</td>
<td>Diffuse random miliary nodules</td>
<td>Normal</td>
<td>(+)/(+)/(+)</td>
<td>25% stenosis of the right upper lobe</td>
<td>Complete</td>
</tr>
<tr>
<td>5</td>
<td>Fever and cough, loss of appetite</td>
<td>Diffuse random miliary nodules</td>
<td>Normal</td>
<td>(+)/(+)/(+)</td>
<td>25% stenosis of right upper lobe</td>
<td>Complete</td>
</tr>
<tr>
<td>6</td>
<td>Fever and cough</td>
<td>Diffuse miliary nodules</td>
<td>Normal</td>
<td>(+)/(+)/(+)</td>
<td>20% stenosis of left upper lobe</td>
<td>Complete</td>
</tr>
</tbody>
</table>

TABLE 1. Clinical characteristics of patients with miliary tuberculosis who developed endobronchial involvement (n=6, all males aged 22-42 years)
mm in diameter. Chest X-ray showed widespread miliary nodules. Bronchoscopic examination was normal but culture of the bronchial lavage fluid yielded \textit{M tuberculosis} and the transbronchial biopsy revealed necrotizing granulomatous inflammation. The patient was given isoniazid, rifampicin, pyrazinamide and ethambutol. Hemoptysis developed after three weeks of treatment. Spiral CT revealed diffuse random miliary nodules and stenosis (40\%) of the bronchus intermedius (Figure 2). At repeat bronchoscopy moderate to severe narrowing of the bronchus intermedius was observed, to a variable extent (30-40\%) with thickened, irregular and actively caseating mucosa. Local injection of 20 mg methylprednisolone failed to improve the bronchial narrowing.

**Patient 3**

A 28 year-old male presented with a 2-week history of fever (38.2\° C) and malaise. Oscultation revealed few crackles in the left middle zone. The ESR was 60 mm/h and the WBC was 6.3x10^6/ml. The C-reactive protein (CRP) was 32 U/L and the serum biochemistry was otherwise unremarkable. The tuberculin test response was 18 mm. Chest X-ray showed numerous nodules throughout both lungs. Bronchoscopic examination was normal, but the bronchial lavage specimen showed profuse acid-fast bacillus (AFB) on direct staining, and the culture was positive for \textit{M tuberculosis}. Histological examination of the transbronchial biopsy specimens revealed caseating granulomas. Treatment with isoniazid, rifampicin, pyrazinamide and ethambutol was commenced. One month after the start of treatment the patient developed cough and hemoptysis. Spiral CT revealed diffuse miliary nodules and narrowing (60\%) of the bronchus of the apical segment of the left lower lobe. Bronchoscopic examination demonstrated marked variable narrowing (60-75\%) at the apical segment orifice of the left lower lobe bronchus due to granular and tumorous lesions with severe inflammatory change. The bronchial narrowing did not respond to local 20 mg methylprednisolone injection.

**Patient 4**

A 22 year-old male complained of malaise, loss of appetite and 4 kg weight loss in the three weeks prior to investigation. There were no focal signs in the chest and no abnormal findings on general examination. The ESR was 42 mm/h and WBC was 8.2x10^6/ml. The CRP was 28 U/L and the other serum biochemistry was within normal limits. The tuberculin test was negative. Chest X-ray on admission was normal, but CT revealed diffuse, random nodules throughout both lungs. Bronchoscopic examination was unremarkable. Culture of the bronchial lavage fluid was positive for \textit{M tuberculosis}. Antituberculous treatment with isoniazid, rifampicin, pyrazinamide and ethambutol was started. The patient was readmitted five weeks later for investigation of hemoptysis. CT revealed a decreased number of nodules. At bronchoscopy mucosal swelling and hyperemia, with granular and shallow ulcerative lesions were seen at the orifice of the right
upper lobe bronchus. Less than 25% narrowing of right upper lobe was observed. Histological examination of the bronchoscopic biopsy specimen showed granulomatous inflammation with central areas of caseation necrosis. The patient made an uncomplicated recovery following local 20 mg methylprednisolone injection, and subsequent bronchoscopy was normal.

**Patient 5**

A 38 year-old male was admitted with fever (38.5°C), cough and loss of appetite for two weeks. Physical examination was unremarkable. The blood test showed a normal blood count, Hb 11.6 g/dl and ESR 84 mm/h, with normal biochemical parameters. The tuberculin test response was 15 mm. Chest X-ray and CT revealed randomly distributed diffuse miliary nodules in both lungs. Bronchoscopic examination showed no pathological findings, but culture of the bronchial lavage fluid was positive for *M. tuberculosis*. The patient developed severe cough at the sixth week of treatment with isoniazid, rifampicin, pyrazinamide and ethambutol, at which time CT showed a decreased number of miliary nodules. Repeat bronchoscopy revealed inflammation and superficial ulcerative lesions at the right upper lobe bronchial orifice with mild narrowing (20-25%) of the lumen. Histological examination of the bronchial biopsy was consistent with granulomatous inflammation and caseation necrosis. Local 20 mg methylprednisolone injection was used for the treatment of the bronchial lesions. Follow-up bronchoscopy was normal.

**Patient 6**

A 42 year-old man presented with fever and cough for one month. Over the previous three weeks the patient noted a 3 kg weight loss. A tuberculin test performed two years earlier was positive. His vital signs and physical examination were normal. The ESR was 52 mm/h and WBC was 6.4x10⁹/ml. CRP was 38 U/L and the rest of the serum biochemistry was within normal limits. The tuberculosis test produced an induration of 14 mm. The chest X-ray showed a normal blood count, Hb 11.6 g/dl and ESR 84 mm/h, with normal biochemical parameters. The bronchoscopic biopsy revealed granulomatous inflammation and caseation necrosis. Complete resolution of the mucosal inflammation and narrowing was observed following local 20 mg methylprednisolone injection.

**DISCUSSION**

EBTB is a not uncommon manifestation of tuberculosis. It has been reported in 10-40% of patients with pulmonary parenchymal tuberculosis who underwent bronchoscopy⁴. An et al reported endobronchial involvement in about 50% of 458 patients with pulmonary tuberculosis⁴. The diagnosis is confirmed by the culture of *M. tuberculosis* from bronchial lavage fluid samples, in addition to the bronchoscopic finding of specific endobronchial inflammation. The exact pathogenesis of EBTB is currently unknown. Direct extension from an adjacent parenchymal focus, implantation of organisms from infected sputum, hematogenous dissemination, lymph node erosion into a bronchus or spread of infection via the lymphatics have all been suggested as possible mechanisms of the disease⁵. Most cases are secondary either to pulmonary tuberculosis in the adjacent lung parenchyma or to endobronchial eruption of a lymph node.

Miliary tuberculosis is defined as the hematogenous dissemination of the bacilli resulting in widespread tubercle formation with radiologic or pathologic evidence of pulmonary micronodules⁶. Transmission of the organisms via the lymphatics to the circulation or direct invasion of blood vessels by liquefied caseous material may occur due to rupture or erosion of a contagious focus⁷,⁸. Although miliary tuberculosis presents with various clinical and pathological manifestations, endobronchial involvement due to miliary tuberculosis is uncommon⁹. The development of EBTB during treatment of miliary tuberculosis in this series of patients, not present on admission, strongly suggests that hematogenous dissemination was the primary pathogenetic mechanism for the development of their EBTB, as none of the patients had an infiltrative parenchymal focus, mediastinal lymphadenopathy, infected sputum or lymph node erosion into the bronchus which have been suggested as the possible mechanisms of endobronchial involvement. Hematogenous dissemination, which is known to be the cause of miliary tuberculosis, led to endobronchial involvement in this series, and it is suggested that this type of spread is probably the primary pathogenetic mechanism for the inflammatory airway lesions.
Another interesting point in this study is that EBTB may occur during the course of miliary tuberculosis in spite of treatment, because none of the patients had any apparent bronchial lesions on bronchoscopy at the time of initial investigation. The diagnosis of endobronchial involvement in miliary tuberculosis requires a high level of suspicion because it simulates other diseases, the patients may present with nonspecific respiratory symptoms and the chest X-ray may be normal\textsuperscript{10-12}. In the first three cases presented here, bronchial or segmental narrowing was evident on CT. In the remaining patients, bronchoscopic examination demonstrated superficial granular and mild ulcerative lesions which were not apparent on CT. The authors believe that EBTB should be considered in the clinical context of miliary tuberculosis, and bronchoscopic evaluation is necessary for the definitive diagnosis. CT may be used as a noninvasive diagnostic tool to demonstrate bronchial stenosis associated with miliary tuberculosis, but although CT is a useful diagnostic adjunct for evaluating stenosis, it is not adequate to show the definitive mucosal changes of endobronchial inflammation if the lesions are superficial or mild.

Evidence of moderate or severe bronchial or segmental narrowing on CT appears to be a reliable sign of severity to contraindicate the use of local steroid injection for the treatment of EBTB lesions. This radiologic finding implies the presence of advanced fibrostenotic tuberculosis, for which local steroid injection would be ineffective. Once EBTB has progressed to the advanced stage, causing more than 25% obstruction of the bronchial lumen as demonstrated by CT or bronchoscopy, local steroid application for treating the stenosis is not effective. Conversely, local treatment is useful for mild or superficial mucosal inflammatory lesions causing less than 25% obstruction, which is not evident on CT but demonstrated only on bronchoscopy.

The six cases reported here presented over a period of four years. Bronchoscopic examination is crucial in patients with miliary tuberculosis to rule out or confirm endobronchial involvement. The characteristic hyperaemic, granular or shallow ulcerative lesions may not be apparent on CT, although CT may be useful for identifying moderate or severe stenosis in tumorous, actively caseating and fibrostenotic EBTB at the bronchial or segmental level. Routine bronchoscopy should be conducted to determine the incidence of endobronchial involvement in miliary tuberculosis, to identify superficial inflammatory lesions and to aid the decision on whether local steroid injection would be effective. This type of treatment is useful for early EBTB but not advanced or stenotic lesions obstructing more than 25% of the bronchial lumen. Local methylprednisolone treatment of endobronchial tuberculous stenotic lesions obstructing less than one quarter of the bronchial lumen may result in complete cure with no further stenosis. Moderate or severe bronchial and segmental narrowing on CT constitutes a useful sign, contraindicating the use of local steroid treatment. The evolution of endobronchial involvement in this series of cases indicates that hematogenous dissemination of the bacilli probably plays the predominant role in the development of EBTB.

**CONCLUSION**

Although EBTB is a complication of active tuberculosis that may result in severe bronchostenosis, it is not commonly diagnosed in miliary tuberculosis. This may be due to the low incidence of miliary tuberculosis and to the fact that bronchoscopy is not performed in every patient. Clinicians should bear in mind that endobronchial involvement may be a feature of miliary tuberculosis and that it may develop during treatment. Bronchoscopic examination is essential in miliary tuberculosis to confirm endobronchial involvement because CT does not reveal superficial inflammatory lesions or mild bronchial stenosis. Early detection with prompt treatment is essential to prevent subsequent bronchostenosis. Local steroid injection appears to be a useful treatment modality for early lesions and may prevent further stenosis, but it is not effective for more advanced lesions. Evidence of bronchial stenosis on CT is indicative of advanced involvement and is a contraindication for the use of local steroid treatment. The knowledge gained from this series of cases suggests that hematogenous dissemination of the tubercle bacilli is the most likely mechanism for the development of EBTB.

**REFERENCES**

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