Study of paradoxical response to chemotherapy in tuberculous pleural effusion

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Background: Paradoxical worsening of disease, in spite of effective chemotherapy for tuberculosis, has been reported to occur in cases of intracranial tuberculoma, lymph node, and pulmonary tuberculosis. However, only rare case reports describe such paradoxical response in tuberculosis pleurisy.

Methods: Sixty-one patients with proven tuberculous pleural effusion were retrospectively screened in Riyadh, Saudi Arabia, in three major hospitals to look systematically at the incidence and features of paradoxical response.

Results: Paradoxical increase in the size of the effusion was detected in 10 of 61 patients. In six patients, the effusion became massive with worsening of dyspnoea requiring the use of corticosteroids in five patients and therapeutic aspiration in all six. However, complete resolution occurred in all 10 patients within 1–3 months. Three out of the 10 patients developed residual pleural thickening.

Conclusion: An incidence of 16% (10/61) paradoxical worsening of tuberculous effusion following the start of anti-tuberculous treatment has been documented. This resulted in respiratory distress necessitating therapeutic re-aspiration in six of 10 patients.

Introduction

Unusual expansion or new formation of tuberculous lesion during treatment has been referred to as 'paradoxical response' (1). Paradoxical worsening of the tuberculous lesions has been frequently described to occur weeks or months after the start of antituberculous therapy in the case of lymphadenopathy or intracranial tuberculoma (1–3). Similarly, paradoxical response has been observed during treatment of pulmonary tuberculosis which can lead to an adult respiratory distress syndrome (4). On the contrary, paradoxical worsening of tuberculous pleural effusion is mentioned only in rare case reports (5). Therefore, this systematic study was conducted to find the incidence and features of the phenomenon in tuberculous pleural effusion.

Materials and Methods

This is a retrospective study which screened all patients with tuberculous pleural effusion diagnosed between July 1991 and September 1994 in the following hospitals – King Khalid University Hospital, Chest Hospital, National Guard Hospital, Riyadh, Saudi Arabia. The criteria for the diagnosis of tuberculous effusion were either caseating granuloma in the pleural biopsy, acid-fast bacilli (AFB) in the pleural fluid or biopsy, or positive culture of Mycobacterium tuberculosis in the fluid.

Patients with other aetiology of pleural effusion such as congestive heart failure, pneumonia, malignancy or collagen disorder were excluded from this study. Patients with parenchymal involvement in addition to the tuberculous pleural effusion were also excluded. Parenchymal involvement was excluded for two reasons: the fluid extended up to the chest wall in a ‘typical’ mantle distribution on P.A. and lateral film which Frazer et al. considered as evidence that the underlying lung is free of disease (6). Cases which did not have that typical appearance were excluded. In addition, six of 10 patients had a computerized tomography at the time of worsening of effusion which again confirmed the lack of parenchymal lung involvement. A standard regimen of rifampicin, isoniazide, pyrazinamide and ethambutol or streptomycin were given for the first 2 months. Thereafter, only rifampicin and isoniazide were continued for an additional 4 months. Compliance was ensured by supervised treatment for the first 2 months (all were inpatients). All chest radiography films performed before and after the start of chemotherapy were...
Table 1  Patients’ data

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age/sex</th>
<th>Initial symptoms</th>
<th>Initial chest X-ray</th>
<th>New symptoms following worsening of effusion</th>
<th>Degree of worsening of effusion</th>
<th>Time of worsening of effusion</th>
<th>Intervention</th>
<th>Long-term outcome of effusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20/M</td>
<td>Fever, cough, chest pain</td>
<td>Left-sided moderate effusion</td>
<td>Dyspnoea</td>
<td>Massive</td>
<td>1 week</td>
<td>Pleural fluid aspiration</td>
<td>Total resolution</td>
</tr>
<tr>
<td>2</td>
<td>30/M</td>
<td>Cough, fever</td>
<td>Bilateral mild effusion</td>
<td>-</td>
<td>Right-sided moderate</td>
<td>1 month</td>
<td>-</td>
<td>Total resolution</td>
</tr>
<tr>
<td>3</td>
<td>35/M</td>
<td>Fever, chest pain</td>
<td>Right-sided moderate effusion</td>
<td>Dyspnoea</td>
<td>Massive</td>
<td>1 week</td>
<td>Fluid aspiration + prednisolone orally</td>
<td>Plural thickening</td>
</tr>
<tr>
<td>4</td>
<td>33/M</td>
<td>Fever, cough weight loss</td>
<td>Left-sided mild + pneumothorax</td>
<td>-</td>
<td>Moderate</td>
<td>3 weeks</td>
<td>-</td>
<td>Pleural thickening</td>
</tr>
<tr>
<td>5</td>
<td>60/M</td>
<td>Dypnoea, cough, fever</td>
<td>Left-sided mild</td>
<td>-</td>
<td>Moderate</td>
<td>1 month</td>
<td>-</td>
<td>Total resolution</td>
</tr>
<tr>
<td>6</td>
<td>40/F</td>
<td>Cough fever, chest pain</td>
<td>Right-sided mild</td>
<td>Dyspnoea</td>
<td>Massive</td>
<td>1 month</td>
<td>Intra-pleural hydrocortisone 200 mg + pleural aspiration</td>
<td>Total resolution</td>
</tr>
<tr>
<td>7</td>
<td>32/M</td>
<td>Cough, chest pain, fever</td>
<td>Left-sided mild</td>
<td>Dyspnoea</td>
<td>Massive</td>
<td>1 month</td>
<td>Fluid aspiration + prednisolone orally</td>
<td>Total resolution</td>
</tr>
<tr>
<td>8</td>
<td>69/M</td>
<td>Cough, fever, chest pain</td>
<td>Right-sided moderate</td>
<td>Dyspnoea</td>
<td>Massive</td>
<td>14 days</td>
<td>Fluid aspiration + prednisolone orally</td>
<td>Pleural thickening</td>
</tr>
<tr>
<td>9</td>
<td>60/F</td>
<td>Cough, dypnoea</td>
<td>Right-sided mild</td>
<td>Dyspnoea worsened</td>
<td>Massive</td>
<td>1 week</td>
<td>Fluid aspiration + prednisolone orally</td>
<td>Total resolution</td>
</tr>
<tr>
<td>10</td>
<td>80/M</td>
<td>Cough, chest pain, fever</td>
<td>Left-sided mild</td>
<td>-</td>
<td>Moderate</td>
<td>2 weeks</td>
<td>-</td>
<td>Total resolution</td>
</tr>
</tbody>
</table>

reviewed. The pleural effusion was graded as small (less than one-third of the hemithorax), moderate (one-third to two-thirds of the hemithorax), or massive (more than two-thirds of the hemithorax). The grading of effusion is identical to that used by other workers (7) and it was adopted in this study for the sake of uniformity. Frazer et al. (6) defined moderate effusion as ‘extending to about the mid portion of the hemithorax on a plain chest X-ray’. This is roughly similar to the one adopted by Lee et al. (7) and that used in this paper.

Results

Increase in the size of the pleural effusion was detected in 10 of 61 patients. Table 1 gives the details of the 10 cases with worsening tuberculous effusion. Patients 6 and 7 had positive AFB smear and culture in pleural fluid, while Patients 5 and 10 grew M. tuberculosis in crushed pleural biopsy only; the four isolates were sensitive for INH, rifampicin and ethambutol. Eight of 10 patients had caseating granuloma in the pleural biopsy. The remaining two patients (Patients 5 and 7) had non-caseating granuloma. In six patients, the effusion became massive, and moderate in four patients. The six patients whose effusion became massive experienced worsening of dyspnoea and cough, and were subjected to repeats of pleural aspiration and biopsy, bronchoscopy, and CT scan. The test revealed no other pathology apart from tuberculosis. One of the six cases received 200 mg hydrocortisone intrapleurally once, while another four patients were given prednisolone 30 mg orally daily, tapered over several weeks. The sixth patient required only therapeutic aspiration to relieve dyspnoea. There was gradual improvement in symptoms but total resolution of fluid occurred in 1–3 months. Three of 10 patients developed residual pleural thickening.

Discussion

Although short-course chemotherapy for tuberculosis is associated with good outcome and minimal drug toxicity (8,9); paradoxical increase of the disease manifestations is documented to occur weeks or months following the administration of anti-tuberculous drugs (1–5).

This paradoxical response has been frequently reported in tuberculous lymphadenitis (2) and intracranial tuberculoma (3,10). Up to 30% of patients with tuberculous lymphadenopathy show such a reaction, and tuberculomas start enlarging up to 7 months following chemotherapy before full
resolution is obtained (2). In contrast, such a reaction is rarely reported in tuberculous effusion. Vilaseca et al. reported contralateral pleural effusion during chemotherapy for tuberculous pleurisy in one patient occurring 3 weeks after initiation of chemotherapy (5). Other workers have described tuberculous effusion appearing 3-4 weeks after the start of chemotherapy for pulmonary tuberculosis in two patients (11).

The present study is the first, to the author's knowledge, to look systematically at the incidence of such paradoxical reaction in a series of tuberculous effusion, and establish an incidence of 16% (10/61) which is less than the 30% documented in the case of tuberculous lymphadenopathy (2).

The fact that the patients in this study received potent drugs (INH, rifampicin, PZA) under supervision and showed full resolution eventually supports the view that this is a genuine paradoxical response and not the effect of ineffective chemotherapy.

Workers have speculated on the mechanisms of the paradoxical response in cases of lymphadenitis and tuberculomas, and attributed it to 'immunological rebound' by which the improved cell-mediated immunity after treatment coincided with excessive antigen load (bacterial cell-wall residues) resulting from rapid bacterial lysis (1,12,13). The same workers also suspected that rapid bactericidal drugs like INH and rifampicin could be worse offenders than bacteriostatic drugs. The same mechanisms could be operational in the case of pleural effusion.

Corticosteroids are known to modify the severity of the clinical manifestations of tuberculosis (14,15). However, there is no data that corticosteroids could prevent the paradoxical worsening seen in various organs. We feel a prospective double-blind study is warranted in view of the diagnostic dilemma posed by paradoxical worsening of the disease and in view of the fact that six patients in the present study developed respiratory distress which could have been prevented by corticosteroids.

In conclusion, an incidence of 16% paradoxical worsening of tuberculous pleural effusion was documented. This could result, not infrequently, in respiratory distress necessitating therapeutic re-aspiration.

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References


