

Case Reports

Development of contralateral pleural effusion during chemotherapy for tuberculous pleurisy

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ABSTRACT

Paradoxical worsening of tuberculous lesions, despite effective chemotherapy, has been reported in intracranial tuberculomas, lymph nodes, pulmonary disease, and tuberculous pleurisy. However, development of contralateral pleural effusion during treatment of tuberculous pleurisy is very rare. We report the case of a 22 year old female patient who presented with right sided pleural effusion and was treated with antituberculous drugs. Four weeks later although her right sided pleural effusion was subsiding she developed a left sided pleural effusion. Closed pleural biopsy on the left side showed granulomatous inflammation with early caseation. Antituberculous drugs were continued and a short course of oral prednisolone was added. She recovered completely and her chest x-ray became normal after finishing her treatment.

Keywords: Tuberculosis, paradoxical response, pleurisy.

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Paradoxical response to antituberculous chemotherapy is defined as an unusual expansion of pre-existing lesions or development of new tuberculous lesions inspite of effective chemotherapy.¹ Paradoxical worsening of tuberculous lesions can occur weeks or months after starting antituberculous drugs and is well recognised in tuberculous lymphadenitis² and intracranial tuberculomas.³ Although paradoxical worsening of ipsilateral pleural effusion is not rare,⁴ development of contralateral pleural effusion after starting chemotherapy seems to be very rare.⁵ We report a patient with right sided pleural effusion who developed left sided pleural effusion 4 weeks after starting antituberculous chemotherapy, the new effusion proved to be tuberculous in origin and responded to the same regimen of antituberculous drugs.

Case Report. A 22 year old female university student presented to the tuberculosis centre in Irbid on 12th August 1998 with a 2 week history of right sided pleuritic chest pain associated with fever, night sweats, anorexia and weight loss (53kg down to 50kg). Physical examination revealed signs of right sided pleural effusion, the rest of the examination was unremarkable. Chest x-ray confirmed the presence of the effusion with no apparent parenchymal lung lesion. Tuberculin test was positive (17mm induration). A presumptive diagnosis of tuberculous pleurisy was made and she was started on isoniazide 300mg, rifampicin 600mg, ethambutol 750mg and pyrazinamide 1500mg daily, all given before breakfast. On 22nd August she was admitted to Princess Basma Teaching Hospital with epigastric pain, vomiting and fever. She was not

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Figure 1 - (a) Initial chest radiograph showing moderate right sided pleural effusion. (b) Chest radiograph 3 weeks later showing moderate left sided effusion with resolving right sided effusion. (c) Chest radiograph 3 months after finishing antituberculous drugs showing minimal pleural thickening.

jaundiced and had signs of right sided pleural effusion. Laboratory tests showed normal full blood count with a high erythrocyte sedimentation rate (ESR) of 86mm/hour. Serum alanine (ALT) and aspartate aminotransferases (AST) were raised at 72 and 118U/L, serum bilirubin was normal. Chest x-ray showed right sided pleural effusion (Figure 1A). Ultrasound of upper abdomen was normal. Thoracocentesis revealed an exudative fluid with a lymphocytic reaction (cell count of 2100/mm³, 70% lymphocytes). Smear for acid fast bacilli was negative. Metoclopramide was given and antituberculous drugs were splitted with isoniazide and rifampicin given before breakfast while pyrazinamide and ethambutol were given after lunch. A closed pleural biopsy was planned but as her symptoms subsided and a repeat chest x-ray showed significant resolution of the effusion she was sent home on 2nd September on the same drugs.

On 14th September she was admitted again with a 2 day history of left sided pleuritic chest pain, shortness of breath and fever. No history of joint

pain or skin rash. She was febrile and had signs of left sided pleural effusion. Full blood count was normal, ESR 67mm/hour, ALT 41U/L and AST 79U/L. Antinuclear antibodies were negative and complement levels were normal. Chest x-ray showed moderate left sided pleural effusion with minimal effusion on the right side (Figure 1B). Thoracocentesis on the left side showed an exudative effusion with a neutrophilic reaction (cell count 1900/mm³ with 85% neutrophils). Computed tomography (CT) scan of the chest showed left sided pleural effusion with a subpleural focus (Figure 2) and left sided hilar lymphadenopathy (not shown on the figure). Closed pleural biopsy was taken, using Abram's needle, and histopathology showed granulomatous inflammation with early caseation. Antituberculous drugs were continued and a short course of oral prednisolone was added (30mg daily tapered and stopped after 6 weeks), she was discharged home on 1st October. At follow-up visit on 17th November she was asymptomatic her weight was 51.5kg and ESR 20mm/hour, she was off steroids and was only on isoniazide and rifampicin. On 1st March 1999 antituberculous drugs were stopped and on 15th June she remained well, her weight was 54kg and her chest x-ray showed complete resolution of the effusions with minimal pleural thickening on the left side (Figure 1C).



Figure 2 - CT scan showing left sided pleural effusion with subpleural focus.

Discussion. Our patient developed a left sided pleural effusion at a time when her right sided pleural effusion was subsiding and this occurred inspite of continuing her antituberculous medications. Pleural biopsy showed granulomatous inflammation with early caseation indicative of tuberculous pleurisy. The CT scan findings are consistent with primary tuberculous infection. Tuberculous pleural effusion constitutes about 5% of all disease due to *Mycobacteria tuberculosis*,⁶ and it is thought to result from a delayed hypersensitivity

reaction to mycobacterial antigens in the pleural space.⁷ These antigens probably enter the pleural space either directly following rupture of a subpleural focus⁸ or through hematogenous dissemination. Paradoxical response to antituberculous chemotherapy can occur weeks to months after starting treatment. Intracranial tuberculomas start to enlarge up to 7 months after starting chemotherapy before full resolution is obtained,³ and up to 30% of patients with tuberculous lymphadenitis have such a reaction.² Development of pleural effusion after starting chemotherapy for pulmonary tuberculosis has been reported⁹ and paradoxical worsening of pre-existing pleural effusion is not rare.⁴ However, development of contralateral pleural effusion is very rare, and to our knowledge, only one case has been reported.⁵ In that report a right sided pleural effusion developed 6 weeks after starting chemotherapy for left sided tuberculous effusion, and the authors thought that rupture of caseous lymph nodes was the possible explanation for the pleural effusion although lymph nodes were not visible on the chest x-ray.

In our patient, the initial right sided pleural effusion is probably due to hematogenous dissemination from the primary tuberculous infection in the left lung which was not visible on the chest x-ray, and the later development of the left sided effusion is due to rupture of the subpleural focus, seen on the CT scan, into the pleural space. The initial effusion on the right side was lymphocytic which is expected in subacute and chronic tuberculous effusions, and the neutrophilic reaction in the left sided effusion is also consistent with early tuberculous effusions. An initial neutrophilic reaction is seen in experimental tuberculous effusions and is necessary for the subsequent mononuclear cell influx.¹⁰ The appearance of new lesions or expansion of pre-existing lesions in patients treated for tuberculosis should raise questions about diagnosis, compliance, and drug resistance. In our patient there was no reason to believe that she was not compliant, and full recovery on the same medications excludes the possibility of drug resistance. The other

explanation is a paradoxical response to chemotherapy which is the case in our patient. The underlying mechanism of this response is not clear but probably has an immunological basis. It is speculated that local immunological reactivity might be altered by mycobacterial metabolites released from bacterial lysis as a result of using effective bactericidal drugs.¹ This can lead to expansion of pre-existing lesions and possibly rupture into adjacent structures.

In conclusion, although expansion of pre-existing lesions or development of new lesions or both during chemotherapy for tuberculosis causes anxiety and are strong reasons for concern about diagnosis, compliance or drug resistance, a paradoxical response has to be kept in mind in such cases.

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