CASE REPORT

Pleural tuberculosis following lung cancer chemotherapy: a report of two cases proven pathologically by pleural biopsy

Karan Madan,¹ Navneet Singh,¹ Ashim Das,² Digambar Behera¹

¹Department of Pulmonary Medicine, Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh, India

²Department of Histopathology, Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh, India

Correspondence to

Dr Navneet Singh,
navneetchd@hotmail.com

SUMMARY

Malignancy per se and cytotoxic chemotherapy given for its treatment both are recognised risk factors for the development of tuberculosis (TB). However, individual case descriptions of pleural tuberculosis (TB-PE) following chemotherapy for lung cancer (LC) have not been published previously. We herein report the first two cases of histopathologically proven TB-PE following LC chemotherapy. The first patient was a 38-year-old man with stage IV non-small cell LC (adenocarcinoma) who developed TB-PE following four cycles of chemotherapy (pemetrexed-cisplatin). The second patient was a 49-year-old man with extensive disease small cell LC who developed TB-PE after six cycles of chemotherapy (irinotecan-cisplatin). In both patients, diagnosis of TB-PE was established by demonstration of granulomatous inflammation, caseous necrosis and positive stain for acid-fast bacilli in pleural biopsy specimens. Both cases responded to standard four-drug antitubercular therapy. These cases highlight the importance of carrying out an extensive evaluation for exudative pleural effusions in LC patients receiving chemotherapy, especially in countries with high TB prevalence. Attributing such pleural effusions to disease progression, without histopathological confirmation, may be associated with disastrous consequences.

BACKGROUND

Malignancy per se and cytotoxic chemotherapy given for its treatment both are recognised risk factors for the development of infections in patients with cancer. Infection with *Mycobacterium tuberculosis* (MTB) is common among people residing in endemic (high prevalence) countries.^{1 2} Lung cancer (LC) is the most common cancer and the leading cause of cancer-related mortality in men.³ Majority of the patients present with advanced disease for whom systemic chemotherapy forms the mainstay of treatment.^{4 5} Occurrences of LC following pulmonary tuberculosis (PTB) and vice versa as well as coexistence of PTB with LC all have been described.^{6–8} However, individual descriptions of pleural tuberculosis (TB-PE) following chemotherapy for LC have not been previously published. In this manuscript, we report the first two cases of pathologically proven TB-PE following chemotherapy for LC.

CASE PRESENTATION

The clinical and outcome profiles of the two index cases with tuberculous pleural effusion are presented in detail below.

Case 1

A 38-year-old man, never-smoker, presented with a history of streaky haemoptysis and bony pains of 3 months duration, progressively worsening dyspnoea for 1 month and left auricular region swelling for 2 weeks. Physical examination showed the presence of a swelling in left parotid region, left axillary and inguinal lymphadenopathy and reduced intensity of breath sounds over right mammary area. Chest x-ray (CXR) (figure 1, top left panel) showed right lower zone opacity. Contrast-enhanced CT (CECT) examination of the neck, thorax and abdomen was performed which demonstrated a 5×4×2.5 cm spiculated right lower lobe (RLL) lung mass (figure 1, top right panel) with multiple enlarged ipsilateral hilar and mediastinal lymph nodes. Multiple hypodense lesions of varying sizes were seen in both lobes of the liver. Multiple mixed lytic sclerotic bony lesions were present in the cervical spine. Positron emission tomography-CT scan showed increased 18F-fluorodeoxyglucose uptake in the right lung, liver, bilateral adrenals, bilateral kidneys, pancreas, left parotid gland, thyroid gland and mediastinal lymph nodes. Flexible bronchoscopic examination demonstrated mucosal infiltration and stenosis in the right intermediate bronchus. Histopathological examination of left axillary lymph node and fine needle aspiration cytology (FNAC) examination smears from the left parotid swelling (figure 2, panel A) as well as inguinal lymph node showed features of metastatic adenocarcinoma. Since it is unusual for disseminated lung cancer to have clinically overt involvement of parotid gland or axillary/inguinal lymphadenopathy at presentation, a CT-guided FNAC was performed from the RLL mass (figure 2, panel B) which confirmed the presence of non-small cell lung cancer (adenocarcinoma). A diagnosis of Stage IV (T2aN2M1b) lung adenocarcinoma was thus established and chemotherapy (pemetrexed 500 mg/m² and cisplatin 65 mg/m² each on day 1 of a 3 weekly cycle) along with best supportive care started.

After four cycles of chemotherapy, patient developed right-sided chest pain and dry cough. Repeat CXR and CECT thorax (figure 1, bottom left panel) demonstrated moderate right-sided pleural effusion though the RLL mass had reduced in size. A possibility of progressive disease was initially kept and diagnostic pleurocentesis performed. Pleural fluid analysis showed a cell count of 400 cells/mm³ with predominance of lymphocytes, protein of 4.5 g/dl, glucose of 45 mg/dl and adenosine deaminase (ADA) level of 80 U/ml. Stain for

To cite: Madan K, Singh N, Das A, et al. *BMJ Case Reports* Published online: [please include Day Month Year] doi:10.1136/bcr-2012-008196

Figure 1 Chest radiograph at baseline showing mass in right middle zone (top left panel).

Contrast-enhanced CT scan of thorax showing the mass in the right hilar region with enlarged subcarinal lymph node (top right panel). Chest x-ray obtained after four cycles of chemotherapy showing reduction in size of right lung mass with appearance of moderate sized right pleural effusion (bottom left panel). Photomicrograph of right parietal pleural biopsy specimen showing multiple epithelioid cell granulomas, central areas of caseation necrosis and scattered multinucleate giant cells (H&E; $\times 40$; bottom right panel).

acid-fast bacilli (AFB) and bacterial cultures were negative. Cytological examination of three serial samples was negative for malignant cells. For evaluation of this undiagnosed exudative pleural effusion, medical thoracoscopy was performed. There were multiple adhesions between the parietal and visceral pleural surfaces. In addition, diffuse fine pleural nodularity (figure 3) was present. Adhesiolysis was performed and a pleural biopsy obtained. Postprocedure, a right-sided intercostal drain

was inserted that was removed 5 days later following iodopovidone pleurodesis. Histopathological examination of pleural biopsy (figure 1, bottom right panel) demonstrated epithelioid cell granulomas with central areas of caseation necrosis and scattered multinucleate giant cells. Stain for AFB was positive. A final diagnosis of TB-PE was made and standard four drug antitubercular therapy (ATT) comprising of isoniazid, rifampicin, pyrazinamide and ethambutol initiated. The patient showed

Figure 2 Microphotographs of fine needle aspiration cytology (FNAC) smears from left parotid swelling and right lung mass (case 1) showing loosely cohesive clusters of malignant cells (May-Grünwald Geimsa stain; $\times 40$; A). These malignant cells had moderate amount of eosinophilic cytoplasm, round to oval nuclei with prominent nucleoli and acinar formation (H&E; $\times 40$; B). The overall features were suggestive of adenocarcinoma. FNAC smears from right lung mass (case 2) showing malignant cells having high nuclear cytoplasmic ratio and scanty cytoplasm (May-Grünwald Geimsa stain; $\times 40$; C) and loosely cohesive cluster of malignant cells in a haemorrhagic background (H&E; $\times 40$; D). The morphological profile was consistent with that of small cell carcinoma of lung.

Figure 3 Diffuse pleural nodularity on the parietal pleural surface observed during medical thoracoscopy performed for evaluation of undiagnosed exudative pleural effusion that developed following chemotherapy in index case 1. This clinical photograph also shows a biopsy being taken from the involved parietal pleura using a forceps inserted through the thoracoscope.

improvement within 3 weeks of starting ATT and continues to be under follow-up.

Case 2

A 49-year-old male patient presented with cough for 2 months, dyspnoea and left hip pain of 1-month duration. General

physical examination was unremarkable. Chest examination revealed reduced intensity of breath sounds over the right infra-scapular area. A mass was seen in the right mid-zone on CXR (figure 4, top left panel). CECT of the thorax (figure 4, top right panel) demonstrated a well-defined mass 3.5×3.5 cm in size in the right upper lobe (posterior segment) with enlarged ipsilateral mediastinal lymph nodes. Flexible bronchoscopy was normal. CT-guided FNAC from right lung mass (figure 2C,D) showed features consistent with small cell carcinoma. Bone scan showed evidence of increased tracer uptake in left iliac crest suggestive of skeletal metastasis. A diagnosis of small cell LC—extensive disease (ED) T2aN2M1b was made. Chemotherapy (Irinotecan 65 mg/m² and cisplatin 30 mg/m² each on days 1 and 8 of a 3 weekly cycle) was started. After four cycles, repeat CECT thorax showed partial response and two additional cycles were administered.

Two weeks following the last chemotherapy dose, the patient developed fever and right-sided chest pain. Chest radiograph (figure 4, bottom left panel) demonstrated right-sided moderate pleural effusion and diagnostic thoracentesis was performed under ultrasonographic guidance. Pleural fluid was an exudate with protein of 3.8 g/dl, glucose of 1 mg/dl, cell count of 120 cells/mm³ with a predominance of lymphocytes and ADA level of 33 U/l. Pleural fluid stain for AFB was negative and three pleural fluid cytological specimens were negative for malignant cells. Conventional pleural biopsy using Abrams needle was performed. Histopathological examination (figure 4, bottom right panel) demonstrated many epithelioid cell granulomas with Langhans' giant cells and central areas of caseation necrosis. Stain for AFB was positive. Patient was started on standard four drug ATT for TB-PE. Subsequently, he received external beam radiation (20 Gy/20 fractions/5 days) for pelvic bony metastasis. Two months after the initiation of ATT, CXR showed a resolution of pleural effusion and the patient was shifted to continuation phase. Four months after initiation of ATT, the patient presented with altered behaviour. CECT scan of head

Figure 4 Chest radiograph at baseline showing mass in right lower zone (top left panel). Contrast-enhanced CT scan of thorax showing the mass in the posterior segment of the right upper lobe (top right panel). Chest radiograph obtained after patient developed right sided chest pain (subsequent to completion of six cycles of chemotherapy) showing reduction in size of right lung mass with appearance of moderate-sized right pleural effusion (bottom left panel). Photomicrograph of right parietal pleural biopsy specimen showing epithelioid cell granulomas, central areas of caseation necrosis and Langhans' giant cells (H&E; ×40; bottom right panel).

demonstrated multiple brain metastases and he received cranial irradiation for the same. The patient completed 6 months of ATT and expired 2 weeks after completion of ATT from progression of basic disease (lung cancer).

DISCUSSION

The prevalence of MTB infection is approximately 40% in India while globally one out of every three individuals is estimated to be infected.^{1–2} Several types of cancers including LC have been associated with the occurrence of tuberculosis (TB).^{8–11} Tubercular pleural effusion occurs in approximately 5% of patients with MTB infection and is the second most common form of extrapulmonary TB after lymph nodal TB.¹² Tubercular pleural effusions are usually unilateral and small to moderate in size. They may manifest as an acute illness with duration of symptoms of 1 month or less.¹² Such a profile was also observed for both the index patients being reported by us.

The two index cases of TB-PE highlight a very important learning point namely the need to perform histopathological examination of pleura for an evaluation of pleural effusion occurring in the setting of LC with a negative cytological examination. It is not uncommon to use an elevated pleural fluid ADA as a surrogate marker for establishing a diagnosis of TB-PE. In case 2, pleural fluid ADA levels were 33 U/ml which is not beyond the cut-off value. It should, however, be remembered that the definite diagnosis of TB-PE depends on the demonstration of AFB (with/without the presence of necrosis and granulomatous inflammation) in pleural fluid or pleural biopsy specimens. Pleural fluid ADA levels even if elevated only provide supportive evidence for the same.¹² Based upon a meta-analysis, the maximum joint sensitivity and specificity of ADA for the diagnosis of TB-PE was observed to be 93%.¹³ However, its sensitivity ranges from 47.1% to 100% indicating that even in cases with normal ADA levels, a diagnosis of TB-PE cannot be ruled out as was seen in index case 2.¹⁴ In pleural fluid real-time PCR is another diagnostic marker that has been evaluated for TB-PE and been shown to have lower sensitivity as compared with pleural fluid ADA estimation for both confirmed and probable TB-PE.¹⁵

An interesting observation from both these cases is that TB-PE occurred on the same side as the primary lesion of LC. Unilaterality of primary LC and tubercular lesions was noted in approximately 40% in a cohort of 36 LC patients with concurrent or sequential diagnosis of thoracic TB.⁸ This study included two LC patients (5.6%) who were diagnosed with TB-PE. However, whether TB-PE was diagnosed concurrently or subsequent to administration of chemotherapy was not mentioned.

The procedure used to obtain pleural biopsy was conventional (closed) in case 2 and thorascopic in case 1. In general, medical thorascopy is preferred for evaluation of undiagnosed exudative pleural effusions since it has been reported to have very high diagnostic accuracy for obtaining a histological diagnosis of TB-PE.^{16–17} Index case 2 did not consent undergoing medical thorascopy prompting us to use the conventional method.

In summary, this manuscript provides a description of the clinical, diagnostic and therapeutic profile of two patients with advanced LC who developed histopathologically proven TB-PE following chemotherapy and to the best of our knowledge, represent the first confirmed reports for this clinical scenario.

Learning points

- ▶ Pleural tuberculosis (TB-PE) is an uncommon occurrence following chemotherapy for lung cancer.
- ▶ It is of paramount importance that an extensive evaluation should be undertaken for aetiology of any new-onset exudative pleural effusion that develops in a patient with advanced cancer who is currently receiving or has recently received systemic chemotherapy.
- ▶ Thorascopic pleural biopsy is the preferred modality for establishing diagnosis in such cases and can help determine whether the effusion is a result of pleural metastasis or due to secondary infection which in high-prevalence countries can be due to *Mycobacterium tuberculosis*.
- ▶ Diagnosis of TB-PE is established by demonstration of granulomatous inflammation and a positive stain for acid fast bacilli in pleural biopsy specimens.
- ▶ TB-PE following chemotherapy should be treated with standard four-drug antitubercular therapy.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 TB India 2011. Revised National Tuberculosis Control Programme Annual Status Report. New Delhi: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India. 2011. <http://www.tbcindia.nic.in/pdfs/RNTCP%20TB%20India%202011.pdf> (accessed 9 May 2012).
- 2 Global Tuberculosis Control 2011. Geneva: World Health Organization, 2011. Global Tuberculosis Control. 2011. http://www.who.int/tb/publications/global_report/en/ (accessed 9 May 2012).
- 3 Singh N, Aggarwal AN, Behera D. Management of advanced lung cancer in resource constrained settings: a perspective from India. *Expert Rev Anticancer Ther* 2012;12:1479–95.
- 4 Singh N, Aggarwal AN, Gupta D, *et al*. Unchanging clinico-epidemiological profile of lung cancer in North India over three decades. *Cancer Epidemiol* 2010;34:101–4.
- 5 Singh N, Aggarwal AN, Behera D, *et al*. Intercycle delays during chemotherapy of non-small cell lung cancer in a health care resource-constrained setting and their effect on overall survival. *J Thorac Oncol* 2010;5:236–9.
- 6 Chen YM, Chao JY, Tsai CM, *et al*. Shortened survival of lung cancer patients initially presenting with pulmonary tuberculosis. *Jpn J Clin Oncol* 1996;26:322–7.
- 7 Cienas S, Vencevicius V. Lung cancer in patients with tuberculosis. *World J Surg Oncol* 2007;5:22.
- 8 Cha SI, Shin KM, Lee JW, *et al*. The clinical course of respiratory tuberculosis in lung cancer patients. *Int J Tuberc Lung Dis* 2009;13:1002–7.
- 9 Kaplan MH, Armstrong D, Rosen P. Tuberculosis complicating neoplastic disease. A review of 201 cases. *Cancer* 1974;33:850–8.
- 10 Karnak D, Kayacan O, Beder S. Reactivation of pulmonary tuberculosis in malignancy. *Tumori* 2002;88:251–4.
- 11 Kim DK, Lee SW, Yoo CG, *et al*. Clinical characteristics and treatment responses of tuberculosis in patients with malignancy receiving anticancer chemotherapy. *Chest* 2005;128:2218–22.
- 12 Gopi A, Madhavan SM, Sharma SK, *et al*. Diagnosis and treatment of tuberculous pleural effusion in 2006. *Chest* 2007;131:880–9.
- 13 Greco S, Girardi E, Masciangelo R, *et al*. Adenosine deaminase and interferon gamma measurements for the diagnosis of tuberculous pleurisy: a meta-analysis. *Int J Tuberc Lung Dis* 2003;7:777–86.
- 14 Goto M, Noguchi Y, Koyama H, *et al*. Diagnostic value of adenosine deaminase in tuberculous pleural effusion: a meta-analysis. *Ann Clin Biochem* 2003;40:374–81.
- 15 Kalantri Y, Hemvani N, Chitnis DS. Evaluation of real-time polymerase chain reaction, interferon-gamma, adenosine deaminase, and immunoglobulin A for the efficient diagnosis of pleural tuberculosis. *Int J Infect Dis* 2011;15:e226–31.
- 16 Diacon AH, Van de Wal BW, Wyser C, *et al*. Diagnostic tools in tuberculous pleurisy: a direct comparative study. *Eur Respir J* 2003;22:589–91.
- 17 Mootha VK, Agarwal R, Singh N, *et al*. Medical thorascopy for undiagnosed pleural effusions: experience from a tertiary care hospital in north India. *Indian J Chest Dis Allied Sci* 2011;53:21–4.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow