Migratory pulmonary infiltrates

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Introduction

Patients with migratory infiltrates on serial chest radiographs are rare. Migratory infiltrates are generally believed to represent simple pulmonary eosinophilia (Loeffler's syndrome), although bronchiolitis obliterans-organizing pneumonia (BOOP) may also present in this way (1). In the case of women undergoing breast surgery followed by chemotherapy and radiotherapy, we are only aware of cases with migratory pulmonary infiltrates diagnosed as BOOP (2,3). At present it is known that radiation therapy and chemotherapy may give rise to pulmonary complications. Alveolar septal thickening and interstitial fibrosis are common after chemotherapy (4,5). Pneumonitis is the main complication of radiation therapy, occurring 4–12 weeks after treatment has been completed. Pneumonitis is more frequent when chemotherapy is received before radiation therapy (4).

Case Report

A 65-year-old non-smoking woman underwent breast surgery for a ductal carcinoma of the right breast (stage II) in August 1994. She then received six cycles of chemotherapy with 600 mg m \(^{-2}\) cyclophosphamide, 10 mg m \(^{-2}\) mithoxanthrone and 600 mg m \(^{-2}\) fluorouracil. She completed chemotherapy in May 1995. She underwent radiation therapy between June and July 1995. External radiation, using photon X, with 50 Gy total (180 cGy per fraction) was given over the tumoral zone, the axilar area and the upper clavicular and right internal mammary ganglionary chain. No infection, neoplastic disease, thrombosis, inhalation toxicity or connective tissue disease were identified, only a calcified hydatid liver cyst being found. In July 1995, after completion of her radiation therapy, the patient developed fever and a dry cough. A combination of antibiotics and mucolytics was given for 3 weeks, but this resulted in no clinical improvement. The patient developed progressive dyspnoea on exertion and was admitted in November 1995. On examination, the patient's oral temperature was 37.5°C and right lung inspiratory crackles were heard. Cardiac sounds were normal. The abdomen was free of organomegaly, and no peripheral adenopathy was found. The right breast scar was painless and the left breast was normal. Digital clubbing was absent. A chest roentgenogram showed airspace infiltrates in the right upper and middle lobes. High resolution computed tomography (HRCT) confirmed airspace opacities in the right upper and middle lobes (Plate 1). The lung function test showed FVC=1.740 l (77%), FEV\(_1\)=1.440 l (77%) and FEV\(_1\)/FVC=83%. Carbon monoxide transfer was 63% of the predicted value. Arterial blood gases at rest showed arterial oxygen tension (PaO\(_2\)) at 62 mmHg and arterial carbon dioxide tension (PaCO\(_2\)) at 36.4 mmHg. Haemoglobin was 11.7 mg dl \(^{-1}\); the white blood cell count revealed 7-2 \(\times\) 10\(^3\) with 69% neutrophils, 22% lymphocytes, 4% monocytes and 3% eosinophils, and the platelet count showed 343 \(\times\) 10\(^3\). The 1-h erythrocyte sedimentation rate was 78. Total proteins, albumin, immunoglobulins, immune antibodies and rheumatoid factor were normal.

PLATE 3. (a) Normal large bronchiole. (b) Small bronchiole showing a chronic inflammatory infiltrate in its wall (haematoxilin–eosin, × 375).

Investigations for micro-organisms in sputum were negative. Fibre-optic bronchoscopy showed a normal bronchial tree. Bronchoalveolar lavage (BAL) was performed on one segment of the middle lobe. High lymphocyte cell counts suggested alveolitis. A careful search for pathogens in the BAL fluid was negative. Transbronchial biopsy afforded a small sample of normal lung tissue. Surgical biopsy was performed under videothoracoscopy. Histological findings revealed alveolar septal thickening with fibrosis (Plate 2). The large bronchioles were normal [Plate 3(a)] while the small ones showed a chronic inflammatory infiltrate in their walls [Plate 3(b)]. No obliteration of respiratory bronchioles was found. The patient was discharged from the hospital in November 1995. Two months later she was doing well, although she referred to dyspnoea on exertion. The 1-h sedimentation rate was 51. Arterial blood gases at rest showed $P_{aO_2}$ at 61 mmHg and $P_{aCO_2}$ at 41 mmHg. A chest roentgenogram showed airspace infiltrates in the left upper lobe and small residual linear opacities in the right upper and middle lobe (Plate 4). HRCT confirmed the airspace opacities. The patient was admitted again in January 1996. A second fibre-optic bronchoscopy showed a normal bronchial tree. BAL fluid was negative for pathogens and malignant cells. Transbronchial biopsy of the apical segment of the left upper lobe showed interstitial fibrosis. A diagnosis of migratory pulmonary infiltrates with pneumonitis secondary to chemotherapy and/or radiation therapy was given. Treatment with 32 mg day$^{-1}$ methylprednisolone that was progressively tapered off resulted in rapid clinical improvement and complete resolution of airspace opacities (Plate 5).

Discussion

Patients with breast cancer are frequent, and most of them receive chemotherapy and radiation therapy after surgery, a clinical syndrome of pulmonary toxicity developing in a substantial number of them. Cyclophosphamide, a drug commonly used in chemotherapy protocols, has been associated with significant pulmonary toxicity; in particular, with interstitial fibrosis (4). Additionally, the compound has been shown to cause interstitial fibrosis in experimental animals (6,7). In rats, cyclophosphamide increases the deposition of collagen in lung tissue and the production of oxidants by macrophages (8). Radiation therapy appears to exacerbate pre-existing cyclophosphamide toxicity. In several patients that had received cyclophosphamide and radiation therapies, Todd et al. (5) found increased dyspnoea and coughing. CT scans of the chest at this time also showed airspace opacities in the lung included
within the radiation tangent. Therefore, radiation therapy, although it does not seem to be a primary cause of the toxicity syndrome, appears to exacerbate pre-existing drug toxicity.

In our case, the airspace lung infiltrates were first observed in the right lung (included within the radiation tangent). During the evolution of the disease they were also seen in the left lung. In this sense, we report here a case of migratory pulmonary infiltrates as a probable complication of the treatment of patients with breast carcinoma. Few disease processes have been described in which fleeting or migratory infiltrates are common. These are mainly seen in syndromes associated with pulmonary eosinophilia, parasitic infection, allergic bronchopulmonary aspergillosis, Churg-Strauss vasculitis and hypersensitivity to drugs (9).

In our case, although the clinical and radiological aspects were reminiscent of BOOP, surprisingly the histopathological diagnosis was alveolar septal inflammation and fibrosis, compatible with usual interstitial pneumonia (10) and also with radiation pneumonitis (11). This diagnosis seems to render our case different from those reported by Bayle et al. (2) and Crestani et al. (3). These latter authors reported several cases of women receiving breast radiation therapy following surgery for breast carcinoma who were diagnosed as having BOOP. The main difference between these studies and our own report is that our patient received cyclophosphamide after surgery but before radiation therapy. Accordingly, treatment with cyclophosphamide might have been the cause of the pulmonary toxicity and the radiation therapy might have potentiated the drug toxicity. BOOP changes normally appear in the mid-course of disease after radiation injury of the lung, followed by fibrosis without BOOP after 9–12 months (9). These data differ from our own since in our patient a histological picture of alveolar septal thickening and fibrosis was discovered after only 4 months of radiation (although it should be noted that we do not know when and how these findings developed first after the radiation). Nevertheless, we cannot exclude the possibility that our case might also reflect a later (post-BOOP) fibrosis stage of the radiation injury, accelerated by cyclophosphamide treatment. As in BOOP cases, our patient also responded properly to corticosteroid therapy. It has been proposed that corticosteroid would interrupt an inflammatory cascade triggered by oxidant-due injury to epithelial and endothelial cells (5).

In conclusion, we suggest that adjuvant therapy for breast cancer (chemotherapy with cyclophosphamide and radiation therapy) may produce migratory pulmonary infiltrates with a histopathological picture of toxic pneumonitis with interstitial fibrosis.

References

A case of diffuse panbronchiolitis effectively treated with low-dose macrolide antibiotics and leukotriene D₄/E₄ receptor antagonist

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Introduction

Diffuse panbronchiolitis (DPB) is a disease with chronic inflammation that is exclusively located in the region of the respiratory bronchioles (1). The pathological features of this disease are characterized by a thickening of the wall of the respiratory bronchioles due to the infiltration of lymphocytes, plasma cells, and histiocytes (1). The disease is prevalent in Mongolians and its prognosis is considered to be poor when not properly treated. Although DPB has been treated with corticosteroids, most patients ultimately suffer from a colonization of Pseudomonas aeruginosa. To avoid such a complication, 'low-dose and long-term' erythromycin treatment has been introduced as an effective regimen for DPB, but the effectiveness of this treatment still remains to be elucidated (2).

Case Report

A 23-year-old man was admitted to the hospital because of an exacerbation of a productive cough, and a fever of 38.6°C. He had a long history of cough, purulent sputum, and paranasal sinusitis beginning in his youth. The patient had a reddish complexion and complained of dyspnoea. However, he had no history of bronchial asthma. The chest was symmetric, and normally resonant. On auscultation, scattered rales and rhonchi were heard, mainly in the lower lung fields. A haematological examination showed the white blood cell count to be 18 000 μl⁻¹, with 87% neutrophils, 13% lymphocytes. The value of the C-reactive protein (CRP) was 4.4 mg dl⁻¹. The blood chemistry findings were all within the normal limits except for a slightly elevated γ-globulin (21.7%). His IgE titre was within the normal limit. A chest X-ray showed a nodular and reticular shadow predominantly located at the bilateral lower lung fields associated with the tram line, thus suggesting bronchiectatic changes. Computed tomography (CT) of the thorax exhibited diffusely disseminated fine nodular shadows at the bilateral lower lung fields and bronchiectatic changes in the left lower lobe (Plate 1). His vital capacity was 2970 ml, 69% of the predicted value and FEV₁, 69% of his forced vital capacity. The PaO₂ was 66.4 mmHg; PaCO₂, 40.2 mmHg; and pH, 7.419 breathing room air. Parenteral administration of ampicillin was started and the patient became afebrile 2 days later. The CRP value and white blood cell count improved to 1.1 mg dl⁻¹ and 8540 μl⁻¹, respectively; however, improvements were incompletely observed on the auscultatory findings or chest roentgenogram. A transbronchial biopsy was carried out under a possible diagnosis of diffuse panbronchiolitis. As shown in Plate 2, the alveolar wall near the bronchiole was thickened due to the histiocytic accumulation and chronic inflammatory cell infiltrate composed of lymphocytes, plasma cells, and scattered eosinophils. The bronchial wall showed no serious changes except for a mild chronic inflammatory cell infiltrate.

Under the diagnosis of DPB at an early stage, the administration of macrolide antibiotics (clarithromycin, 400 mg day⁻¹) was started. Six months later, he had another acute exacerbation of an airway infection and demonstrated the following levels at admission: CRP, 4.2 mg dl⁻¹; WBC 11 800 μl⁻¹ with 74% neutrophils, 25% lymphocytes, and 1% eosinophil. The parenteral administration of cefmetazole effectively ameliorated this episode. The oral administration of macrolide antibiotics continued for a further year. However, the patient continued to complain of coughing, sputum production and no further