Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Bronchiolitis obliterans organising pneumonia: a consequence of breast radiotherapy

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Summary

The authors describe a case of 51-year-old woman who presented with breathlessness following radiotherapy for breast carcinoma. A chest radiograph and thoracic CT scan revealed extensive airspace consolidation affecting right upper and lower lobes. A trans-bronchial biopsy revealed evidence of foamy macrophages and fibroblastic plugs within alveoli, consistent with organising pneumonia. Indirect immunofluorescence microscopy revealed evidence of antiepithelial antibodies. Gradual but complete resolution occurred without any specific treatment. This case highlights the importance of considering radiation induced bronchiolitis obliterans organising pneumonia in the context of parenchymal shadowing following radiotherapy. Although corticosteroids are widely recommended for treatment, this case illustrates that organising pneumonia may resolve spontaneously.

BACKGROUND

This case illustrates an unusual complication of breast radiotherapy in the form of organising pneumonia. This case will raise the awareness about this clinical entity which is probably under-recognised and hence underdiagnosed. Moreover, it demonstrates that spontaneous resolution without corticosteroid therapy may occur. A novel mechanism of pathogenesis in association with antiepithelial antibodies has been described which, to our knowledge, has not been reported before.

CASE PRESENTATION

A 51-year-old woman with a background of situs inversus presented to chest clinic with a 4-week history of gradual onset breathlessness and a productive cough which was unresponsive to oral antibiotic treatment. A grade I invasive ductal carcinoma of the right breast had been treated with wide local excision followed by localised radiotherapy (40 Gy) in 15 fractions 6 weeks previously.

There was no history of any respiratory symptoms and she was not taking any regular medications. She was an ex-smoker with a 5-pack-year history and there had been no avian exposure. Physical examination revealed tachycardia and fever of 38.3°C and she was normotensive. Oxygen saturations were 92% breathing room air and there were reduced breath sounds on the right side of her chest. The jugular venous pressure was not elevated and remainder of the systemic examination was unremarkable.

INVESTIGATIONS

A chest radiograph (figure 1) showed dense consolidation in the right upper and mid zones. In terms of laboratory findings, inflammatory markers were raised with white cell count of $14\,000\,10^9$ cells/l and C reactive protein of

54 mg/l. The remainder of biochemical profile was unremarkable. In view of minimal response to antibiotics, a thoracic CT scan was organised. The CT scan (figure 2) revealed extensive airspace consolidation affecting the right upper lobe and apical segment of right lower lobe with associated volume loss. Furthermore, there was no evidence of bacterial, viral or fungal infection on microbiological examination of blood and sputum.

She underwent a bronchoscopy that showed normal endobronchial anatomy and a trans-bronchial lung biopsy specimen (figure 3) was obtained from the right upper

Figure 1 Chest radiograph demonstrating right upper lobe consolidation and volume loss.

Figure 2 Thoracic CT scan showing air space consolidation affecting the right upper lobe (small arrow) and apical segment of the right lower lobe (large arrow) with associated volume loss.

Figure 4 Follow-up CT scan of thorax demonstrating migratory consolidation affecting the left side (arrow). The right-sided consolidation has essentially resolved.

Figure 3 Trans-bronchial biopsy specimen from right upper lobe shows evidence of fibroblastic plugs (also known as Masson bodies; marked with arrows) within the alveolar spaces. These are the histological hallmark of organising pneumonia.

lobe. Histopathological examination showed evidence of foamy macrophages and multiple fibroblastic plugs within alveoli (Masson bodies), without significant inflammatory changes, consistent with a pathological diagnosis of organising pneumonia.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses for this case include community acquired pneumonia, radiation induced pneumonitis or organising pneumonia, pulmonary embolism with associated infarction or atypical viral or fungal infection. In view of raised inflammatory markers, fever and consolidation on chest radiograph, bacterial pneumonia should be the first consideration in the differential diagnosis. However,

Figure 5 Evidence of antiepithelial cell antibodies of IgM type following incubation of the patient's serum with A549 (alveolar epithelial) cells, followed by detection with a fluorescein-conjugated antihuman IgM antibody. There is a membranous pattern of enhancement on immunofluorescence (arrows).

poor initial response to antibiotics suggests the need to consider other diagnoses. The migratory pattern of consolidation on follow-up CT scan (figure 4) is highly suggestive of bronchiolitis obliterans organising pneumonia (BOOP) rather than radiation induced pneumonitis.

TREATMENT

The patient was commenced on oral prednisolone but could not tolerate the drug because of mental alterations after a single dose. However, there was gradual improvement without any specific treatment over the next few weeks and made a complete recovery over the next 6 months.

OUTCOME AND FOLLOW-UP

At 9 months follow-up appointment, all respiratory symptoms had completely resolved with a clear chest radiograph and normal lung function. Hence, she was discharged from respiratory follow-up.

DISCUSSION

BOOP or cryptogenic organising pneumonia is an interstitial lung disease of uncertain aetiology associated with areas of consolidation and deposition of fibroblastic plugs within the alveolar airspaces. This clinical entity is also encountered in the context of a range of pathological processes including connective tissue disorders, infectious and toxic agents, drugs and malignancy. Rarely, it may be a consequence of radiotherapy for lung or breast carcinoma.¹

This case highlights the importance of considering radiation induced BOOP in the context of parenchymal shadowing following radiotherapy. The likelihood of this disorder is substantially increased if the radiological abnormalities have a migratory pattern beyond the radiation field, as demonstrated in this case. The frequency of this disorder has been reported to be approximately 2–3%^{2–3} following radiotherapy and the clinico-radiological picture is similar to radiation pneumonitis which adds to the difficulty of diagnosing this clinical entity. Although corticosteroids are the recommended treatment in this condition,⁴ this case illustrates that there may be a complete resolution without any specific treatment. Furthermore, a novel mechanism of pathogenesis of radiation induced organising pneumonia in relation to circulating IgM antibodies against alveolar epithelial cells is demonstrated which has not been described before.

The exact pathogenesis of radiation induced BOOP is poorly understood. An immune mediated mechanism of pathogenesis is plausible in view of the bronchoalveolar lavage (BAL) pattern of lymphocytic alveolitis observed in the idiopathic variety of this disorder in a number of studies.^{5–7} BAL findings consistent with BOOP include increased total cell count and are frequently characterised by a mixed cellular pattern of lymphocytosis, neutrophilia, eosinophilia and increased foamy macrophages. In a study of 26 cases of idiopathic BOOP, Nagai *et al* showed a BAL pattern of BOOP consisting of lymphocytosis with a decreased CD4⁺/CD8⁺ ratio and an increase in lavage neutrophil and eosinophil count. However, this pattern is non-specific and may be seen in hypersensitivity pneumonitis and chronic eosinophilic pneumonia. In addition to the above BAL findings, TH-1 related cytokines, including IL-12, IL-18 and interferon- γ have been found to be increased in lavage fluid.⁶ These findings do substantiate the role of T lymphocytes in the pathophysiology of BOOP and this aspect of immune dysregulation is worthy of further investigation.

Alveolar epithelial injury has been demonstrated in an ultrastructural study of nine patients with idiopathic BOOP.⁸ Myers and Katzenstein examined biopsy specimens with electron microscopy and found evidence of epithelial damage predominantly involving alveolar ducts and cells lining the alveolar septa. Moreover, there was extensive epithelial necrosis with denudation of

epithelial basal laminae. In the present case, we used indirect immunofluorescence staining using patient's serum to evaluate for the presence of antiepithelial and antienothelial antibodies. As there is evidence of antiepithelial antibodies in the pathogenesis of radiation pneumonitis,⁹ we hypothesised that epithelial and or endothelial antibodies may be involved in the pathogenesis of radiation induced organising pneumonia. We found increased IgM mediated immunofluorescence on alveolar epithelial (figure 5) and to a lesser extent on endothelial cells (data not shown) after staining with patient's serum as compared to a control patient's serum or 0.1% bovine serum albumin/phosphate buffered saline control. The predominant staining pattern was membranous suggesting the possibility of an autoimmune mechanism of cellular injury of alveolar epithelial cell lining. These findings may be a consequence of type I and II pneumocyte damage, vascular atrophy and ischaemic injury during the radiation treatment period.¹⁰

Learning points

- ▶ Radiation induced BOOP should be considered in the differential diagnosis of parenchymal shadowing following breast or lung radiation.
- ▶ Spontaneous resolution may occur without corticosteroid administration.
- ▶ Chest physicians and oncologists should be aware of this interesting clinical entity and further research into the pathogenesis of this disorder is needed.

Competing interests None.

Patient consent Obtained.

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