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ARTIGO DE REVISÃO/REVIEW ARTICLE

# Doença pulmonar induzida pelas radiações ou pelos fármacos citostáticos

## Radiation- and drug-induced pneumopathies

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**RESUMO**

**O artigo discute dois temas afins: 1) doença pulmonar induzida pela radioterapia nas suas diferentes apresentações: pneumonite de radiação clássica e fibrose pulmonar e outras duas mais recentemente descritas, BOOP e alveolite linfocitária bilateral. São discutidos os mecanismos patogénicos, clínica e tratamento; 2) a patologia intersticial induzida por fármacos citostáticos nas suas várias formas de apresentação.**

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**Palavras-chave:** Radioterapia; Citostáticos; BOOP; Alveolite Linfocitica

**ABSTRACT**

**In this paper two topics are adressed: 1) the radiation induced lung injury in its possible forms: classical radiation pneumonitis and radiation fibrosis or two other newly recognised sindromes BOOP and bilateral lymphocitic alveolitis. The mecanism and treatment are discussed; 2) the cytotocic drug-induced lung diseases and their pulmonary reaction patterns.**

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**Key-words:** Radiation; Cytotocic Drugs; Lymphocitic Alveolitis

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## RADIATION-INDUCED LUNG INJURY

Radiation-induced lung damage is a limiting factor for radiotherapy not only of primary lung tumors but also of those arising in the breast, mediastinum and chest wall, as well as for total body irradiation in hematological malignancies. The risk and severity of pulmonary complications following irradiation are influenced by total dose, dose fractionation, and the irradiated lung volume. The effects of radiation are increased by a prior course of radiotherapy, by previous or concomitant treatment with cytotoxic drugs, by pre-existing lung disease, by hyperoxia and by discontinuation of treatment with corticosteroids. For unilateral irradiation, total doses of less than 30 Gy usually have little effect, whereas radiographic changes are usual with doses exceeding 40 Gy (9). Beside the classical well-recognised syndromes related to thoracic radiation that occur in the radiation field, i.e. radiation pneumonitis and radiation fibrosis, recently two other syndromes have been recognised, occurring outside the field of radiation: bronchiolitis obliterans organising pneumonia and bilateral lymphocytic alveolitis (2,8,14,15).

### Mechanisms

Recent data suggest that there are two separate and distinct mechanisms involved: First, the classical radiation pneumonitis which automatically leads to pulmonary fibrosis. Here the primary damage is to pulmonary endothelial cells and type II pneumocytes by the generation of free radicals which damage cell membranes and DNA. This results in alteration of surfactant and surfactant lipoproteins, as well as in local cytokine production and release of pro-fibrotic mediators (11,15). Second, the sporadic radiation pneumonitis, resulting in bilateral lymphocytic alveolitis or bronchiolitis obliterans organising pneumonia. Here the process is immunologically mediated, with increase in activated T-lymphocytes in bronchoalveolar lavage fluid suggestive of a hypersensitivity pneumonitis (15).

### Clinical features

Radiation pneumonitis occurs one to six months after completion of radiation therapy. It is characterised by non-productive cough, dyspnoea and fever. Characteristically, the radiological findings are confined to the field of radiation and consist of hazy shadowing progressing to more dense consolidation, often with an air bronchogram, limited with a sharp margin to the irradiated field. Radiation fibrosis is the end result of radiation pneumonitis, occurring six to twelve months after irradiation. The fibrosis may be mild and asymptomatic, and may be detected without being preceded by a clinical radiation pneumonitis. Bronchoalveolar lavage may reveal in the field of irradiation, but also in the contralateral lung, an increase in lymphocytes (7,14,16). There have been several case reports on the development of bronchiolitis obliterans organising pneumonia in irradiated patients with breast cancer, developing from 6 to 17 months after the completion of radiotherapy, with recurrent and migrating lung infiltrates outside the radiation field (1,2,8).

### Treatment

In most cases, the disease spontaneously resolves and no treatment is needed. In symptomatic patients, corticosteroids are given. Although no controlled studies are available, there is strong clinical evidence of their effectiveness. Corticosteroids are also effective in radiation-induced BOOP. Recurrence of radiation pneumonitis as well as of BOOP may occur after withdrawal of corticosteroids (1).

## DRUG-INDUCED LUNG DISEASES

Pulmonary complications are frequent in the course of malignant disease. Drug-induced reactions should always be considered. One third of clinical articles published about drug-induced lung disease

are related to antineoplastic agents (3,10).These include chemotherapeutic agents, most frequently implicated being bleomycin, methotrexate, cyclophosphamide, busulphan, melphalan, mitomycin, chlorambucil, and nitrosoureas. Also antiandrogen agents such as nilutamide and bicalutamide have been reported to induce interstitial pneumonitis and/or eosinophilic pneumonia. Recently, cytokines such as interferon or GM-CSF have been added to the list. The following discussion is limited to drugs used in antineoplastic therapy.

## Incidence and risk

The incidence is difficult to estimate. The risk ranges from below 1% to 4% and higher. For some drugs the risk is related to the cumulative amount of drug received (carmustine, bleomycin, cyclophosphamide). Other drugs, for instance methotrexate, do not show such a dose relationship. The disease may develop after treatment periods varying from a few days to many years (5,6).

## Mechanisms

Two major mechanisms are implicated in drug-induced lung injury: First, a direct toxicity, mediated through reactive oxygen metabolites by inducing lesions in the DNA, particularly in type II pneumocytes, or interference with collagen metabolism, implicated for instance for bleomycin. Second, an immunologically mediated hypersensitivity reaction. Cell mediated hypersensitivity can be tested on the basis of a lymphoblast transformation test of blood lymphocytes or a migration inhibition of blood leukocytes. These tests are not applied in routine diagnosis, however. Bronchoalveolar lavage may show a lymphocytic alveolitis with a CD8 predominance (exception methotrexate, here a CD4 predominance). Lung biopsy may reveal poorly defined granuloma formation, hyperplastic type II pneumocytes, and lymphocytic or eosinophilic infiltration of septal and intraalveolar spaces (12).

## Pulmonary reaction patterns

Although the clinical presentation is non-specific and rather uniform, there are several pulmonary reaction patterns to be discriminated (5,6,10,17):

- acute reversible cellular interstitial pneumonitis (methotrexate, nilutamide, bleomycin, chlorambucil, hydroxyurea, iphosphamide, interferon-alpha, interleukin-2, GM-CSF) (10).
- Interstitial pneumonitis with alveolar damage (bleomycin, cyclophosphamide, melphalan, mitomycin, nitrosoureas). Here BAL-neutrophilia is present (13).
- Pulmonary fibrosis (busulphan, bleomycin, cyclophosphamide, nitrosoureas) (13,18).
- Pulmonary eosinophilia (bleomycin, nilutamide, bicalutamide) (19).
- BOOP (bleomycin). BOOP induced by bleomycin is distinctive in that radiographic infiltrates are often round or stellate, and thus may mimic lung metastasis (4).

## Clinical presentation and diagnosis

The clinical presentation is usually variable and non-specific, and so are the chest roentgenographic findings. The most common pattern is bilateral peripheral alveolar infiltrates, with or without a migratory component. Pulmonary function shows a restrictive pattern and a reduced diffusing capacity. Occasionally peripheral blood eosinophilia is noted. In the subacute cellular interstitial pneumonitis, patients present with dyspnoea, cough and fever.

Correct diagnosis of drug-induced lung disease is difficult and is based mainly on clinical grounds. Ideally, 5 criteria should be fulfilled:

- Definite exposure to the drug.
- Consistent clinical picture.

- Careful exclusion of other possible causes (infection, pulmonary involvement by underlying malignancy, inhalational causes such as extrinsic allergic alveolitis).
- Improvement of symptoms after withdrawal of the drug (although improvement is less likely in drug-induced pulmonary fibrosis or alveolar damage). In some cases improvement occurs only once steroids are given.
- Symptoms should recur if the drug is re-administered. Re-challenges raise several problems, however, because the risks are poorly known. Re-administration of the drug should not routinely be used to confirm diagnosis.

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