Fatal Pulmonary Toxicity by the Association of Radiotherapy and Medroxyprogesterone Acetate

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This report describes a fatal pneumonitis occurring in a breast cancer patient while on adjuvant treatment with radiotherapy and medroxyprogesterone acetate. The clinical and radiologic features, as well as the timing of this pneumonitis, make a radiation pneumonitis more than probable. A radiation pneumonitis was also observed in other patients treated in the same way. Medroxyprogesterone acetate thus seems to act as a radiosensitizer since no such effects were seen in patients treated with radiotherapy alone. The radioenhancing effect is not limited to the lungs, since radioesofagitis was also encountered in similarly treated patients.

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COMBINED MODALITIES are increasingly being used in the primary treatment of cancer in an attempt to increase cure rate. One example is the treatment of locoregional breast cancer in which surgery has been supplemented by radiotherapy and/or chemotherapy. In this connection, trials were initiated to define the role of adjuvant hormonal therapy.[1,2]

This report describes a breast cancer patient who received simultaneous radiotherapy and medroxyprogesterone acetate (MPA)* (Farlutal^{R} depot, Farmitalia, Italy) in an adjuvant setting and eventually succumbed to a devastating pneumonitis.

Case Report

A 67-year-old woman without any other underlying disease underwent a Patey operation for a moderately differentiated invasive ductal carcinoma of the right breast. She was pathologically staged as a T2N0M0 and randomized in a clinical adjuvant trial with MPA.

Two weeks postsurgery, she received radiotherapy with Co^{60} using two opposite tangential fields delivering 45 Gy to the midline of the thoracic wall in 20 fractions over 4 weeks. Forty Gy were administered to the supraclavicular and internal mammary lymphnodechain by perpendicular fields touching the tangential fields. Ten days earlier, a 4-week course of MPA, in a dose of 500 mg per day intramuscularly (IM) was initiated, followed by 500 mg IM biweekly for 5 months.

Two weeks after the beginning of the radiotherapy, the patient developed symptoms of mild radiation esofagitis and radiodermitis. Her body weight increased by 3 kg. After 6 weeks, a dry cough and exertional dyspnoea appeared with progression to severe dyspnoea at rest, increasing dry cough eliciting right chest pain, fever (up to 39°C), and cyanosis. Physical examination further revealed signs of right heart failure and important hypoventilation and inspiratory crackling over the entire right lungfield.

Laboratory examinations, performed 5 weeks after initiation of symptoms, showed an increased ESR (59 mm/hr), fibrinogen (650 mg/100 ml), LDH (692 IU), ALT (39 IU), AST (39 IU) and gamma-GT (43 IU). The leukocyte count was 8400/mm^3 (80% neutro, 11% lympho). An important hypoproteinemia of 4.8 g/100 ml (albumine 2.3 g/100 ml, gamma-globulines 0.5 g/100 ml) was also noted. Repeated hemocultures remained negative, as were the several routinely performed counter immuno electrophoreses on serum. Viral complement fixation test was only elevated for cytomegalovirus (CMV) to a titer of 40. Urinalysis and culture were normal. The ECG showed a sinustachycardia and P-pulmonale with slowed r-progression in V_1-V_3.

A chest x-ray (Fig. 1) showed interstitial and alveolar infiltration of the whole right lung extending within 5 days to the perihilar region of the left lung. The right diaphragm was elevated and the trachea deviated to the right.

Macroscopic examination with fibrobronchoscopy was not contributive, and results of a transbronchial lung biopsy study disclosed only chronic, nonspecific mucosal irritation on microscopy. There were no signs of viral, mycotic or pneumocystis carinii infection. Bronchial washings and aspirations proved to be negative on culture for bacteriae, mycobacteriae, and fungi.

Treatment with oxygen, prednisone (10 mg three times daily), diuretics and ampicillin abated the fever but did not influence clinical and radiological disease progression. The patient finally died of respiratory insufficiency 6 weeks after initiation of symptoms.

A postmortem examination was performed. Gross examination of the lungs revealed a firm consistency and a nodular

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pleural surface due to extensive fibrosis. Fibrotic changes were most pronounced in the right lung. At the cut surface the parenchyma of both lungs was plum-colored.

Microscopic examination of the right lung showed extensive interstitial fibrosis with only a discrete chronic inflammatory cell infiltrate. Certain areas showed a smooth muscle hyperplasia (Fig. 2). Alveoli were lined by highly atypical type II pneumocytes, most of which were sloughed off into the alveolar spaces. Their nuclei were enlarged, hyperchromatic, and contained prominent nucleoli. Moreover, alveoli contained hyaline membranes, foamy macrophages and a few multinucleated giant cells. The cytoplasm of some macrophages contained phagocytosed hyaline membranes. Only rare enlarged alveolar macrophages showed a dark intranuclear inclusion surrounded by a clear halo, typical for a cytomegalovirus infection. Some bronchioles were lined by a squamous epithelium. The left lung presented similar lesions but less pronounced interstitial fibrosis. A few very small and recent emboli were found in the peripheral arteries of the left lung only, without pulmonary infarction.

Viral cultures were negative, and bacterial cultures of biopsy specimens from the right lung were positive only for *Citrobacter freundii* and *Klebsiella oxytoca.* Only *Citrobacter freundii* was isolated from the left lung.

A diagnosis of radiation pneumonitis with extensive fibrosis, complicated by a recent infection with cytomegalovirus, was made.

Discussion

This report describes a previously healthy patient with early-stage breast cancer who developed a fatal pneumonitis while under adjuvant treatment with radiotherapy and medroxyprogesterone acetate. The clinical and radiologic features described are all compatible with, if not typical for, the whole picture of a radiation pneumonitis.[3]

Superimposition of a bacterial or CMV infection might have contributed to the final phase of this patient's illness, but there are no arguments favoring an infectious disease as the initial or main pathologic event. Pathologic examination also excludes pulmonary thromboembolic disease or congestive heart failure as the primary cause of death.

Of 112 consecutive patients treated previously at this center with the same technique and doses of radiotherapy, without adjuvant hormonal therapy, clinical symptoms of radiation pneumonitis were never encountered, in spite of localized fibrosis in the treatment fields in most of the patients.

It has been reported that for large-field radiotherapy, using anteroposterior Co^{60} radiation fields, the dose for the average patient is about 16% higher in the lung than it is to unit density tissues, varying between 10% and 24%.[4] This means that for an uncorrected dose of 45 Gy, assuming unit density tissues, the irradiated part of the lung by tangential fields has possibly received a maximum dose of 52.5 Gy. This does not, however, explain the anatomopathologic findings in the entire right lung in this case.

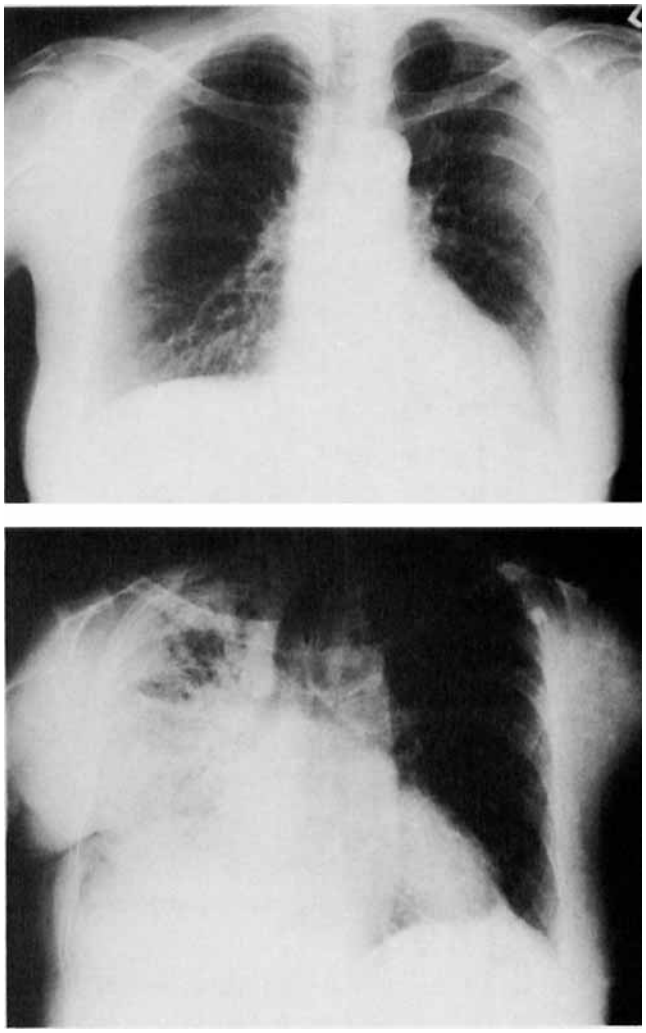

FIG. 1. Chest x-ray before radiotherapy (A, top) and 1 week before death (B, bottom).

An accidental irradiation of the entire right lung has been excluded in view of the treatment conditions. Only the right anterior lung segment was included in the radiation port, the lung top receiving at most 46.2 Gy corrected according to the above mentioned method. The extension of pneumonitis beyond the limited irradiated lung fields and finally to a part of the contralateral lung is troublesome and unexplained.[3] Fatal lung toxicity by known radiosensitizers has been described earlier.[5]

Recently, medroxyprogesterone acetate was shown to have a radiosensitizing effect on endometrial cancer cells *in vitro.*[6] Prolongation of the more radiosensitive late G_2-phase of the cell cycle is suggested as a possible mechanism. The authors also postulate that the presence of progesteron receptors is a prerequisite for radiosensitation. Our findings could be in line with this, as progesteron receptors have been demonstrated in the adult rat.[7]

Since the inception of this still ongoing randomized

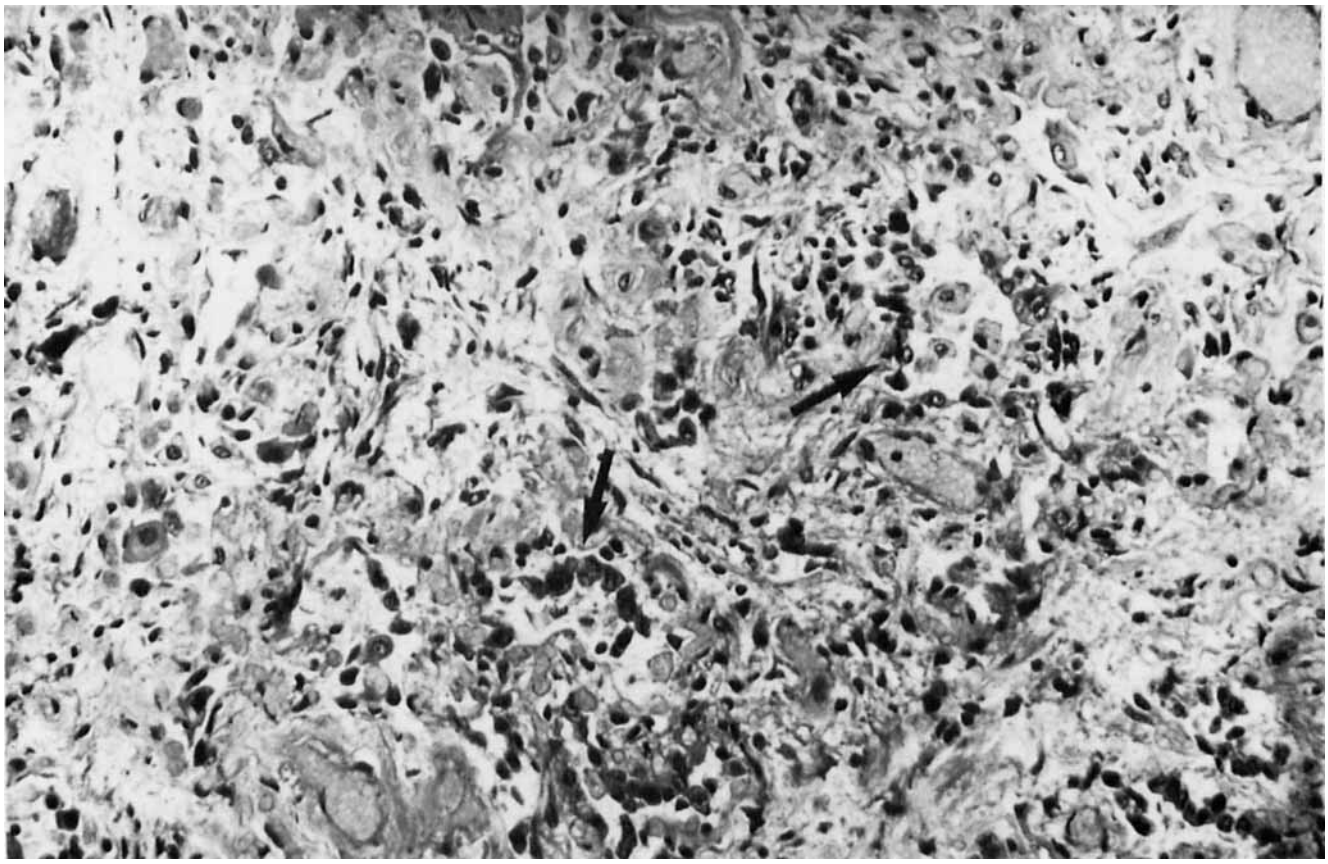

FIG. 2. Microscopic section of postmortem lung showing interstitial fibrosis with prominent hyperplasia of alveolar lining cells and cellular sloughing (arrows).

adjuvant breast cancer trial with MPA, several patients have shown clinical signs of moderate to severe pneumonitis with exclusion of thromboembolic disease by clinical examination or isotopic lung ventilation perfusion scans. None had preexisting pulmonary or cardiac disease. In the MPA treatment arm, we encountered pneumonitis (confined to the irradiated lung fields) in 4 of 13 patients *versus* none of 9 in the treatment arm without MPA. Moreover, radiation induced esofagitis has never been an important problem with radiotherapy alone, whereas it occurred in 4 of 13 patients in the population allocated to MPA treatment, necessitating hospitalisation and nutritional support in three of them. The total number suffering from moderate to severe pneumonitis and/or esofagitis thus far amounts to 7 of 13 patients on MPA, *versus* only 1 patient with mild esofagitis out of 9 in the arm treated with radiotherapy alone ($P < 0.05$).

Although the pathogenetic mechanisms involved are still unclear, we thought it necessary to report this unexpected and potentially fatal toxicity in patients who otherwise might have been cured of their disease. Future patients to be included in this trial will be screened prospectively by means of scheduled isotopic lung ventilation perfusion scans, chest x-rays and lung function tests. We are also currently investigating the issue in a rat model. The search for clinically usable radiosensitizers is an active field of investigation.[8] However, the goal of an improved therapeutic ratio has still to be achieved and proven, also for MPA.

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