Raltitrexed-related Pulmonary Toxicity

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Raltitrexed (Tomudex®) has recently been registered for the treatment of metastatic colorectal cancer. This drug was shown to produce response, time to progression and survival rates identical to those with 5-fluorouracil-based regimens. The most frequent side effects relate to the hematopoetic and gastrointestinal systems (1). To the best of our knowledge, pulmonary toxicity has never been reported.

Case report. A 68-year-old female patient without any significant previous medical history underwent a left hemicolectomy for: Dukes B adenocarcinoma of the sigmoid colon on March 1998. Surgery was uneventful and no adjuvant therapy was undertaken. During follow-up, a rise in serum CEA-level and detection of liver metastasis (CT scan) indicated recurrence. Ambulatory treatment with Raltitrexed 3 mg/m^2 repeated every 3 weeks was initiated (October 15, 1998). Chest roentgenogram (Fig. 1a) and thoracic CT scan were completely normal at baseline. Owing to a significant increase in hepatic enzyme levels after course 2, the dosage of the drug was reduced by 20% as from course 3. A few days after each administration, the patient reported asthenia and dyspnoea on exercise, which resolved completely and spontaneously within days. A clinical examination of the heart (including ECG, cardiac enzymes and Doppler echography) and lungs after course 2 revealed no abnormalities. A partial remission (PR) was documented after 4 courses (January 6, 1999) and it was decided to continue the same chemotherapy, despite the unexplained and apparently increasing degree of dyspnoea and prolongation of time to recovery between the subsequent courses. A chest roentgenogram carried out at the time of the restaging investigations was normal.

After 7 courses of therapy, stable disease (with respect to January 6, 1999, was documented on April 22nd. At that time, the chest roentgenogram showed a mild reticulonodular image in both lung bases (Fig. 1b). On May 18, 21 days after course 8, the patient was admitted to the hospital with progressive severe dyspnoea and fever. A few days after the 8th course the patient had again experienced the typical dyspnoea that accompanied each infusion. This time, however, no 'spontaneous' recovery occurred, but the symptoms progressively worsened and necessitated hospital admission.

At admission, clinical examination showed a conscious, febrile (38°C) patient, extremely dyspnoeic at rest, with fine crackling bibasal lung rales. No signs of deep peripheral venous thrombosis were present.

A chest roentgenogram revealed striking bilateral interstitial infiltrates, compatible with interstitial pneumonitis (Fig. 1c). Arterial hypoxemia was present in breathing room air (PaO_2 56 mmHg; $PaCO_2$ 41 mmHg). The blood examination revealed only an accelerated sedimentation rate and a slightly elevated white blood cell count (10600 elements/mm^3) with normal differential count. A perfusion/ventilation scintigraphy of the lungs showed lacunar mismatched perfusion defects in the laterobasal and posterobasal segments of the right lower lobe, compatible with lung emboli.

During the first few days of hospitalization the patient received supportive therapy (nasal oxygen supplementation, bed rest, IV hydration), large spectrum IV antibiotics and SC low molecular weight heparin. Hemocultures on admission and viral/bacterial serology failed to demonstrate infection. The results of thoracic CT scan suggested interstitial pneumonitis; no intravascular perfusion defects were observed in the right lower pulmonary artery. Two attempts to perform a transbronchial biopsy by bronchoendoscopy (to establish a histopathological diagnosis) failed because of severe hypoxemia. We were able to perform a bronchoalveolar lavage (BAL) on the second occasion but no abnormal cells were seen in the BAL fluid. Epithelial cells did not stain for CEA immunochemistry. Cytology showed a neutrophilic alveolitis with 9% neutrophilis. Total nucleated cell count was 210/mm^3 (normal): Lymphocyte count was normal on BAL fluid and no eosinophils were present. The patient refused a transthoracic open-lung biopsy.

Without a specific diagnosis and any clinical and laboratory amelioration while on empiric treatment, it was decided to start corticotherapy (methylprednisolone 32 mg/day). The response was strikingly favorable, with clinical recovery of respiratory function and a progressive increase in oxygen arterial blood saturation. Furthermore, the radiological lung parenchyma-image on the chest roentgenogram and CT scan improved significantly. The patient was discharged from the hospital in good general condition on June 21st. She was not rechallenged with Raltitrexed and modulated 5-fluorouracil (leucovorin/fluorouracil) chemotherapy was initiated on June 29th uneventfully.

Discussion. We believe there are several reasons to suggest that the interstitial pneumonitis that occurred in this patient was caused by the administration of Raltitrexed. First, Raltitrexed was the only drug used in this patient, who had presented a non-lung related cancer and no concomitant lung comorbidity. Second, there was a

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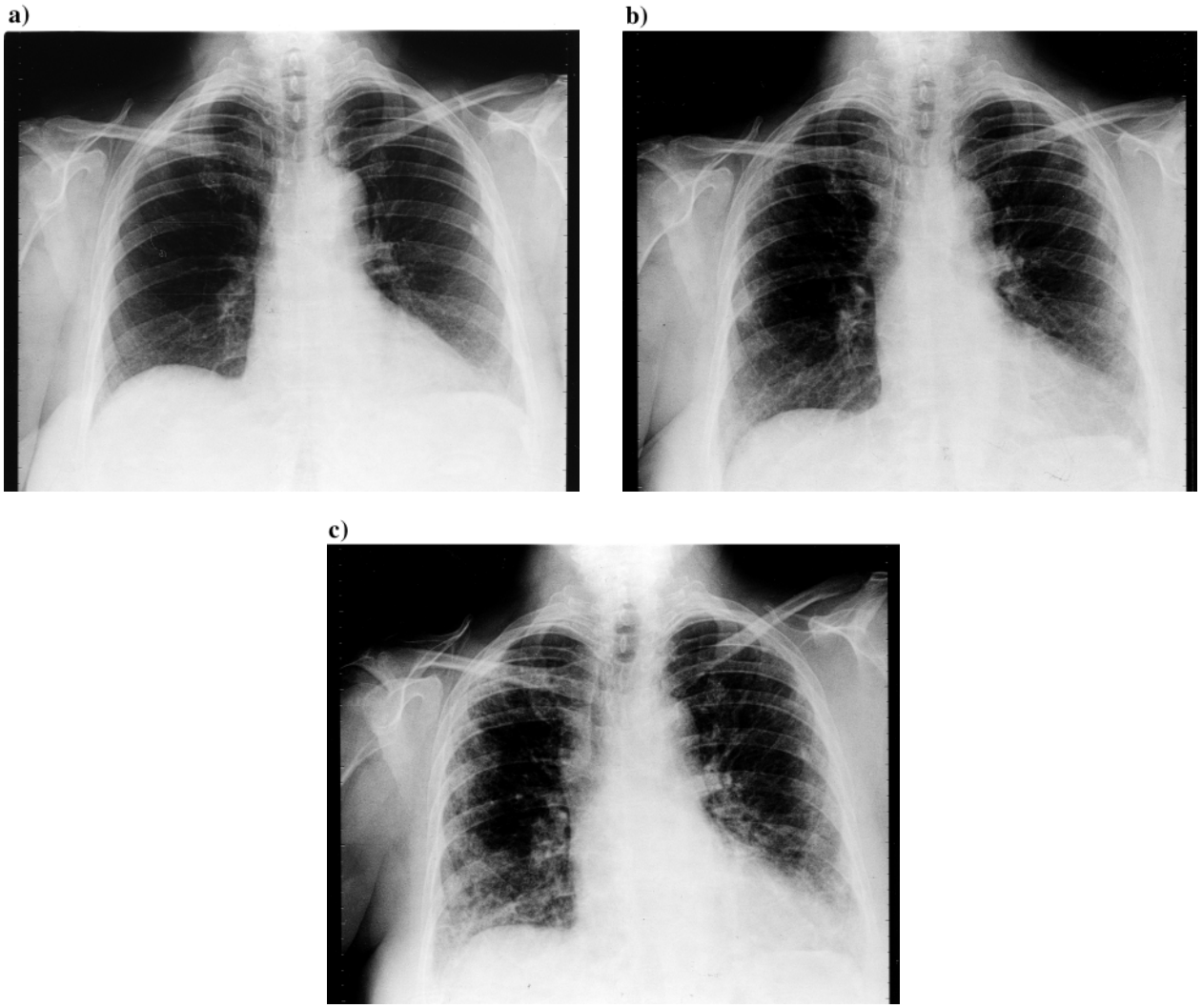

Fig. 1. Chest roentgenogram a) before, b) after 7 and c) after 8 courses of Raltitrexed.

clear-cut temporal association between the administration of the drug and the occurrence of the (initially unexplained) symptomatology. Third, the episodes of dyspnoea worsened and time to recovery lengthened between the courses, which might point towards a cumulative effect. Fourth, the symptoms did not improve until corticotherapy was initiated, which suggests an inflammatory lung condition. Fifth, the absence of diagnosis of other possible intercurrent lung pathologies (such as viral or bacterial infection, massive lung emboli, carcinomatous lymphangitis) either through diagnostic tests and/or the response to specific treatment.

With respect to the underlying mechanism of action, according to the clinical presentation of this patient and without any histological documentation, one can only be speculative. Because of its insidious clinical course, its late full-blown clinical and radiological phase, this case mimics, at best, lung toxicity produced by alkylating agents though there was no cell atypia in this case (2). However, owing to its reversibility upon treatment with corticosteroids and favorable outcome, this case mimics methotrexate pulmonary toxicity. Conversely, the hypersensitivity syndrome (eosinophilia in up to 40% of patients with lung toxicity) observed with methotrexate was absent in our patient (3). Furthermore, it is not known whether the presence of disturbed liver function tests observed throughout the entire course of treatment in this patient could be predictive for the development of lung toxicity. Apparently, the mechanism of action did not involve the thymidilate synthase (TS) enzyme system, since there were no consequences of rechallenge with another TS-inhibitor (5-fluorouracil).

In any case, we think that Raltitrexed should be added to the list of cytotoxic agents that have the potential to induce interstitial pneumonitis in susceptible patients. Patients who develop pulmonary symptoms after the administration of Raltitrexed should be monitored closely with appropriate lung function tests to detect any changes and if so to change to alternative treatment as early as possible.

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