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CASE STUDY

Acute lung injury associated with 5-fluorouracil and oxaliplatinum combined chemotherapy

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Acute lung injury associated with 5-fluorouracil and oxaliplatinum combined chemotherapy. R. Trisolini, L. Lazzari Agli, D. Tassinari, D. Rondelli, A. Cancellieri, M. Patelli, F. Falcone, V. Poletti. ©ERS Journals Ltd 2001.

ABSTRACT: Diarrhoea, T-CD4+ lymphopenia and bilateral patchy pulmonary infiltrates developed in a male 60 yrs of age, who was treated with oxaliplatinum and 5-fluorouracil for unresectable rectum carcinoma. The findings from transbronchial lung biopsy and bronchoalveolar lavage (BAL) were consistent with an organizing diffuse alveolar damage pattern. Once extensive microbiological studies proved negative, corticosteroids were given and a complete remission of clinical and radiological abnormalities was achieved. It is concluded that the aforementioned pathological manifestations were due to chemotherapy and included a pulmonary adverse reaction, a feature never previously associated with oxaliplatinum and 5-fluorouracil regimens.
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Oxaliplatinum (L-OHP) and 5-fluorouracil (5-FU) combined chemotherapy currently represents a valid approach for treating advanced colorectal cancer and has a very favourable safety profile [1–4]. In a recent cohort study of 490 patients who received >2,700 courses of L-OHP plus 5-FU, gastrointestinal, haematological and neurosensory (usually low-grade) toxicities were the most common [4]. Reviewing literature, no reports on pulmonary complications have been published to date in association with this treatment.

Case report

In February 2000, a nonsmoking male, 60 yrs of age, was referred to the Dept of Thoracic Diseases (Bellaria and Maggiore Hospitals, Bologna, Italy) complaining of a 10-day history of nausea, anorexia, diarrhoea, asthenia and dyspnoea. He was affected by unresectable rectum carcinoma and had received seven cycles of L-OHP (130 $mg \cdot m^{-2}$ at day 1, as a 2 h infusion) plus 5-FU (300 $mg \cdot m^{-2}$ as bolus infusion at days 1–5, reduced to 250 $mg \cdot m^{-2}$ after the first course, because of the onset a grade 3 World Health Organization neutropenia) and folinic acid (20 $mg \cdot m^{-2}$ as bolus infusion at days 1–5) combined chemotherapy. His past clinical history only included mild arterial hypertension. On admission, the patient had a body temperature of 36.5°C, a blood pressure of 110/80 mmHg, a heart rate of 135 min^{-1}, and a respiratory frequency of 26 min^{-1}. Physical examination revealed a marked dehydration. Lung auscultation revealed bibasilar inspiratory crackles. A chest radiograph film showed parenchymal infiltrates in both the lower fields. Blood cell count was significant for a T-CD4+ lymphocyte count of 211 $\cdot mL^{-1}$. Erythrocyte sedimentation rate at 1 h was 131 mm. Blood chemistries revealed signs of renal failure (urea 265 $mg \cdot dL^{-1}$; creatinine at 4.6 $mg \cdot dL^{-1}$); reduction of K^+ at 2.9 $mEq \cdot L^{-1}$; elevation of lactate dehydrogenase at 368 $U \cdot L^{-1}$ and of Ca19.9 at 76.7 $mg \cdot dL^{-1}$. Arterial blood gas analysis while breathing room air were: arterial oxygen tension (P_{a,O_2}) 55 mmHg; arterial carbon dioxide tension (P_{a,CO_2}) 18.5 mmHg; pH 7.5; HCO_3^- 14.9 $mEq \cdot L^{-1}$; base excess -5.0. Once a 7-day broad-spectrum antibiotic IV therapy had failed to achieve any clinical and/or radiological improvement

of respiratory abnormalities, high-resolution computed tomography (HRCT) of the chest (areas of ground glass attenuation and alveolar consolidation, mainly involving the lower lobes; fig. 1) and rigid bronchoscopy with fluoroscopic-guided transbronchial lung biopsies (TBBs) and bronchoalveolar lavage (BAL) were performed. BAL-fluid analysis demonstrated 230,000 cells·mL^{-1} with 48% macrophages, 32% neutrophils, 18% lymphocytes, 2% eosinophils and a reverse CD4+/CD8+ ratio (0.2). BAL cultures for common bacteria, acid fast bacilli and fungi, as well as cell vial cultures and/or immunofluorescence tests for viruses (cytomegalovirus, adenovirus, herpes symplex viruses, syncytial respiratory virus, influenzae and parainfluenza viruses) and *Legionella* proved negative. On examination of BAL cytospin preparations stained by both Diff-Quick and Papanicolaou methods, the presence of cuboidal hyperplastic/dysplastic epithelial cells (diffuse alveolar damage (DAD) cells) was evident, whereas neither malignant cells nor viral inclusions and *Pneumocystis carinii* cysts were identified. TBB showed fibroblastic plugs in the alveolar spaces and the presence of DAD cells lining the intraluminal plugs and the alveolar septa (fig. 2). Blood lymphocyte stimulation test at different dilutions with either L-OHP or 5-FU did not significantly differ from controls. A regimen of prednisone (50 mg once daily, tapered down and then stopped over 6 months) was started and a progressive, complete remission of clinicoradiological abnormalities was achieved.

Discussion

The acute onset of nausea, diarrhoea (with dehydration and secondary renal failure), T-CD4+ lymphopenia and lung damage were reported in a patient who had been treated with seven courses of combined chemotherapy with L-OHP and 5-FU. Unlike gastrointestinal and haematological toxicity, no pulmonary adverse reactions had been associated with this regimen up to now [2–4].

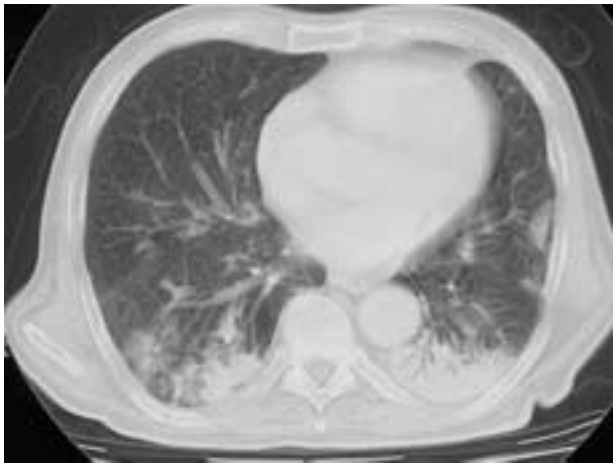

Fig. 1. – High-resolution computed tomography scan through the lower lobes: areas of alveolar opacification with air-bronchogram and ground glass attenuation are evident.

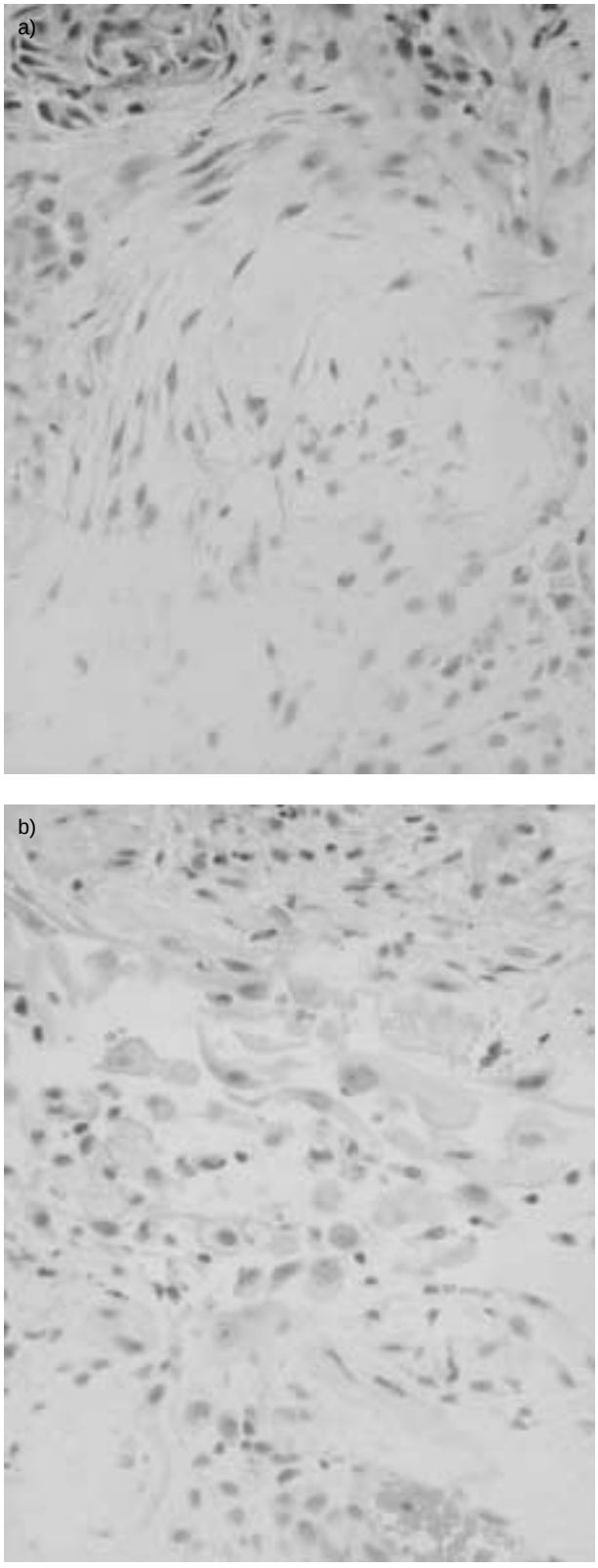

Fig. 2. – Transbronchial lung biopsy: a) alveolar spaces are almost completely obliterated by loose fibrotic buds (stained using haematoxylin and eosin (H&E)); b) atypical type II pneumocytes are "desquamated" into the alveolar space (H&E).

Based on HRCT and/or histological findings, the differential diagnosis of the pulmonary changes in the present case report could be narrowed to a few pathological conditions such as infections, malignancies, pulmonary haemorrhage and drug-induced toxicity. An infectious aetiology, which was strongly considered mainly due to the concomitant presence of a T-CD4+ lymphopenia, was reliably ruled out by extensive microbiological studies on BAL-fluid and lung biopsy. Moreover, the patient had never experienced fever and did not improve in spite of a broad spectrum antibiotic therapy, whereas it was cured by using corticosteroids. The hypothesis of malignancies, either primary lung cancer (*i.e.* bronchioloalveolar carcinoma and mucosa-associated lymphoid tissue (MALT) lymphomas) or metastatic involvement could also be raised by chest HRCT features [5–7]. In particular, colorectal cancer may spread in the lung with a rare pattern, known as "lepidic growth", which is histologically characterized by the growth of malignant cylindrical cells over the alveolar wall and can be associated with HRCT findings like those observed in this case [8]. Such a diagnosis was, however, easily excluded by examining lung biopsy and ascertaining the favourable outcome. Besides, BAL and lung biopsy findings did not support the diagnosis of pulmonary haemorrhage.

Together with the careful exclusion of these causes, several elements led to the suspicion that the lung damage was expression of drug-induced toxicity. In the first instance, the onset of the respiratory changes was concomitant with that of gastrointestinal and haematological ones, which are among the most common complications of L-OHP and 5-FU treatment [2–4]. Furthermore, both cytological (BAL) and histological pulmonary findings, although not specific, could support the diagnosis of drug-induced toxicity [9]. Finally, corticosteroids had to be given to achieve a complete remission of clinicoradiological respiratory abnormalities after broad spectrum antibiotics had failed to warrant any improvement.

It is, however, difficult to define the individual contributions of L-OHP and 5-FU in the determinism of this pulmonary damage, mainly because no cases of lung toxicity have been attributed either to platinum derivative (cisplatinum, carboplatinum, oxaliplatinum) or 5-FU when used as monotherapy. The present authors are only aware of cases of pharyngolaryngeal discomfort and inspiratory stridor observed after L-OHP administration [10]. Conversely, three cases of interstitial lung disease/fibrosis have been associated with combined chemotherapy including 5-FU. JEANFAIVRE *et al*. [11] described a case of acute pulmonary fibrosis in a patient treated with 5-FU and cisplatinum. FIELDING and coworkers [12, 13] reported two cases of interstitial lung disease complicating 5-FU plus mitomycin C combined chemotherapy [12, 13].

The pathological findings in this report's patient had an alveolar rather than interstitial distribution and were consistent with a DAD pattern in the organizing phase. In fact, TBB specimens revealed intra-alveolar fibrotic buds and hyperplastic/dysplastic epithelial cells. BAL-fluid analysis confirmed the presence of DAD cells and showed a marked increase of the neutrophils percentage. These findings, coupled with clinicoradiological data, led to the categorization of such an adverse reaction as organizing acute lung injury.

As far as the pathogenesis is concerned, the negativity of lymphocyte stimulation tests with either L-OHP or 5-FU tends to suggest the importance of a direct toxic effect of the drugs on the parenchymal structures rather than that of immunologically-driven mechanisms.

It is concluded that oxaliplatinum and 5-fluorouracil combined chemotherapy can cause acute lung toxicity. In the case reported, a good clinical and radiological respiratory abnormalities responsiveness to corticosteroids was assessed.

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