

# Pulmonary Fibrosis Secondary to FOLFOX Chemotherapy: A Case Report

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## Key Words

Pulmonary fibrosis · Interstitial pneumonia · Chemotherapy · FOLFOX · Pneumothorax

## Abstract

A 54-year-old female presented with a 2-week history of increasing shortness of breath and fever. She had a history of a poorly differentiated sigmoid adenocarcinoma for which she underwent an anterior resection 6 months prior to admission, followed by 12 cycles of adjuvant FOLFOX chemotherapy. The patient was treated for a severe community-acquired pneumonia; however, she remained hypoxic. A chest CT revealed extensive right-sided fibrotic changes, tractional dilatation of the airways and ground glass density, which had developed since a staging CT scan performed 2 months previously. Although her symptoms improved with steroid therapy, repeat imaging revealed that right hydropneumothorax had developed, and this required the insertion of a chest drain. Following its successful removal, the patient continues to improve clinically and radiographically. The rapid onset and nature of these changes is consistent with a drug-induced fibrotic lung disease secondary to FOLFOX chemotherapy. The phenomenon is underreported and yet, it is relatively common: it occurs in approximately 10% of patients who are treated with antineoplastic agents, although information specifically relating to FOLFOX-induced pulmonary toxicity is limited. It is associated with significant morbidity and mortality, but is often hard to differentiate from other lung conditions, making the diagnosis a challenge. Pulmonary toxicity is an important complication associated with antineoplastic agents. It should be considered in any patient on a chemotherapeutic regimen who presents with dyspnoea and hypoxia in order to try to reduce the associated morbidity and mortality.

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## Case Report

A 54-year-old female presented with a 2-week history of increasing shortness of breath and fever. She had a history of a poorly differentiated sigmoid adenocarcinoma for which she underwent an anterior resection 6 months prior to admission, followed by 12 cycles of adjuvant FOLFOX chemotherapy. Her last course was completed 1 month prior to this presentation. She had been thought to have a mild pneumonia, seen on her chest CT 2 months earlier. She was treated with antibiotics alone and with no radiological follow-up.

On examination, she was tachycardic and hypoxic with oxygen saturations of 87% on room air. Expiratory crackles and bronchial breathing were noted at the right lung base alongside reduced air entry and dullness to percussion. Inflammatory markers were raised (white cell count  $17.8 \times 10^9/l$  and C-reactive protein 91 mg/l) and blood gas on room air revealed a pH of 7.46,  $pO_2$  of 9.8 kPa,  $pCO_2$  of 4.0 kPa and  $HCO_3^-$  of 24 mmol/l. A chest radiograph revealed a mediastinal shift to the right, associated with an extensive volume loss in the right lung. This was accompanied by a right middle and lower zone consolidation (fig. 1).

Initial treatment consisted of nebulisers, intravenous fluids and antibiotics for a severe community-acquired pneumonia. Urine legionella and pneumococcal antigens were negative, as were blood and sputum cultures.

After 1 week and despite a broadening and escalation in her antibiotics, she remained hypoxic and short of breath on minimal exertion. Given her poor response to an appropriate therapy for a community-acquired pneumonia, further imaging was done. A chest CT revealed extensive right-sided fibrotic changes, tractional dilatation of the airways and ground glass density (fig. 2a). As noted above, a chest CT performed 2 months prior to admission as part of tumour surveillance identified a small area of consolidation in the right lung (fig. 2b). This had been treated as a chest infection and the patient appeared to respond to the antibiotic therapy.

The rapid onset and the nature of these changes are consistent with a drug-induced fibrotic lung disease secondary to FOLFOX chemotherapy. Further investigations such as lung function and fibre-optic bronchoscopy were not appropriate due to the clinical picture, and she was treated with intravenous methylprednisolone (1 g/day for 3 days). There was a marked improvement in terms of symptoms and oxygen requirements, intravenous antibiotics were stopped and oral prednisolone commenced.

A repeat chest radiograph revealed a large right-sided hydropneumothorax (fig. 3) and a repeat CT scan showed a partial resolution of the fibrosis, but a large right-sided pneumothorax had developed (fig. 4).

A Seldinger chest drain had initially been inserted, but following a poor resolution of the pneumothorax and concerns about a possible bronchopleural fistula, a surgical drain was sited. A repeat chest radiograph after 5 days confirmed a marked reduction in the size of the pneumothorax, and the drain was removed. The patient was discharged home with oral prednisolone and has continued to improve symptomatically and radiologically.

## Discussion

Pulmonary toxicity secondary to antineoplastic agents, is relatively common, occurring in approximately 10% of patients and is associated with significant morbidity and mortality. However, it is often difficult to differentiate it from other lung conditions (such as pneumonia, pulmonary oedema, pulmonary haemorrhage, pulmonary embolism or malignancy) and

it remains a diagnostic challenge [1]. Chemotherapy agents, which are most commonly implicated in pulmonary toxicity, include bleomycin, methotrexate, mitomycin C and carmustine [2].

FOLFOX therapy, also known as oxaliplatin modified de Gramont, is a combination chemotherapy regimen comprised of 5-fluorouracil, leucovorin calcium and oxaliplatin. It is recommended as a first-line combination chemotherapeutic regimen in patients with advanced or metastatic colon cancer [3]. In 2007, pulmonary toxicity secondary to oxaliplatin combined with FOLFOX was estimated to be 0.2% [4]. Information regarding FOLFOX-induced pulmonary toxicity is limited. Upon reviewing the literature, it is apparent that there have been only a small number of published case reports of FOLFOX-induced interstitial pneumonia.

Previous reports have noted a high incidence of haematological, gastrointestinal and neurological toxicities in patients treated with FOLFOX [5]. A large three-arm randomized controlled trial assigned 795 patients to FOLFOX, irinotecan/oxaliplatin or irinotecan/fluorouracil/leucovorin. FOLFOX was associated with a significantly lower incidence of toxicity and no reported cases of pulmonary toxicity [6].

Analysis of over 5,000 patients treated with oxaliplatin alone or FOLFOX for advanced or metastatic colorectal carcinoma, reported cases of acute dyspnoea secondary to laryngopharyngeal dysesthesia. The actual incidence of these cases was not reported in this study. This phenomenon was thought to be associated with a hypersensitivity to oxaliplatin treatment [7].

It is difficult to determine which agent in the FOLFOX regimen was involved in the pathogenesis of interstitial lung disease (ILD) in this case. A previous case report of FOLFOX-associated ILD noted that the patient improved following the discontinuation of oxaliplatin [8]. A case series of 26 patients with various lung diseases, who had received oxaliplatin therapy, identified 3 patients who had a radiological diagnosis of ILD prior to the commencement of oxaliplatin. All 3 patients experienced a worsening of both their respiratory symptoms and the radiological appearances of their ILD. One developed refractory respiratory failure whilst the other 2 improved following the discontinuation of oxaliplatin treatment [9]. These papers support the view that oxaliplatin is the probable causative agent of ILD in our patient.

The exact pathogenesis of FOLFOX-induced interstitial pneumonia is unknown. Glutathione as an antioxidant therapy may be protective against oxidative lung damage [10] and its depletion secondary to oxaliplatin may account for the development of ILD. One case exhibited a marked response to N-acetylcysteine therapy as a means of glutathione repletion [9]. Oxaliplatin-induced lung damage may be due to direct toxic injury as opposed to an immunologically driven mechanism, based upon the negative response of oxaliplatin to the lymphocyte stimulation test [11]. However, another case report noted elevated levels of serum IgE, eosinophils and a positive result of the drug lymphocyte stimulation test, suggesting a combination of type 1 and 4 hypersensitivity reaction towards oxaliplatin. After discontinuing oxaliplatin, the patient received the FOLFIRI regimen (5-fluorouracil, levofolinate calcium and irinotecan hydrochloride) and did not experience any allergic events [4].

The patient in our case report responded very well to intravenous methylprednisolone. Cessation of chemotherapy and high-dose corticosteroids are generally accepted as the recommended treatment for chemotherapy-induced pulmonary fibrosis.

Previous cases of FOLFOX-induced pulmonary fibrosis have noted marked clinical and radiological improvement following the cessation of oxaliplatin [12], and in another case, complete remission followed 2 months of corticosteroid therapy [13]. However, other case

reviews have noted that 4 out of 11 [14] and 7 out of 16 [15] patients died despite receiving corticosteroid therapy. Further research into the treatment of chemotherapy-induced pulmonary toxicities would be invaluable in establishing the role of corticosteroids in treating this condition.

There are no reported cases linking the usage of FOLFOX or oxaliplatin alone to the development of pneumothorax. We speculate that in this case it may have resulted from injury to the bronchial tree and pleural space secondary to the underlying pulmonary fibrosis. There was no history of pulmonary resection, radiotherapy to the chest or tuberculosis, and it is unlikely that the pneumothorax occurred spontaneously.

A case of pneumothorax in a patient with metastatic colon cancer treated with bevacizumab and a FOLFOX-containing therapy, FOLFOXIRI, was noted. The authors postulated that the bevacizumab was the cause of the pneumothorax, based upon 2 reasons. Firstly, bevacizumab has been reported to cause gastrointestinal perforations in patients with underlying colon, lung or ovarian tumours [16]; secondly, a phase III trial evaluating FOLFOXIRI as a first-line chemotherapy contained no reports of pneumothoraces or gastrointestinal perforations [17]. However, in the case of our patient, FOLFOX was the only chemotherapeutic regimen received, suggesting that this and other FOLFOX-containing regimens may be associated with the development of pneumothoraces.

## Conclusion

Pulmonary complications of chemotherapy regimens are underreported. These are often multi-drug combination therapies with various spectra of toxicities. ILD secondary to chemotherapy is a recognized and important complication that should be considered in patients presenting with dyspnoea and hypoxia.

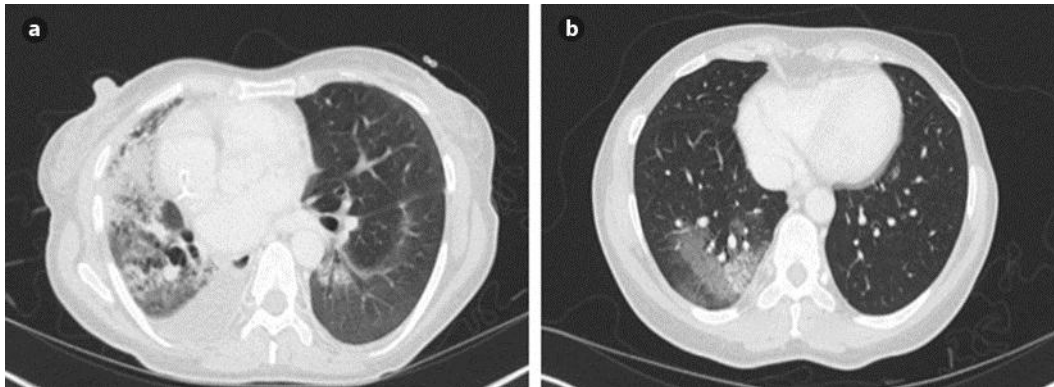
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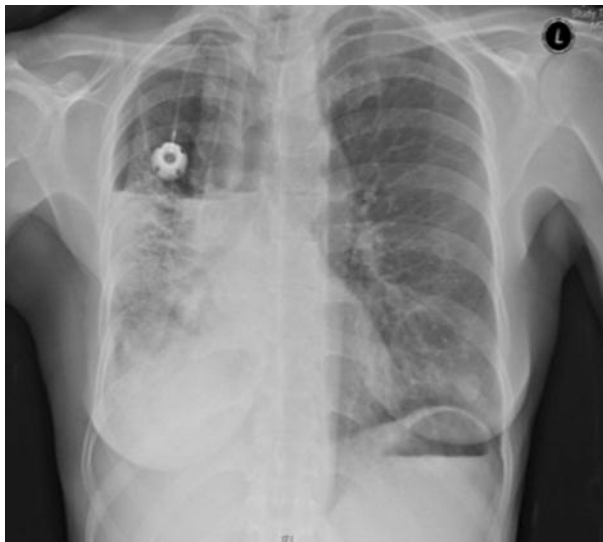
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**Fig. 1.** Chest radiograph on admission showing extensive loss of volume in the right lung associated with mediastinal shift to the right. This was accompanied by right middle and lower zone consolidation.

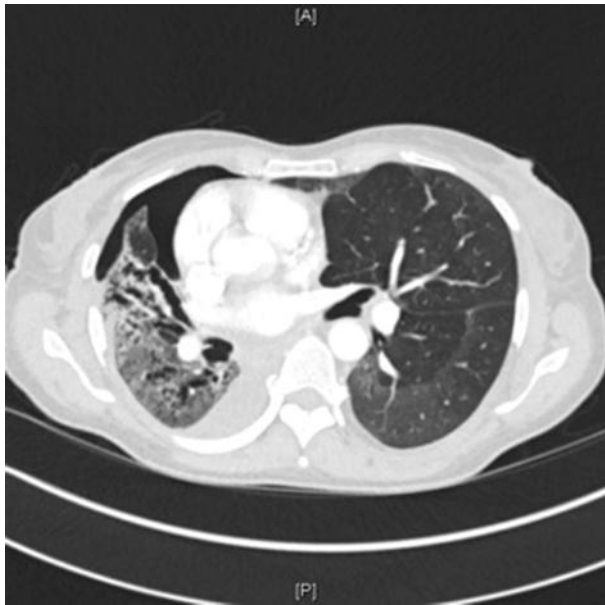


**Fig. 2.** **a** Chest CT revealed extensive fibrotic changes in the chest and right-sided pleural effusion. **b** Chest CT, which was done 2 months prior to admission, showed a small area of consolidation in the right lung.



**Fig. 3.** Chest radiograph showing a hydropneumothorax in the right lung.





**Fig. 4.** Large amount of gas within the pleural space on the right with a few locules of gas tracking into the mediastinum. A persistent moderate right-sided pleural effusion was also noted.