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64.1 The Case

An 80-year-old man was generally healthy until 2004, when he noticed progressive enlargement of a growing right sub-mandibular mass. On physical examination and in computerized tomography (CT) scan, the patient was found to have generalized lymphadenopathy on both sides of the diaphragm. A lymph node biopsy from the right sub-mandibular mass revealed a follicular grade 3B non-Hodgkin's lymphoma (NHL) that was in clinical stage 3A with an international prognostic index (IPI) of 2. The patient was treated with cycles of combination immunochemotherapy with rituximab (375 mg/m²)-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) every 21 days. After three uneventful cycles of therapy, he had a good clinical response, and an interim mid-treatment positron emission tomography-computed tomography (PET-CT) was performed, which showed disappearance of all the previous imaging findings, and no uptake of ¹⁸F-deoxyfluoroglucose (¹⁸F-FDG) was detected in these sites. However, on the same PET-CT scan, new abnormal sites of ¹⁸F-FDG uptake were detected as opacities in the sub-pleural areas of the lung, mostly on the right side (Fig. 64.1).

At the same time, the patient complained of mild dyspnea on effort, and bilateral basilar crackles were present on physical examination. Pulse oximetry and chest X-ray were performed, which were within normal limits. Treatment with rituximab-CHOP was continued as scheduled, but 2 days after starting the fifth cycle of therapy, the patient was admitted to the hospital because of a dry cough and worsening dyspnea. On examination, the patient had a normal body temperature, but was tachypneic, and hypoxemic and bilateral basal inspiratory crackles were present. Chest X-ray showed reticulo-nodular infiltrates (Fig. 64.2), and

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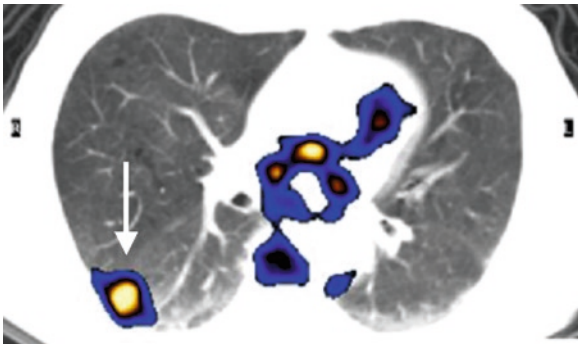


Fig. 64.1 Early radiological findings of rituximab-related pulmonary toxicity as detected in mid-treatment PET-CT. Abnormal uptake of ^{18}F -FDG is evident in sub-pleural lung opacities, mostly on the right side



Fig. 64.2 Chest X-ray. Showing bilateral reticulo-nodular infiltrates

a contrast-enhanced chest CT scan revealed further progression of the sub-pleural air-space consolidation. “Ground-glass” opacities, small pulmonary cysts and thickening of the interlobular septa were also evident (Fig. 64.3).

Bronchoscopy was performed and was within normal limits, and the bronchoalveolar lavage revealed no evidence of bacteria; acid-fast bacilli, *Pneumocystis jirovecii* (*P. jirovecii*) and cytomegalovirus (CMV) were also negative. Trans-bronchial biopsy was performed and revealed interstitial inflammation of the lung parenchyma, as well as swelling and hyperplasia of atypical type II alveolar cells, which showed

increased nuclear size and hyperchromasia, and an accumulation of foamy histiocytes with cytoplasmic vacuoles was evident within the alveoli (Fig. 64.4). Treatment with intravenous methylprednisolone (1 mg/kg) was started, but the patient developed rapidly progressive respiratory insufficiency requiring mechanical ventilation and unfortunately died 10 days after admission.

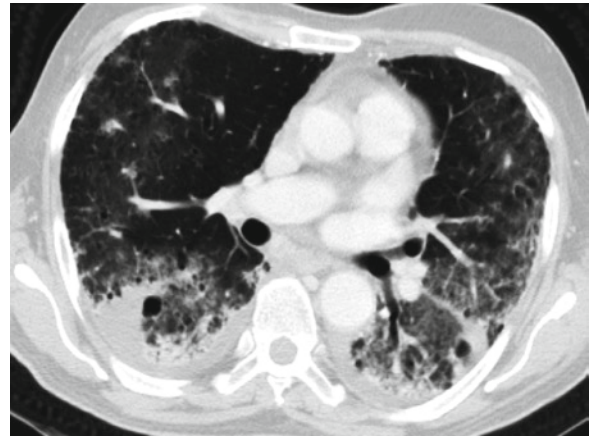


Fig. 64.3 Contrast-enhanced chest CT scan. Progression of the sub-pleural areas of intraalveolar consolidation, “ground-glass” opacities, small pulmonary cysts and thickening of the interlobular septa

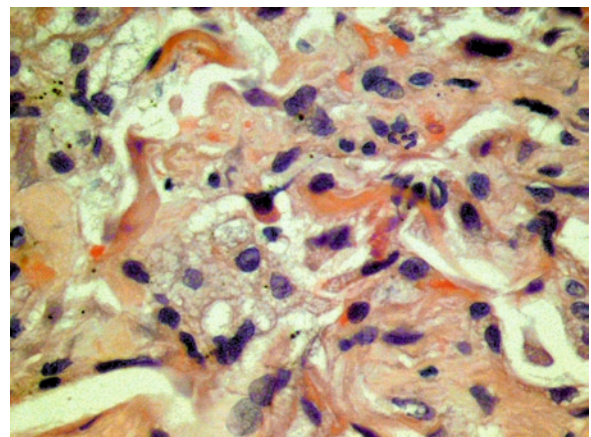


Fig. 64.4 Transbronchial biopsy. Showing interstitial inflammation as well as swelling and hyperplasia of atypical type II alveolar cells. Accumulation of foamy histiocytes with cytoplasmic vacuoles is seen in alveoli

64.1.1 Rituximab-Related Pulmonary Toxicity

Rituximab is a genetically engineered, chimeric murine/human monoclonal IgG₁ antibody that binds specifically to the CD20 antigen, which is expressed on normal B-cells and on the vast majority of malignant cells in B-cell lymphoproliferative disorders [1]. The binding of rituximab to the CD20 ligand causes cell lysis through a variety of mechanisms, including complement-mediated cytotoxicity, antibody-dependent cell (e.g., NK cells)-mediated cytotoxicity and direct induction of cell apoptosis [1]. Rituximab has been extensively studied and used to treat CD20 positive, B-cell lymphoproliferative disorders, either as a single agent or more commonly in combination with chemotherapy; in recent years it has also been used for the treatment of autoimmune disorders. It has currently been approved by the Food and Drug Administration (FDA) and/or by the European Medicines Agency (EMA) for the treatment of: (1) low-grade/follicular non-Hodgkin's lymphoma (NHL) as first-line treatment as well as for relapsed or refractory disease and for maintenance therapy in this disorder; (2) diffuse large B-cell NHL as first-line treatment in combination with anthracycline-based chemotherapy regimens; (3) chronic lymphocytic leukemia (CLL) in previously untreated patients, in combination with chemotherapy; (4) rheumatoid arthritis, in combination with methotrexate, for patients with an inadequate response to one or more of the TNF antagonist therapies [1]. In addition to rheumatoid arthritis, rituximab has been shown to be effective in the treatment of a variety of other autoimmune disorders, including autoimmune cytopenias, such as immune thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA), as well as in systemic lupus erythematosus (SLE), Sjogren's syndrome, vasculitides, and autoimmune neurologic and dermatologic disorders [2].

Rituximab is generally well tolerated and safe to use. Its major adverse effects appear to be infusion-related reactions [1]. During the first infusion, patients may develop fever, chills and dyspnea, and occasionally hypotension; however, it rarely causes anaphylactic shock or acute respiratory distress syndrome (ARDS). Patients with high numbers of circulating neoplastic lymphoid cells may develop cytokine-release syndrome [3] and/or tumor lysis syndrome [4]. Other infrequent adverse effects include delayed neutropenia

[5], hepatitis B virus reactivation [6], Stevens Johnson syndrome [7] and serum sickness [8].

With regard to pulmonary toxicity, more than 40 cases, most probably related to therapy with rituximab, have been reported until now [9–26]. Rituximab-associated lung toxicity has been described more commonly in elderly patients (mean age 65 years, range, 43–80 years), with a slight male predominance (male:female ratio of 2:1) [9]. These patients had either received rituximab as a single agent [11, 14, 16] or in combination with different chemotherapy regimens (COP, CHOP, CEOP, ACVBP, VNCOP, fludarabine, cladribine) [9–12, 15, 16, 22] with or without the addition of growth factors for NHL, CLL, ITP, rheumatoid arthritis and SLE [10–12, 14–16, 23, 24]. In most cases the patients developed acute or subacute symptoms after one or more cycles of therapy [10–12, 14–16].

64.1.2 Acute Pulmonary Reactions

Rituximab-associated acute adverse pulmonary reactions were reported during or shortly after the first infusion of the agent and included bronchospasm, hypoxia, pulmonary infiltrates as well as ARDS [27–29]. The latter syndrome has been reported in several patients within a few hours after initiating rituximab infusion. All these patients required mechanical ventilation, and although all were treated with corticosteroids, this complication was associated with a high mortality rate of around 40% [27–29]. In one patient, in whom a lung biopsy was performed, diffuse alveolar damage and hemorrhages were also seen [29].

64.1.3 Subacute Pulmonary Reactions

The majority of cases of rituximab-associated pulmonary toxicity occurred within days and up to 3 weeks after the first infusion of the antibody or following subsequent cycles with rituximab treatment. It appeared to occur most commonly after the fourth cycle of therapy and within a mean of 12 weeks after the initial rituximab infusion [9]. Patients usually presented with dyspnea, dry cough, signs of hypoxemia and occasional fever [10–16]. Crackles are present on physical

examination in approximately a third of the patients [9]. Chest radiographs may reveal patchy or diffuse mixed interstitial and alveolar infiltrates [8, 18, 23, 24, 26, 30], while CT scan typically shows multiple focal alveolar infiltrates and areas of “ground-glass” shadowing [11, 15, 17, 23, 24, 26]. Pulmonary function tests are mostly compatible with restrictive abnormalities associated with a reduced diffusion capacity [11, 14, 30]. In some cases, a PET scan, performed for the evaluation of lymphoma response to treatment, showed some form of uptake, thereby detecting early pulmonary changes [8, 31, 32] while patients were still basically asymptomatic. In other cases, a PET-CT scan revealed late-onset pulmonary infiltrates, occurring between 1 and 3 months after the treatment of rituximab was discontinued, appearing as linear subpleural FDG uptake, which sometimes persisted for several months [33]. Bronchoalveolar lavage (BAL) fluid was negative for infectious disease, and cytology was negative for malignant cells, whereas normal CD4+ T-lymphocytes predominated [15, 18, 25]. Transbronchial or lung biopsies most commonly showed histological findings compatible with organizing pneumonia and interstitial pneumonitis [9, 19–21, 23, 30, 34]; diffuse alveolar hemorrhage and acute pulmonary fibrosis were less commonly observed [15, 16, 18].

64.1.4 Mechanism of Toxicity

Acute lung toxicity, mostly ARDS, is considered to be the result of a cytokine release syndrome with tumor necrosis factor- α (TNF- α), interferon- γ (INF- γ), interleukin-6 (IL-6) or interleukin-8 (IL-8) [3, 9] released in high concentrations. This clinical picture occurs shortly after the first infusion of rituximab, at a time when the patient still has a large tumor burden [9]. The more insidious onset reactions described appear to be due to hypersensitivity reactions, and continuing treatment with rituximab results in recurrence of the same symptoms, but of increasing severity [9, 15, 26]. This type of rituximab-associated pulmonary toxicity seems to respond favorably to corticosteroid therapy [9]. It has also been suggested that the mechanism of toxicity seen in the latter reaction may also be linked to the release of inflammatory cytokines, including TNF- α , INF- γ , IL-6 and IL-8 [11, 35], complement activation [15] or indirect cytotoxic T lymphocyte activation

[15], all of which are known to occur during therapy with rituximab [36, 37]. Along this line, results of an experimental in vitro model have suggested that apoptotic lymphoma cells undergo phagocytosis by dendritic cells (DC). This leads to DC maturation and thereafter promotes induction of a cytotoxic T-cell response against these lymphoma cell-associated antigens [37, 38].

64.1.5 Differential Diagnosis

The appearance of pulmonary infiltrates in lymphoma patients receiving rituximab is a challenging situation. Several diagnoses can be considered, namely cardiogenic pulmonary edema, infection, progressive lymphoma, exacerbation of underlying chronic lung disease and drug-related pulmonary toxicity. Rituximab-related pulmonary toxicity is basically a diagnosis of exclusion. In immunocompromised patients, infectious causes, such as bacterial pneumonia, mycobacterial infections, viral pneumonitis including CMV, *P. jirovecii* pneumonia (PCP) and fungal infection, should all be considered in the differential diagnosis. In this respect, the development of PCP has been reported during rituximab therapy, particularly in patients with NHL co-treated with the antibody and combination chemotherapy [39–44]. A few cases of cytomegalovirus (CMV) reactivation have also been recorded in the rituximab-treated patients [45–47]. After excluding the above-mentioned infectious causes, special consideration should be given to the possibility of drug-related pulmonary toxicity. Many cytotoxic agents are known to cause lung injury. In this respect, cyclophosphamide in particular, one of the most common agents used in combination with rituximab for the treatment of NHL and CLL, should be considered as one of the possible agents causing this clinical and radiological picture. As in the case of rituximab, the incidence of cyclophosphamide induced-pulmonary toxicity is low [48, 49], and the interval between exposure to cyclophosphamide and the appearance of the pulmonary insult varies from weeks to several years [48]. Early onset toxicity usually appears about 1–6 months after exposure to cyclophosphamide, and typically patients present with 1–2 weeks of dyspnea on effort and a dry cough [48, 49]. Bilateral basal reticular or reticulo-nodular infiltrates are seen on chest X-ray [49], “ground-glass” shadowing is evident on CT scan [49], and pulmonary function tests

show restrictive abnormalities with reduced diffusion capacity [49]. Late-onset toxicity generally appears in patients who had received relatively low doses of cyclophosphamide given over a prolonged period of time [49], and these may occur years after discontinuation of the drug [49]. While the prognosis of early onset toxicity is generally good and corticosteroids are beneficial, late-onset toxicity has a poorer outcome and often progresses despite therapy with steroids [48, 49]. The histopathological spectrum of cyclophosphamide-induced lung injury includes: nonspecific interstitial pneumonia, organizing pneumonia, diffuse alveolar damage and diffuse alveolar hemorrhage [49]. In this regard, the endogenous production of reactive oxygen radicals was suggested as the most probable underlying mechanism for this pulmonary toxicity [48]. G-CSF is a growth factor commonly used in cancer patients to shorten the period of neutropenia following chemotherapy and is also utilized to mobilize hematopoietic progenitor cells for stem cell transplantation. Common adverse effects of G-CSF include fever, bone pain and fatigue. Pulmonary toxicities attributed to G-CSF include cough, dyspnea, interstitial pneumonitis and ARDS [50]. When used as a single agent, among 1,801 published cases of healthy stem cell donors given G-CSF for stem cell mobilization, lung toxicity was reported in 1 case only [50]. G-CSF-related pulmonary toxicity is more frequently reported in patients receiving this growth factor in combination with chemotherapeutic agents, and in these cases G-CSF may actually exacerbate chemotherapy-related pulmonary toxicity, particularly when cyclophosphamide, bleomycin or methotrexate is the chemotherapeutic agent involved [50]. G-CSF related-pulmonary toxicity can be fatal, with a relatively high mortality rate (24.6%) [50]. Because neutropenic patients treated with G-CSF frequently develop their pulmonary symptoms during or after recovery from the neutropenia, it was suggested that neutrophils play a central role in mediating this toxicity [50]. Treatment with G-CSF not only increases the number of neutrophils, but also enhances their functions [51, 52], thereby promoting neutrophil entrapment in the pulmonary vascular capillaries, and release of their oxygen radicals and proteolytic enzymes, which may cause subsequent endothelial and pulmonary damage [53–57]. G-CSF is commonly given for patients who have been treated with rituximab-containing regimens, and these combinations of drugs may potentially increase the risk of pulmonary toxicity [19, 30].

64.1.6 Clinical Investigations

Non-invasive studies such as arterial blood gas analysis, sputum examination, chest X-ray, pulmonary function tests, echocardiogram and chest CT scans are all helpful in determining the pattern of the pulmonary insult. However, bronchoscopy with BAL and biopsy of the lung tissue are eventually required to establish a more definitive diagnosis to be sure to rule out any infection before deciding for drug-related pulmonary toxicity. Sputum as well as the BAL fluid should be evaluated by direct smear and cultures for bacterial infections, including mycobacterium, and for possible opportunistic pathogens, such as fungi (*Pneumocystis*, *Aspergillus*, *Candida*). In addition, nasopharyngeal aspirates should also be evaluated for viral antigens, such as respiratory syncytial virus, adenovirus, influenza and parainfluenza viruses. The peripheral blood should also be sent for cultures and evaluated for CMV antigenemia or CMV-DNA PCR titer, β -D-glucan (antigens for *Candida* and *Aspergillus*), serology test for viruses, *Mycoplasma pneumonia* and *Chlamydo-philum pneumoniae*, while the urine should be tested for *Legionella* antigen.

An early lung biopsy either by open or a thoracoscopic approaches may be helpful to define the lung pathology more precisely as well as to exclude other alternative diagnoses, such as opportunistic infection or lymphoma. Trans-bronchial biopsy can be an alternative to lung biopsy; however, it has the disadvantage of ending up more frequently without an adequate sample for diagnosis.

64.1.7 Clinical Course and Treatment

In all the reported cases of pulmonary toxicity, rituximab was discontinued after the appearance of toxicity, and the majority of patients gradually recovered within a few days. Nevertheless, this complication is known to be fatal in 20% of the patients [9], and although some of these patients developed lung toxicity while receiving corticosteroids [10, 14], most appeared to respond favorably to early corticosteroid treatment [9]. Re-treatment with rituximab was uneventful in a proportion of these cases [12], whereas in others, re-treatment with rituximab, as a single agent or in

combination with chemotherapeutic drugs, did cause pulmonary deterioration [10, 15], which was fatal in some cases [8, 15]. Accordingly, it is recommended that in patients suspected of having rituximab-related pulmonary toxicity, any possible agent known to cause pulmonary toxicity should be stopped. Furthermore, in addition to any empirical anti-infectious therapy given, corticosteroid therapy should also be initiated early on. After pulmonary recovery, rituximab re-challenge is best avoided.

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