Severe pulmonary complications after initial treatment with rituximab for the Asian-variant of intravascular lymphoma

Rituximab improves response to treatment and outcome for patients with CD20⁺ B-cell lymphoma. Herein, however, we report the occurrence of severe pulmonary complications shortly after rituximab infusion in three patients with the newly diagnosed Asian variant of intravascular lymphoma. It is suggested that patients with this subtype of lymphoma are monitored carefully for possible drug reactions during the use of rituximab.

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Intravascular large B-cell lymphoma (IVL) is a rare subtype of CD20⁺ large B-cell lymphoma.[1-3] Recently, it has been proposed that there is an Asian-variant of IVL (AIVL) which is characterized by frequent bone marrow involvement, hemophagocytosis, cytopenia and hepatosplenomegaly, but not the central nervous system symptoms or skin lesions that are typical features of classical IVL.[4] We report here a rare adverse reaction to rituximab in three Taiwanese patients with AIVL. From June 1996 to December 2004, seven patients were diagnosed with IVL in our institution; five (71.4%) of these fulfilled the criteria for AIVL. Rituximab was used as part of the initial treatment in three of the patients with AIVL and as salvage treatment after relapse in the remaining two patients. All the former three patients, but neither of the latter two, developed severe pulmonary complications after rituximab infusion and are the subjects of this report (Table 1). None of these three cases had underlying cardiopulmonary diseases or symptoms or signs suggesting respiratory tract infection. Furthermore, chest X-ray films taken before treatment showed no active lung lesions. The rituximab was introduced as part of front-line induction chemotherapy for the presented patients, all of whom were premedicated with intravenous injections of corticosteroid (betamethasone 4 mg), antihistamine (diphenhydramine 30 mg) and oral acetaminophen (500 mg) before commencement of intravenous rituximab infusion (375 mg/m^2, starting rate 30 mg/hr) 1 day before induction chemotherapy. Strikingly, all of them experienced severe systemic reactions including dyspnea, hypoxia, tachycardia and hypotension within 24 hours of the pre-chemotherapy rituximab infusion. Two (cases 2 and 3) required endotracheal intubation and mechanical ventilation support, with chest X-rays revealing newly developed bilateral lung infiltrates (Figure 1). High-resolution computed tomography done in case n. 2 revealed interstitial pneumonitis (Figure 2). Pathological examination of the thoracoscopic lung biopsy specimen from the same individual revealed acute capillaritis, but no microorganisms or lymphoma-cell infiltration. There was no clinical or laboratory evidence of respiratory tract infection in the three presented cases. The pulmonary status of case n. 2 deteriorated due to post-operative hemopneumothorax, as well as uncontrolled hemophagocytosis, and this male patient finally died 3 weeks after the rituximab treatment. In case n. 1, respiratory distress subsided 2 days after commencement of supportive care. This man then received one course of COP (cyclophosphamide, vincristine, prednisolone), two courses of R-CNOP (rituximab, COP and mitoxantrone), and four courses of monthly rituximab infusion. In case n. 3, the lung infiltrates cleared 10 days after initiation of supportive care. This female patient received four courses of monthly rituximab thereafter. No further adverse effects were noted after subsequent rituximab infusions in the two surviving patients, who had remained disease free for 21 and 6 months, respectively, at the time of writing. The two AIVL patients who received rituximab as part of salvage treatment after relapse, but not as front-line treatment at diagnosis, did not suffer similar complications

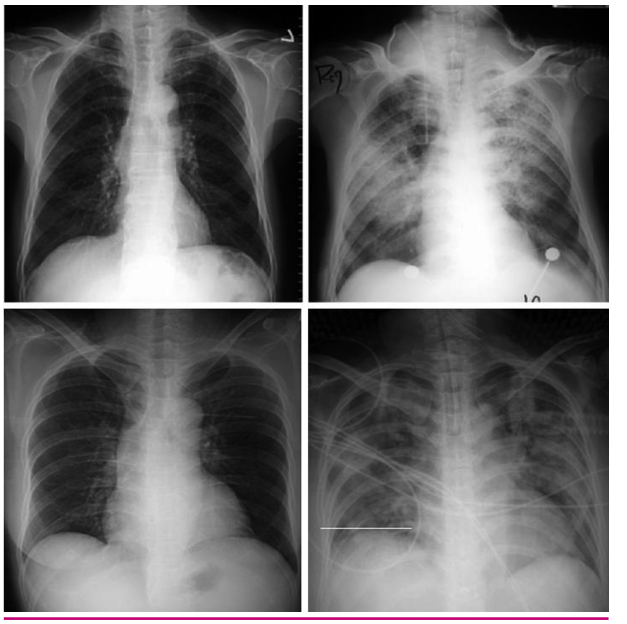

Figure 1. The chest X-ray before (left) and after (right) rituximab administration in case n. 2 (upper) and case n. 3 (lower). The post-rituximab chest films showed newly developed infiltrations and consolidation.

Table 1. Clinical and Laboratory features at presentation of three patients with asian-variant of intravascular lymphoma.

Case	*Age/sex*	*Fever**	*Respiratory symptoms*	*Marrow involved*	*HPS*	*Other Organ involved*	*Peripheral blood*					*LDH***
							Hb (g/dL)	*Platelet (10^9/L)*	*WBC (10^9/L)*	*PMN/ Lym(%)*	*Lymphom cells*	*(U/L)*
1	77/M	+	–	+	+	–	8.7	127	4.65	52.5/26.3	–	2190
2	79/M	+	–	–	+	Adrenal gland	9.4	66	2.69	63.0/12.0	–	1267
3	54/F	+	–	+	+	–	8.1	156	10.36	68.1/15.6	–	4838

*M: male; F: female; HPS: hemophagocytosis in bone marrow aspiration; PMN: polymorphonuclear leukocyte, including segmented and band froms of neutrophil; Lym: lymphocyte. * Secondary to hemophagocytosis, not infection. **Normal range of LDH: 230 ~ 460 in our institution.*

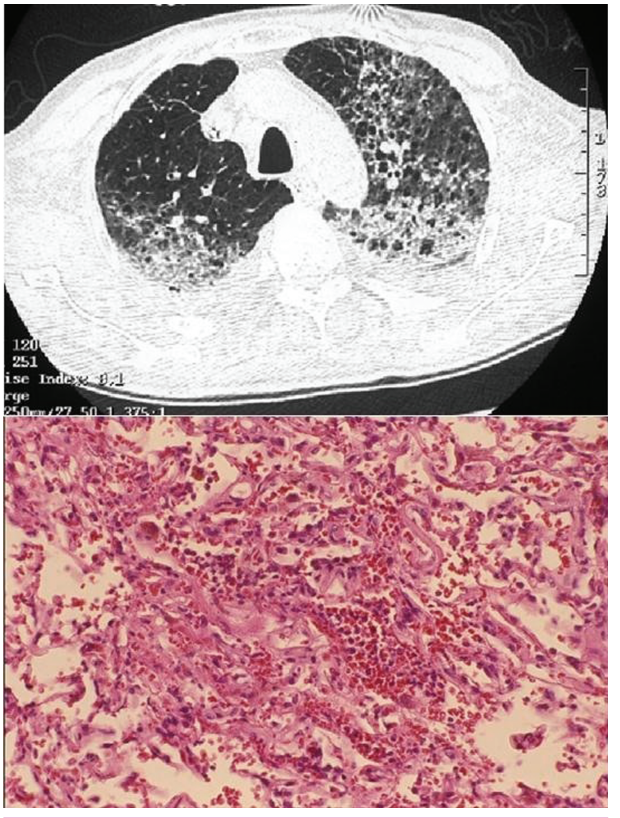

Figure 2. High-resolution computed tomography (HRCT) of the chest and histopathology of the lung biopsy tissue of case n. 2 after rituximab administration. The HRCT (upper) showed ground-glass opacity and consolidation associated with reticulation in both lungs as well as moderate bilateral pleural effusions. The diagnostic impression was interstitial pneumonitis. The histopathological examination (lower) showed pulmonary hemorrhage with an intra-alveolar proteinaceous exudate containing erythrocytes and necrotic neutrophils suggestive of acute capillaritis.

during treatment. Reports of respiratory distress syndrome after rituximab infusion in patients with lymphoma are rare; most such events have been associated with the use of this monoclonal antibody in chronic lymphocytic leukemia.[5,6] All three AIVL patients reported in this study developed severe pulmonary complications soon after rituximab infusion, indicating an association specific to this lymphoma variant. The pulmonary complications did not appear to be an allergic reaction to rituximab as repeated administration of the same drug in the two surviving patients did not reproduce the adverse response. Previous studies of patients with IVL-associated hemophagocytosis have revealed elevation of several cytokines that could be key factors in a systemic inflammatory response syndrome.[4,7-9] Furthermore, elevations of inflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, have also been reported during rituximab infusion.[5,6] It appears probable, therefore, that rapid clearance of intravascular lymphoma cells after rituximab in AIVL cases may lead to further increases in already-elevated pro-inflammatory cytokines. Additionally, the intravascular lymphoma cells may occlude vessels, resulting in vessel wall damage and increased permeability.

The combination of an overwhelming elevation of cytokines and a damaged vascular barrier may result in severe systemic inflammatory response and acute respiratory distress.

In spite of the adverse effect, rituximab was a highly effective treatment for AIVL in our presented Taiwanese patients, confirming the findings in another reported case of IVL.[10] However, because of the potential risk of pulmonary distress syndrome after rituximab infusion as initial treatment for AIVL, the use of the drug for this subtype of lymphoma is recommended only after reduction of the tumor burden by systemic chemotherapy.

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