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Case Report

Delayed COVID-19 Respiratory Failure in Patients with Lymphoma on Rituximab-based Chemoimmunotherapy

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Clinical Practice Points

- COVID-19 can present with delayed onset of symptoms in patients with lymphoma receiving rituximab-based chemoimmunotherapy.
- Despite delayed onset of symptoms with prolonged asymptomatic period, outcomes can be particularly severe, including respiratory failure, thrombotic complications, and death.

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Introduction

Reports of prolonged COVID-19 viral shedding in immunosuppressed patients with hematologic malignancies[1] and subsequent reactivation after receipt of rituximab-containing chemotherapy[2] have been not only sobering but also regrettably reflective of our institutional experience. Herein we report institutional experience with 3 patients with diffuse large B-cell lymphoma (DLBCL) who, differing from the report earlier, were identified to have COVID-19 during routine asymptomatic screening tests obtained prior to chemotherapy. All patients were appropriately quarantined and subsequently treated with rituximab-containing chemoimmunotherapy with delayed onset of symptoms from COVID-19, severe infection, and poor outcomes.

Case Report

Similar to many centers, we have been universally testing asymptomatic patients prior to giving cytotoxic chemotherapy. In each case presented, patients were identified during asymptomatic screening tests prior to administration of chemotherapy. Pursuant to initial American Society of Clinical Oncology (ASCO) guidelines for cancer care during COVID-19,[3] our current algorithm suggests a 14-day quarantine after a positive test and then reconsideration regarding resumption of therapy. Because of immune suppression in cancer patients on active therapy, we did not elect to decrease the quarantine period to 10 days with the August 3 Centers for Disease Control and Prevention (CDC) update.[4] In each of these cases, the patients were either symptomatic from the DLBCL or at risk of a treatment failure for high-risk disease, and it was felt that continuing chemoimmunotherapy was in their best interest.

In each case, after hospitalization a comprehensive evaluation with both infectious disease and pulmonary consultants was performed. All patients had computed tomography (CT) scans of the chest that revealed multifocal infiltrates and early development of fibrosis consistent with coronavirus pneumonia and its pulmonary sequelae. Patients 1 and 2 underwent a bronchoscopy with bronchioalveolar lavage, and patient 3 had conventional sputum analysis. Bronchoscopy for patient 3 was deferred owing to development of acute stroke on day 2 of hospitalization. Extensive evaluation for fungal, bacterial, and other viral pathogens was performed and, in all cases, was negative. In each case, the respiratory syndrome was felt to be related to progressive lung injury as a result of COVID-19. The underlying lymphoma histologies, treatment plans, and characteristics regarding their infection history are detailed in Table 1.

Patient 1 had multiply relapsed low-grade follicular lymphoma and presented October 2020 to our referral center with relapsing disease. Her clinical course and imaging studies were suggestive of transformation to DLBCL, and biopsy proved transformed disease. She was naive to anthracyclines, and therapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) was planned with possible consolidation with autologous stem cell transplant. At her presentation for her first cycle of therapy her asymptomatic screening test was positive for COVID-19 infection. She was observed for 14 days per protocol. Because of progressive worsening symptoms of her lymphoma, treatment was indicated, and she received R-CHOP on December 8, 2020, 22 days after her positive test. She presented with respiratory failure and

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Table 1 Patient Outcomes

	Patient 1	Patient 2	Patient 3
Age (yrs)	68	60	75
Sex	Female	Male	Male
Histology	DLBCL, FL	DLBCL, FL	DLBCL
Treatment	R-CHOP	R-ICE	R-CHOP
Date of first positive test	11/16/2020	11/4/2020	11/24/2020
Date of treatment	12/8/2020	11/20/2020	12/9/2020
Date of symptom onset	12/17/2020	12/27/2020	12/30/2020
Days between positive test and symptoms	31	53	36
COVID complications	Hypoxic respiratory failure ICU admission	Hypoxic respiratory failure ICU admission	Hypoxic respiratory failure ICU admission Acute stroke
COVID antibody production?	Negative 12/18/2020	Negative 12/28/2020	Not assessed
Disposition	Recovering	Death from respiratory failure	Death from respiratory failure
Date of death	N/A	1/11/2021	1/20/2021
Days between positive test and death	N/A	68	57

Abbreviations: DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; ICU, intensive care unit; N/A = not available; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-ICE = rituximab, ifosfamide, carboplatin, and etoposide.

pancytopenia on December 17, 2020, 11 days after her first cycle of R-CHOP and 31 days after her initial positive test. She had a prolonged hospital stay including intensive care unit (ICU) admission for respiratory failure but never required mechanical ventilation. She is currently recovering and off oxygen therapy.

Patient 2 presented to our center in September 2020 with multiply relapsed high-grade follicular lymphoma with prior transformation to DLBCL. In addition to transformation events, additional high-risk factors included early relapse of his follicular lymphoma after therapy. He was planned to undergo salvage chemoimmunotherapy with R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) and, if chemosensitive, to be consolidated with an autologous stem cell transplant. He underwent his first cycle of R-ICE in October 2020 uneventfully with no significant toxicities. However, on presentation for his second cycle of therapy, he had a positive coronavirus test and therapy was delayed for 14 days. Given lack of symptoms and his high-risk disease, it was felt in his best interest to continue therapy. He received R-ICE therapy on November 20, 2020, and was admitted December 27, 2020, with progressive respiratory failure, 53 days after his first positive test and 37 days after treatment. He had a prolonged ICU stay with respiratory failure and unfortunately died of acute respiratory failure January 11, 2021.

Patient 3 was diagnosed with a high-risk presentation of DLBCL with multiple extranodal sites of disease including the stomach and paranasal sinuses in August 2020. He was treated with 5 cycles of R-CHOP chemoimmunotherapy with intrathecal methotrexate for central nervous system prophylaxis. His asymptomatic screening test prior to cycle 6 was obtained on November 24, 2020, and he had no significant symptom development during his quarantine period. His sixth and final cycle of R-CHOP was administered on December 9, 2020, 15 days after his positive test. He was admitted December 30, 2020, with progressive worsening of respiratory failure and unfortunately on the evening of admission developed a large middle cerebral artery stroke and was found to be in atrial fibrillation. Neurologically he improved during his hospital stay but ended up with continuous hypoxic respiratory failure throughout with several exacerbations, each of which was associated with negative workup for alternative infectious etiologies. Given his negative workup and serial CT scans showed progressive worsening of pulmonary fibrosis, his persistent respiratory failure was attributed to progressive pulmonary fibrosis from coronavirus. He eventually died of progressive respiratory failure on January 20, 2021.

These cases illustrate several important principles. First, as has been noted by previous investigators, patients with significant immune suppression will shed active replicating virus over a longer period of time than patients with an intact immune system.[1] Importantly, this report suggests that prolonged shedding places them at risk of delayed symptom onset as well, especially when challenged with immunosuppressive therapy. Second, patients who have immune suppression and are on active therapy can present in a delayed fashion. In each case patients presented well beyond recommended quarantine with persistence of replicating virus and development of a worsening clinical syndrome of coronavirus infection in the context of receipt of rituximab-based chemoimmunotherapy. Third, prior recent receipt of chemoimmunotherapy and subsequent infection may be less problematic than actively treating a patient who is shedding virus. In 2 of these cases (patients 2 and 3), the patients were on active therapy and had received rituximab-based chemoimmunotherapy 19 days prior to their first positive test. In both of these cases, COVID-19-related disease did not worsen during the 14-day period of quarantine and observation. In fact, it was not until after subsequent treatment (21 days in patient 3 and 37 days in patient 2) that these patients presented with symptoms of coronavirus-related respiratory failure.

Conclusions

These observations place the treating hematologist in a difficult position regarding how to manage patients who have an acute

life-threatening hematologic malignancy requiring treatment and present with an asymptomatic positive screening test for coronavirus infection. These cases would argue for an observation period beyond 14 days, but the ideal duration of observation remains unclear. Many patients regrettably do not have the luxury of a long stretch of observation and, as evidenced by the recent communication that inspired this report,[1] even clearance of virus and development of antibodies may not be sufficient to prevent viral reactivation in the context of rituximab-based chemoimmunotherapy.

Disclosure

The authors have stated that they have no conflicts of interest.

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