Discordance Between Radiologic Findings and Molecular Testing in Patients With Underlying Hematologic Malignancy and Coronavirus Disease 2019

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Severe acute respiratory syndrome coronavirus 2 is associated with severe disease in patients with hematologic malignancy. We report a series of patients with underlying hematologic malignancy and coronavirus disease of 2019 with discrepancy between radiographic findings and molecular testing. Initial chest x-ray findings should raise suspicion in immunosuppressed patients with typical clinical presentation even with negative initial testing.

Keywords. COVID-19; hematologic malignancy; radiology; SARS-CoV-2; stem cell transplant.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a pandemic of indomitable proportion ever since the first cases were reported. Despite worldwide spread, there are few reports on SARS-CoV-2/coronavirus disease of 2019 (COVID-19) in hematologic malignancy (HM). Small case series report higher severity of disease in patients within this population, as well as increased incidence of acute respiratory distress syndrome and mortality compared with the general population [1–3]. Nucleic acid amplification tests (NAATs) of respiratory secretions have been the mainstay of establishing a diagnosis, despite limitations in sensitivity with potential for false-negative results [4]. This may impact patient management and challenge hospital infection control. Reverse-transcriptase polymerase chain reaction (RT-PCR) is one such example of NAAT.

Early computerized tomography (CT) imaging can help bridge this gap, because findings of ground-glass opacities may be evident on CT of the chest even with a false-negative RT-PCR test [5]. However, from an infection control standpoint, chest CT of a potentially infected patient requires strategic planning for safe disinfection, because most centers lack portable CT equipment. Chest radiography (CXR) may be preferred, given its portable nature and easy access throughout centers. Although some studies report very low sensitivity of CXR in early stages of disease [5], it may have a role in HM and hematopoietic stem cell transplant (HSCT) patients at increased suspicion for COVID-19.

We reviewed a series of patients with laboratory-confirmed COVID-19 (based on positive laboratory-based RT-PCR result) and underlying HM, and we observed a discrepancy between abnormal CXR findings and time to positivity of RT-PCR results.

METHODS

We conducted a retrospective cohort study of 6 patients with underlying HM (Table 1) who tested positive for SARS-CoV-2 RT-PCR. Data collection included demographics, malignancy type, chemotherapy regimen, symptom onset, clinical presentation, and radiologic findings.

Principal imaging dataset consisted of initial and 1 or more follow-up CXR beginning at the time of clinical suspicion of COVID-19. When available, most recent radiograph or CT obtained before suspected infection was also included. Results of the radiographic reports were noted. Radiographs were also retrospectively reviewed by a thoracic radiology subspecialist in a nonblinded manner. If present, the nature of abnormalities was noted. Radiographs were scored for the relative likelihood of findings representing SARS-CoV-2 infection using a 5-point Likert scale (Table 2), as published in prior literature [6, 7], where "1" = normal and "5" = highly likely to represent COVID-19. Initial and follow up RT-PCR results were also collected for each patient, including nasopharyngeal (NP) as well as bronchoalveolar lavage (BAL) specimens. All patients had an initial NP specimen sent for RT-PCR at the first suspicion of SARS-CoV-2 infection, together with imaging, with follow-up specimens (either NP or BAL) sent for those with a negative initial NP RT-PCR.

Patient Consent

A waiver of consent was obtained, and study was approved by the Institutional Review Board of University of Miami.

Table 1. Characteristics and Test Performances of Patients

Age	Gender	Malignancy	Chemotherapy	History of HSCT	Symptoms	Symptom Onset Before Presentation (Days)	Number of SARS-CoV-2 PCR-NP	Number of SARS-CoV-2 PCR-BAL	Days Between Positive CXR and First Positive SARS-CoV-2 PCR	Days Between Positive CXR and First Negative SARS-CoV-2 PCR	RT-PCR Platform
54	M	DLBCL with relapse	R-CHOP	Autologous Day +138	Fever, chills, abdominal pain, nausea, vomiting and diarrhea	6	5	1	2	0[a]	Abott
63	M	AML	7 + 3	None	Fever, chills, cough, and shortness of breath	14	1	1	15	None	Abott
74	F	Multiple myeloma	Velcade, Revlimid, Dexamethasone	None	Fever, chills, cough, shortness of breath, fatigue, myalgias, and diarrhea	2	6	0	0[a]	30	Diasporin Simplexa
69	F	DLBCL with relapse/refractory disease	R-CHOP	None	Fatigue and myalgias	5	5	0	0[a]	None	Cepheid
55	M	ALL with relapse	Hyper-CVAD	Allogeneic Day +111	Fever, cough, shortness of breath, fatigue, myalgia, and headache	6	1	0	2	None	Abott
77	M	AML	Azacitdine	None	Fever, fatigue, and shortness of breath	5	5	0	6	0[a]	Diasporin Simplexa

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BAL, bronchoalveolar lavage; CXR, chest radiography; DLBCL, diffuse large B-cell lymphoma; HSCT, hematopoietic stem cell transplant; Hyper-CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; NP, nasopharyngeal; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RT-PCR, reverse-transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; 7 + 3, cytarabine, daunorubicin.

[a]Same day.

RESULTS

Before suspected infection, 5 of 6 patients had normal CXR (1 with CT and 4 with CXR), whereas 1 patient had no prior available images. A total of 19 radiographs at and subsequent to suspicion of COVID-19 were reviewed (Table 1). The initial radiograph at the time of suspected infection was clinically reported as abnormal in 4 cases (67%) and normal in 2 (33%). Upon further review, 1 of the 2 initial radiographs that had been reported as negative showed a subtle left lower lobe opacity, confirmed on a chest CT 2 days later. Using that retrospective review, the relative likelihood of COVID-19 based on the initial radiographic appearance was negative (1 patient), indeterminate (3 patients), and probable (2 patients). Of the 5 patients with abnormal initial radiographs, all follow-up radiographs were clinically reported as abnormal, with 4 of the 5 showing worsening on the second radiograph and the fifth showed worsening on the third radiograph (Table 2). The patient with an initially normal radiograph both on clinical report and retrospective review had a normal follow-up radiograph after 7 days, a CT that showed findings not suspicious for COVID-19 after 8 days, and a subsequent abnormal radiograph 13 days after the initial radiograph. Sixty-seven percent of patients with a reported abnormal CXR on clinical suspicion had an initial negative SARS-CoV-2 RT-PCR at the same time, with subsequent follow-up RT-PCR tests that were positive. Time to positivity from abnormal CXR included 2, 2, 6, and 15 days, respectively.

DISCUSSION

There are varied opinions and practices regarding the utilization of chest imaging with COVID-19, and specifically the relative value of CXR and chest CT. Several publications of the Chinese experience place significant emphasis on the use of chest CT [8, 9]. One study of 1099 patients demonstrated CT abnormality in 86% (840 of 975 scans); CXR was significantly less utilized (274 radiographs) with abnormality in 59% of cases, similar to our study [9]. Another large Chinese study claimed a higher sensitivity of initial chest CT (888 of 1014 patients, 88%) than initial PCR (601 of 888, 59%) [8]. Approaches in the United States have placed much less emphasis on chest imaging, either radiography or CT, as a primary diagnostic tool for COVID-19. The American College of Radiology does not recommend CT chest as a screening tool for suspected cases and promotes CXR rather than CT as the initial imaging of choice [10]. Portable radiography also carries obvious benefits for infection control, avoiding the transport of infected patients to the radiology department. In our practice, CXRs have been the primary imaging method used in known and suspected COVID-19 patients. Other centers have described their experience with CXR in this setting, with small studies demonstrating variable sensitivity ranging from 33% [11] to 95% [12]. A direct comparison of 20 pairs of CT scans and same-day CXRs from

Table 2. Radiologic Findings

Patient No.	CXR No. 1 Clinical Report[a]	CXR No. 1 Likelihood of COVID-19[c]	CXR No. 2 Clinical Report[a]	CXR No. 2 Likelihood of COVID-19[c]	Days Between CXR No. 1 and No. 2
1	Abnormal	3	Abnormal	3	4
2	Normal[b]	3	Abnormal	3	15
3	Abnormal	4	Abnormal	5	1
4	Abnormal	3	Abnormal	3	2
5	Normal	1	Abnormal	3	13
6	Abnormal	4	Abnormal	4	2

Abbreviations: COVID-19, coronavirus disease 2019; CXR, chest radiography.

[a]Clinical report issued at the time of the CXR by the reporting radiologist.

[b]Retrospective review of this CXR showed a left lower lobe opacity, confirmed on computerized tomography 2 days later.

[c]Retrospective radiographic review and characterization of the likelihood of severe acute respiratory syndrome coronavirus 2 was performed in a nonblinded manner, using a 5-point Likert scale as used in prior published studies for COVID-19 [6, 7]: 1, normal; 2, unlikely to represent COVID-19; 3, indeterminate; 4, possibly represents COVID-19; 5, highly likely to represent COVID-19 [6, 7].

17 patients with COVID-19 showed that radiographs had a median sensitivity of 25% and specificity 90% [6].

Despite its relative insensitivity versus CT for COVID-19, radiography remains the most commonly ordered chest imaging study for patients with thoracic disease of all types, including immunocompromised patients [13]. In patients with underlying HM and HSCT, respiratory virus infections including influenza may have atypical radiographic features that are neither pathognomonic nor specific [13]. Common practice in such patients is to obtain more advanced imaging including CT when the CXR is normal or equivocal. To date, there have been relatively limited data reported on cases of SARS-CoV-2 in HM patients [1, 2]. These studies have predominantly been from China and thus emphasized chest CT findings, which were used to diagnose SARS-CoV-2 when RT-PCR was unavailable, as in a study of 13 patients with COVID-19 and underlying HM [1]. A French study of 25 HM patients reported bilateral pulmonary opacities seen in 14 patients on chest CT and an additional 7 patients on CXR; no imaging was performed on 4 patients [2]. This suggests that abnormal CXR may be more common in HM patients with COVID-19 than the general population.

In our study of 6 HM patients who developed SARS-CoV-2 infection, 67% of initial chest radiographs were reported as abnormal, rising to 83% on retrospective evaluation. Although these are higher values than published for initial CXR in COVID-19, the small sample size of our study precludes any definitive conclusions regarding radiographic sensitivity for COVID-19 in this population. A more clinically relevant finding is that abnormal chest radiographs in 4 of the 6 patients preceded positive SARS-CoV-2 RT-PCR tests, with 2 of those 4 requiring multiple RT-PCR tests before a positive result was obtained (Table 1). These findings are similar to those of 2 case reports of patients with underlying HM; in both cases, abnormal imaging preceded RT-PCR testing [14, 15]. In 1 of these 2 cases, initial RT-PCR testing was negative, with a positive result 3 days later [15]. Guidelines recommend RT-PCR testing in all patients with suggestive risk factors or clinical findings, regardless of imaging [16]. Our study findings indicate that (1) any abnormal imaging in this population should further raise the level of suspicion for SARS-CoV-2 infection and (2) prompt RT-PCR testing should be undertaken if not already performed. Moreover, a negative initial RT-PCR test along with abnormal radiography and ongoing symptoms should warrant repeat testing, especially in this population due to risk for false-negative test results. Discordant respiratory virus PCR results between upper and lower respiratory tract sampling have been reported in this immunosuppressed population, including non-SARS-CoV-2 coronaviruses [17–19]. In our own study, at least 1 patient had discrepancy between RT-PCR testing from NP sampling and BAL on the same day. This highlights the importance of not only repeat PCR testing in an immunocompromised host with typical clinical presentation of SARS-CoV-2 with negative initial NP RT-PCR, but also of obtaining a lower respiratory tract sample for testing, if feasible. Higher sensitivity of BAL versus NP RT-PCR for detecting SARS-CoV-2 has already been demonstrated in the general population [4, 20, 21], although a negative BAL RT-PCR with typical clinical and radiologic features would not definitively rule out underlying infection, and if clinical suspicion remains high, it may support repeat lower respiratory tract sampling if feasible.

CONCLUSIONS

Limitations of our study include its small size, retrospective nature, as well as nonblinded retrospective review by radiology. In conclusion, clinicians caring for HM and HSCT patients during the COVID-19 pandemic should consider the sensitivity of clinical and CXR findings and appreciate the established discordance of upper and lower respiratory tract PCR specimens. An initial negative SARS-CoV-2 NP RT-PCR in this population does not exclude the diagnosis of COVID-19, particularly in the presence of an abnormal CXR, and continued vigilance can optimize patient outcomes and prevent nosocomial spread.

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