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Case Report

Case Report: Temporary Molecular Relapse of Myeloid Leukemias in the Setting of COVID-19 and Viral-Induced Immunosuppression

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Abstract: Acute promyelocytic leukemia (APML) is one of the most curable leukemia subtypes, where the majority of patients achieve complete remission and also deep molecular remission after therapy, characterized by a PCR-undetectable state. Similarly, chronic myelogenous leukemia (CML) is a leukemia where, thanks to effective targeted treatment with tyrosine kinase inhibitors (TKIs), deep remission detectable only by PCR has become part of the routine management of these patients. Here, we describe a patient who was PCR-negative after induction and consolidation with arsenic trioxide (ATO) and all-trans retinoic acid (ATRA) and stayed PCR-undetectable for 13 months post-consolidation, later experiencing molecular relapse following mild SARS-CoV-2 infection. The patient was able to reestablish molecular remission again without anti-leukemic therapy several weeks later. She remained PCR-negative for the next 42 months. Viral infection-triggered immunosuppression, as in our case, offers a possible explanation for the temporary loss of molecular remission seen in leukemia patients monitored by PCR. Our first case illustrates this period of convalescence from viral infection, which was maybe accompanied by loss of molecular response. Viral infections and temporary immunosuppression may be a culprit in cases where molecular responses are lost temporarily. This loss of the PCR-undetectable state may have implications for other cancer patients where PCR monitoring is used. Thus, our observation may have broader implications for other patients, especially those with CML. We further enforce these findings by describing a second patient with CML who experienced temporary molecular relapse in the setting of post-viral syndrome.

Keywords: APML; AML; COVID-19; COVID; SARS-CoV-2; immunosuppression; relapse; CML

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1. Introduction

Acute promyelocytic leukemia (APML) is classified as a good-risk acute myeloid leukemia (AML), as the majority of patients achieve complete remission and molecular remission after therapy. However, a small subset of patients with APML ultimately relapse, so understanding the potential causes may help prevent relapse. To our knowledge, this is the first case of a patient with APML experiencing a molecular relapse of their malignancy in the setting of recent mild COVID-19 infection, which we suspect induced immunosuppression. We also observed this finding of temporary molecular relapse caused by possible viral-induced immunosuppression in a patient with chronic myeloid leukemia (CML).

2. Case Description #1: APML

A 52-year-old female presented to the hospital with symptoms of pancytopenia, diarrhea, fatigue, dyspnea upon exertion, recurrent bruising, and unintended weight loss in July 2020. After a peripheral blood smear showed the presence of blasts, she was admitted for further diagnostic workup. Bone marrow biopsy confirmed the diagnosis of acute promyelocytic leukemia (APML). FISH analysis and PCR were both positive for the disease-defining APML chromosomal 15;17-translocation causing a fusion of PML/RARα. The fusion protein acts as a transcriptional repressor, blocking the differentiation of promyelocytes into mature white blood cells and leading to an accumulation of immature promyelocytes in the bone marrow [1]. PML/RARα also contributes to leukemogenesis by interfering with the formation and function of PML nuclear bodies, which are involved in apoptosis [2]. Next-generation sequencing at the patient's time of diagnosis showed the presence of an FLT3-ITD mutation. The FLT3-ITD mutation is a marker of poor prognosis, as it is associated with higher white blood cell counts and lower survival rates in APML [3]. The patient was classified as intermediate-risk APML given her pancytopenia, and she was started on induction therapy with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) per the standard of care [4].

The patient originally presented with disseminated intravascular coagulopathy (DIC), for which fibrinogen was given bi-weekly and platelet and hemoglobin transfusions were given as needed. A repeat bone marrow biopsy performed three weeks after diagnosis showed hypercellular bone marrow with marked granulocytic hyperplasia and no increased blasts and promyelocytes. The patient's hospital course was fairly uncomplicated, but she did have QTc prolongation which was appropriately managed with arsenic dose reduction. The patient was discharged on day 41 with improving blood counts indicating bone marrow recovery. A repeat PML/RARα PCR was performed to assess for remission, which came back positive, but the patient was still discharged as she was clinically stable and continued outpatient ATO/ATRA induction therapy.

The patient achieved a negative PML/RARα on day 76 and repeat bone marrow biopsy confirmed she was in molecular remission. She started consolidation on day 88 along with bi-weekly EKGs due to previous QTc prolongation. She completed four cycles of ATRA/ATO consolidation therapy, and subsequent bone marrow biopsy indicated she was in complete remission including negative PCR.

Now a 54-year-old female, the patient tested positive for COVID-19 twenty-two months after her initial APML diagnosis. She recovered well from COVID-19 at home while notably receiving no specific antiviral treatment as her course was mild. She had previously received two doses of the Pfizer vaccine and one Pfizer booster four months before testing positive for COVID-19. Six weeks after her recovery from COVID-19, she presented for her regular APML follow-up post-treatment with a detectable level of PML/RARα transcripts (0.069%) by PCR in her peripheral blood. Two weeks later, repeated peripheral blood PCR and bone marrow biopsy aspirate again showed low levels of PML/RARα transcripts (0.053%), consistent with molecular relapse (Table 1).

Of note, the patient had two consecutive positive PCRs after thirteen months of consistently testing negative for PML/RARα since completing consolidation therapy. The patient was monitored by PCR in peripheral blood every two weeks and was undetectable for the next five months, after which repeat bone marrow biopsy showed remission with negative PCR. At that point, the series of negative PCR results was reassuring for the patient not to start salvage therapy. Nevertheless, after extensive discussion, the patient was started on ATRA maintenance therapy because of concern that her positive PCRs were indicative of residual disease below the threshold of PCR detection, which could perhaps surface with the next viral infection.

Table 1. PML/RARα transcript levels in peripheral blood or bone marrow. Of note, the patient tested positive for COVID-19 703 days after her diagnosis, after which she had two positive PCRs.

Days Since Diagnosis	Specimen Type	PML-RARα Transcript Level	Abnormal?	PCR%
0	Bone marrow	Positive (new diagnosis)	Yes	N/A
17	Peripheral blood	3979.640	Yes	1105.456
38	Peripheral blood	133.560	Yes	37.100
47	Peripheral blood	3.840	Yes	1.067
61	Peripheral blood	0.000	No	0.000
75	PB/BM	0.000	No	0.000
Consolidation	complete			
313	Bone marrow	0.000	No	0.000
528	Peripheral blood	0.000	No	0.000
617	Peripheral blood	0.000	No	0.000
703	Peripheral blood	0.250	Yes	0.069
717	Bone marrow	0.160	Yes	0.053
733	Peripheral blood	0.000	No	0.000
745	Peripheral blood	0.000	No	0.000
754	Peripheral blood	0.000	No	0.000
768	Peripheral blood	0.000	No	0.000
782	Peripheral blood	0.000	No	0.000
817	Peripheral blood	0.000	No	0.000
845	Bone marrow	0.000	No	0.000
948	Peripheral blood	0.000	No	0.000
1041	Peripheral blood	0.000	No	0.000
1139	Peripheral blood	0.000	No	0.000
1230	Peripheral blood	0.000	No	0.000

3. Case Description #2: CML

A 54-year-old woman presented to the hospital with two months of fatigue, night sweats, fever, and chronic left-sided abdominal pain in May 2016. Workup revealed a leukocytosis of 27,000 with a differential including 60% neutrophils, 20% lymphocytes, 4.6% basophils, and some metamyelocytes and myelocytes. Due to concern of basophilia, a BCR-ABL PCR was sent, resulting in a PCR% of 43.8 confirming diagnosis of CML. She was started on imatinib 400 mg as per standard of care due to her co-morbid medical conditions, mainly pulmonary fibrosis. The patient continued to respond to imatinib with the following results of BCR-ABL PCR of 34.9% 2 months later, 0.043% 10 months after diagnosis, and 0.019% 16 months after diagnosis (Table 2).

The patient first presented to our institution 2 years after her diagnosis of CML with fevers, body aches, night sweats, and negative infectious workup. Further workup showed detectable BCR-ABL PCR levels around 5%, and she switched to dasatinib 100 mg 27 months from her diagnosis. Due to intolerance and possible pulmonary toxicity of dasatinib, the patient stopped dasatinib at 35 months from diagnosis. While off TKIs, her CML became detectable at very high levels at 38 months post-diagnosis with cytogenetic relapse. The patient attempted treatment with bosutinib for two weeks, but then started ponatinib 15 mg at 41 months from diagnosis as the fourth line of therapy, which she responded very well to. She achieved a complete molecular response at 57 months post-diagnosis and continued testing PCR-negative for CML through 66 months post-diagnosis, when she decided to discontinue ponatinib due to her personal preference.

At 67 months post-diagnosis, this now 60-year-old woman tested PCR positive for BCR-ABL at an outside hospital. After a negative test at our institution at 68 months from diagnosis, she tested positive again at 69 months post-diagnosis and was re-started on ponatinib. She tested PCR-negative at 70 months from diagnosis and stopped ponatinib 72 months post-diagnosis due to concern for neutrophilic panniculitis. The patient remained BCR-ABL negative off therapy for five months. In late September 2022, she developed a severe viral respiratory infection. She and her husband both were very sick and were not able to go to the hospital or get tested as a result. In late 2022, the dominant viral illness was COVID-19 Omicron variant BA.5, and clinical suspicion was very high that this patient had COVID-19 infection. She cleared her viral respiratory illness at home with no specific antiviral therapy, and subsequently tested BCR-ABL positive two weeks later via PCR at 77 months post-diagnosis. At the time of testing, she denied any B symptoms or vasomotor symptoms. The patient preferred not to restart ponatinib despite molecular detection of BCR-ABL, and subsequently tested PCR-negative for BCR-ABL at 78 months from diagnosis without any specific CML therapy. She has remained in remission while off TKI therapy ever since her temporary molecular relapse after severe viral respiratory infection. Of note, the patient's course was complicated by a spinal abscess due to MRSA, mitral valve endocarditis, bacteremia, and meningitis that was treated with two months of IV vancomycin. This patient's severe bacterial infection occurred while she was off ponatinib, and did not cause molecular relapse or affect her BCR-ABL detectability. She remained PCR-negative at her most recent clinic visit, which is 100 months from her original diagnosis of CML.

Table 2. BCR-ABL PCR percentages in peripheral blood or bone marrow. Of note, the patient had a severe viral illness in late September 2022, after which she had a positive PCR test at 77 months after her diagnosis of CML.

Months from Diagnosis	Days Since Diagnosis	Specimen Type	Q-RT-PCR (CML%)	Abnormal?
0	0	PB	43.795	Yes
2	50	PB	34.904	Yes
10	293	PB	0.043	Yes
16	475	PB	0.019	Yes
24	745	PB	0.448	Yes
25	754	BM	0.399	Yes
27	831	PB	5.624	Yes
27	838	PB	11.598	Yes
28	850	PB	8.247	Yes
28	858	PB	3.511	Yes
29	874	PB	0.675	Yes
29	879	PB	0.564	Yes
29	894	PB	1.234	Yes
31	951	PB	15.072	Yes
32	964	PB	4.341	Yes
32	983	PB	2.368	Yes
34	1026	PB	0.617	Yes
34	1039	PB	0.402	Yes
35	1076	PB	0.114	Yes
36	1095	PB	2.054	Yes
36	1110	PB	5.365	Yes
37	1139	PB	53.219	Yes
38	1160	PB	56.775	Yes
39	1181	PB	169.830	Yes
40	1213	PB	278.584	Yes
41	1236	PB	130.924	Yes
42	1273	PB	79.262	Yes
43	1298	PB	2.631	Yes
44	1356	PB	0.013	Yes
45	1378	PB	0.014	Yes
47	1424	PB	0.015	Yes
49	1488	PB	0.010	Yes
50	1539	PB	0.013	Yes
51	1567	PB	0.003	Yes
52	1600	PB	0.006	Yes
54	1656	PB	0.001	Yes

Table 2. *Cont.*

Months from Diagnosis	Days Since Diagnosis	Specimen Type	Q-RT-PCR (CML%)	Abnormal?
55	1689	PB	0.003	Yes
57	1725	PB	0.000	No
58	1753	PB	0.000	No
58	1775	PB	0.000	No
61	1847	PB	0.000	No
64	1955	PB	0.000	No
67	2040	PB	0.003	Yes
68	2061	PB	0.000	No
69	2096	PB	0.020	Yes
70	2126	PB	0.000	No
73	2230	PB	0.000	No
74	2260	PB	0.000	No
76	2316	PB	0.000	No
77	2349	PB	0.004	Yes
78	2379	PB	0.000	No
79	2412	PB	0.000	No
80	2433	PB	0.000	No
82	2497	PB	0.000	No
85	2596	PB	0.000	No
88	2673	PB	0.000	No
92	2797	PB	0.000	No
95	2887	PB	0.000	No
98	2978	PB	0.000	No
100	3056	PB	0.000	No

4. Discussion

We hypothesize that the episode of mild COVID-19, which our first patient decided not to report and went untreated as she recovered quickly clinically, may have resulted in a temporary immunosuppression which allowed her APML to briefly relapse for two months at the molecular level and subsided later as the patient "fully" recovered from COVID-19. Notably, it took the patient 76 days to initially achieve PCR negativity in blood and bone marrow, and her negativity was sustained for another 20 months after completing consolidation therapy until 6-8 weeks after an episode of COVID-19. We observed a similar effect in our second patient, who tested positive for BCR-ABL two weeks after a severe viral respiratory tract infection that was likely COVID-19. When the patient had multiple PCR positives at 67 and 69 months after diagnosis with CML, she required treatment with ponatinib to achieve PCR negativity, whereas when she tested PCR positive after a viral infection, she achieved negativity the next test without any CML therapy. This suggests that her level of immune surveillance was weakened by the viral illness, allowing for a temporary molecular relapse, which then subsided as she cleared the virus. Viruses such as COVID-19 are immunosuppressive and may cause an immune injury that in turn impacts the results of molecular monitoring of patients with hematological malignancies in

otherwise deep remission. Having a molecular relapse after months of PCR negativity is very distressing for patients and is a phenomenon that physicians should be aware of.

The emerging evidence suggests that SARS-CoV-2, the virus that causes COVID-19, can have lasting effects on nearly every organ and organ system weeks, months, and potentially years after infection [5]. These long-term effects of COVID-19 significantly reduce and functionally exhaust T lymphocytes, resulting in a prolonged period of immunosuppression [6]. COVID-19 can also have more acute effects on immune cells, as the virus infects human CD4+ helper T cells via its spike glycoprotein, allowing for entry into T helper cells and causing impaired cell function and death [7]. This study also showed that helper T cells of patients with COVID-19 express high levels of anti-inflammatory IL-10, which hinders the host immune response. Therefore, we hypothesize that this could have potentially allowed for an opportunity for our patients' APML and CML to relapse.

COVID-19 also suppresses a variety of other immune cells which may in turn lead to malignant relapses. Approximately 33–96% of patients with COVID-19 have been observed to demonstrate lymphopenia, specifically among B cells, CD4+ T cells, CD8+ T cells, and NK cells [8]. This occurs because lymphocytes express angiotensin-converting enzyme 2 (ACE2), the receptor that SARS-CoV-2 uses to enter cells. In this way, infection of leukocytes by COVID-19 affects both the innate and adaptive immune systems—both of which have anti-tumor effects via NK cells and CD8+ T cells, respectively. Additionally, patients over 50 years old display more severely decreased CD8+ T cell and total lymphocyte counts in the setting of COVID-related immunosuppression [9]. This indicates that older patients, such as our patients, may be more likely to experience a malignant relapse from the immune dysregulation caused by COVID-19.

COVID-19 reduces the immune response both during active infection and after recovery from acute disease. Functional abnormalities of B and T lymphocytes have been shown to persist for up to six months following hospital discharge from COVID-19 infection [10]. Long-term immunosuppressive effects may explain why our patient tested positive for PML-RARa PCR two months after recovering from COVID-19. Innate immunity also plays a critical role in the anti-tumor immune response via NK cells, and researchers found that the number of NK and CD8+ T cells were markedly decreased in patients with SARS-CoV-2 infection [11]. These immune deficits in CD8+ T cells persist even after recovery from acute COVID-19, as prior infection with SARS-CoV-2 was shown to significantly reduce activation and expansion of CD8+ T cells [12]. Additionally, infection severity does not correlate with the level of immunosuppression, as a comparison of patients with post-acute COVID syndrome (long COVID) to patients with mild COVID showed that both groups had similar levels of inflammatory markers IFN-β, IFN-λ1, CXCL9, CXCL10, IL-8, and sTIM-3 four months after infection [13]. This demonstrates that even cases of mild COVID-19, like those seen in our patients, still cause significant immunosuppression that can allow malignant relapses to occur.

Another mechanism to explain our patient's relapses is the direct oncogenic effects of COVID-19. Researchers previously found that the nonstructural protein 3 (Nsp3) of SARS-CoV promotes degradation of the p53 protein, which is known to have antiviral effects [14]. Nsp3 is also found on SARS-CoV-2, and given that p53 functions as a tumor suppressor gene by regulating the cell cycle, COVID-mediated knockout of p53 allows for both virus and tumor cell replication. Furthermore, a similar endoribonuclease Nsp15 is also encoded by coronaviruses, which has been shown to decrease levels of the tumor suppressor gene Rb and therefore increase the proportion of cells in the S phase of the cell cycle [15]. In this way, COVID-19 can allow for unchecked and potentially malignant cell cycle proliferation. More recently, SARS-CoV-2 was found to dramatically decrease Rb1 activity while increasing the activity of the transcription factor E2F, confirming that

COVID-19 promotes cell cycle proliferation in a similar way as other oncogenic viruses [16]. These findings, coupled with our patients' case presentations, suggest that patients in remission who contract COVID-19 may need closer follow up with molecular monitoring to detect possible early relapses of their malignancies.

5. Conclusions

In conclusion, there are a plethora of ways in which virus-related immunosuppression may have caused our patients' temporary molecular recurrences. These include but are not limited to suppression of both the innate and adaptive immune systems, immunosuppression during acute infection and persisting after recovery, and the direct oncogenic effects of COVID-19. Our cases illustrate the importance of immune surveillance in patients in molecular remission, as their disease may recur in the setting of post-viral immunological dysfunction. Patients with leukemia (APML and/or CML) in molecular remission may therefore benefit from closer molecular monitoring. Besides proper evaluation, they should also be counselled accordingly about these potential temporary recurrences.

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