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COVID-19 in a Hairy Cell Leukemia Patient: A Rare Case Report

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The detailed clinical course of coronavirus disease 2019 (COVID-19) in patients with hairy cell leukemia (HCL) is rarely reported. We report the first case of HCL diagnosed with prolonged pancytopenia after COVID-19 infection in Japan. We describe the case of a 56-year-old man who was diagnosed with COVID-19. Computed tomography revealed ground-glass opacities in the bilateral lung lobes as well as splenomegaly. Remdesivir and dexamethasone were administered for the treatment of COVID-19. Since the pancytopenia persisted, bone marrow examination was performed, and he was diagnosed with HCL. Although pancytopenia can occur with COVID-19 alone, clinicians should be alerted regarding the presence of hematologic malignancies in patients in whom pancytopenia persists after COVID-19 treatment or in those with splenomegaly. Further, the condition of all previously reported patients with COVID-19 associated with HCL was severe enough to require mechanical ventilation. This is the first case in which the disease was not severe. The interleukin-6 (IL-6) level was lower in this case than in previous cases, suggesting that racial differences in IL-6 production may have contributed to COVID-19 severity.

Keywords: coronavirus disease 2019; hairy cell leukemia; interleukin-6; pancytopenia; splenomegaly
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Introduction

Hairy cell leukemia (HCL) was first reported by Bouroncle et al. (1958) as an uncommon hematological malignancy associated with pancytopenia and splenomegaly. HCL is a rare B-cell lymphoid neoplasm that accounts for 2-3% of all leukemias. It is four to five times more common in males, the median age at diagnosis is 52 years, and it does not occur in children (Maitre et al. 2019). It is three times more common in Caucasians than in other races, and is less common in Asians (Dores et al. 2008). The clinical course of this disease is usually gradual. The cellular morphology of this tumor is characterized by hair-like projections on the surface. Genetic sequencing of HCL has recently revealed the presence of the V-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) V600E mutation, which is absent in other lymphoid malignant neoplasms, and specific treatment has been established (Maitre et al. 2019). Coronavirus disease 2019 (COVID-19) with hematological malignancies (leukemia, myeloma, and lymphoma) have more severe outcomes than patients with solid organ tumors (odds ratio 1.57, 95% confidence interval 1.15-2.15; $p < 0.0043$) (Lee et al. 2020). However, limited data are available on the clinical course and treatment of COVID-19 with HCL. Clinical experience with the course of COVID-19 in patients with HCL is limited to only two reported cases (Kohla et al. 2020; Bellmann-Weiler et al. 2020). In this report, we present a case of HCL that was discovered as a result of pancytopenia and splenomegaly during the course of COVID-19 infection.

Case Presentation

A 56-year-old man who was an ex-smoker (64 pack-years) presented with fever, headache, excessive fatigue,

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and diarrhea. He had no previous history of immunodeficiency or medical comorbidities. He was diagnosed with COVID-19. Since his symptoms continued to worsen, he was admitted 4 days after their onset (Fig. 1). On physical examination, moderate splenomegaly was evident without lymphadenopathy. His oxygen saturation was 90% in room air. A complete blood count revealed pancytopenia. The hemoglobin level was 11.9 g/dL and leukocyte, neutrophil, lymphocyte, and platelet counts were 1,800/μL, 1,020/μL, 450/μL, and 87 × 10^3/μL, respectively. The serum levels of interleukin-6 (IL-6) and tumor necrosis factor (TNF)-α were 60.5 pg/mL (reference range: up to 7 pg/mL) and 3.07 pg/mL (reference range: 0.75-1.66 pg/mL), respectively. Other laboratory test results are shown in Table 1. Computed tomography (CT) revealed ground-glass opacities in the bilateral lung lower lobes and left upper lobe as well as splenomegaly (Fig. 1A). Remdesivir and dexamethasone were administered for the treatment of COVID-19. Other than fever, his symptoms improved immediately on the second day of treatment (Fig. 1B). Remdesivir and dexamethasone were administered for 5 and 10 days, respectively. Since pancytopenia persisted until the 23rd day, bone marrow examination was performed. Bone marrow and peripheral blood smears revealed hairy cells on May-Giemsa staining (Fig. 2). Flow cytometry analysis of the hairy cells revealed a population expressing CD45+, CD19+, CD20+, CD22+, CD11c-dim, CD25+, CD103+, CD123-dim, CD200+, CD5−, CD10−, CD23−, and HLA-DR+ with kappa chain restriction. *BRAF* V600E mutation was also detected by direct Sanger sequencing of polymerase chain reaction products from the bone marrow sample (Fig. 3). Accordingly, the patient was diagnosed with HCL and treated with cladribine. The patient has been in complete remission since then (Fig. 1C).

Written informed consent was obtained from the patient for the publication of this case report and all accompanying images.

Discussion

We have reported a case of COVID-19 in a patient with HCL. Although it is a rare case, two important conclusions can be drawn from it.

First, in a patient with COVID-19, when laboratory data indicate pancytopenia and CT shows splenomegaly, clinicians should carefully consider HCL as a differential diagnosis of pancytopenia. Splenomegaly is a characteristic finding in HCL and is found in 80-90% of HCL cases (Venkatesan et al. 2014). Hairy cells release cytokines, such as IL-6 and TNF-α, that prevent regular hematopoiesis and promote bone marrow fibrosis leading to pancytopenia (Barut et al. 1993). It has been reported that TNF-α levels increase upon COVID-19 infection (Huang et al. 2020). Elevated TNF-α levels resulting from viral infection is known to inhibit apoptosis through the NF-κB signaling response via TNF receptor 1 (Pimentel-Muiños and Seed 1999; Liu et al. 2021). Furthermore, clonal expansion of HCL is known to be mostly the result of increased cell survival rather than proliferation (Zaja et al. 1998; Tiacci et al. 2006). The proliferative properties of HCL are also known to be mediated by autocrine signaling (TNF-α–TNF receptor) and intracellular signaling pathways (including the mitogen-activated protein kinase cascade) (Tiacci et al. 2006). It is possible that the increase in TNF-α levels associated with COVID-19 infection suppressed cell death and induced increased cell survival via autocrine signaling and induced HCL. Patients with COVID-19 display a lower blood lymphocyte count, and pancytopenia is likely to be apparent. Kohla et al. (2020) have reported a case of prolonged pancytopenia after COVID-19 infection, which resulted in the diagnosis of HCL. The exclusion of hematological malignancies such as HCL is necessary in cases of pancytopenia with splenomegaly even after COVID-19 treatment is completed.

Second, not all cases with COVID-19 and HCL become severe enough to require mechanical ventilation. Clinical experience with the course of COVID-19 in patients with HCL is limited to only two reported cases (Table 2) (Kohla et al. 2020; Bellmann-Weiler et al. 2020). These two cases were critical and required mechanical ventilation. The present case is the first that did not require mechanical ventilation. The reason why our case did not worsen is unclear, but ethnic differences may be involved. Multiple reports have reported poor prognosis in cases of COVID-19 associated with hematologic diseases (García-Suárez et al. 2020; Passamonti et al. 2020; Yigenoglu et al. 2021). In a report from Israel, HCL had the highest mortality rate of 44% compared to other hematologic malignancies (Yigenoglu et al. 2021). On the other hand, in a European study of 132 centers and 3,801 cases, the mortality rate for HCL was 34.8%, and the malignancy with the highest mortality rate was myelodysplastic syndrome (up to 45%) (Pagano et al. 2021). It is suggested that mortality rates vary by race for the same underlying disease. Japanese individuals have a lower COVID-19 mortality rate compared to people from other developed countries (Coe et al. 2011). A genome-wide association of over 2,300 people hospitalized with COVID-19 in Japan identified a variant on 5q35 (rs60200309-A at DOCK2). This risk allele is prevalent in East Asians, including Japanese people, but is rarely observed in other races (Namkoong et al. 2021). Another reason may be the difference in cytokine production among different races. Elevated IL-6 levels due to excessive systemic inflammation and dysregulated host immune response are associated with adverse clinical outcomes in patients hospitalized with COVID-19. Sugiyama et al. (2021) reported serum IL-6 values of 58 Japanese patients with COVID-19, which were 3.0 ± 2.6 pg/mL for mild/moderate disease and 25.0 ± 23.2 pg/mL for severe/critical disease. On the other hand, several reports from countries other than Japan have reported even higher IL-6 levels (33.0-41.5 pg/mL) in severe/critical cases (Chen et al. 2020; Gao et al. 2020; Zhang et al. 2020). In the present

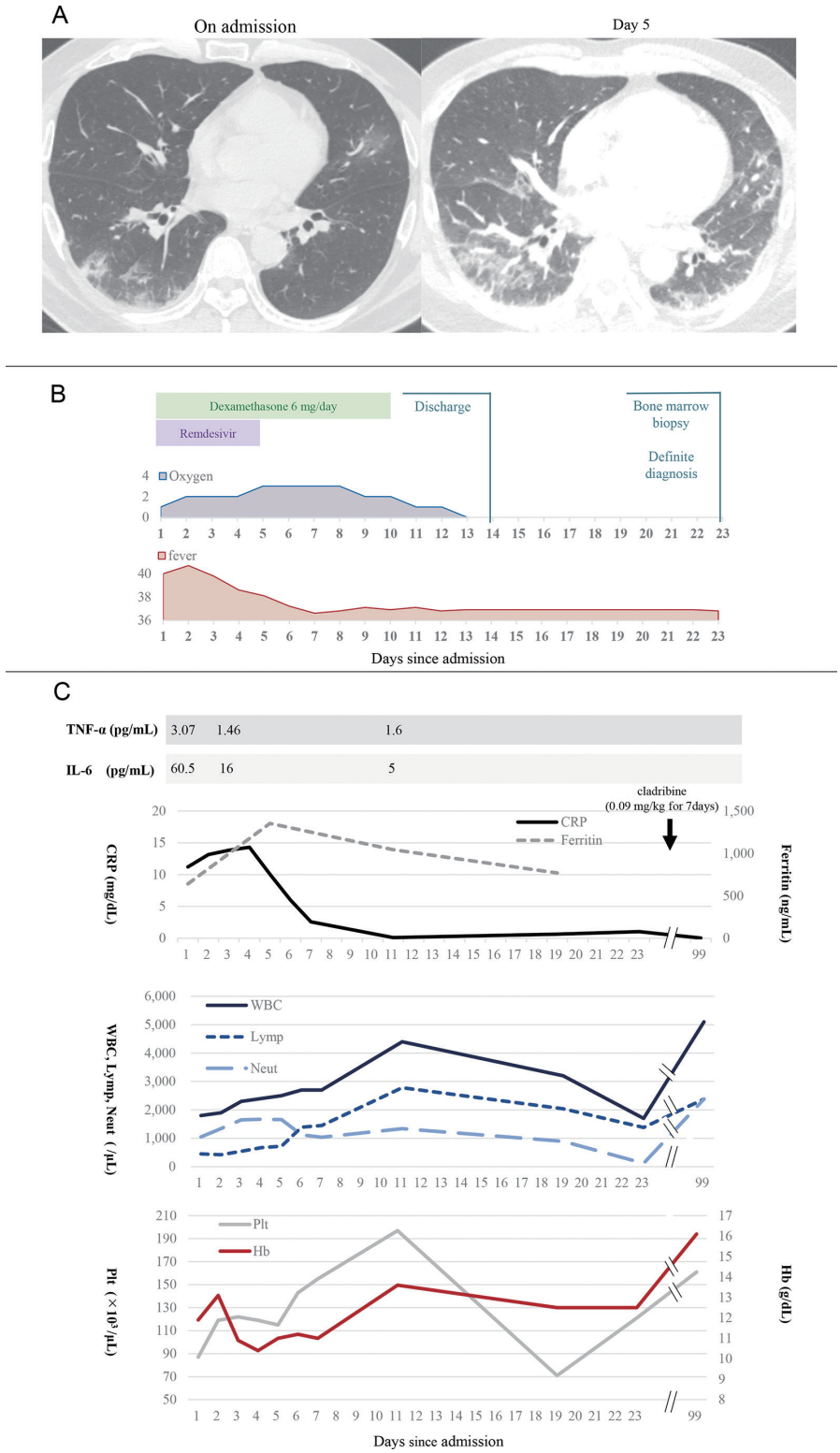

Fig. 1. Computed tomography findings (A), clinical course (B), and time-course of hematological parameters (C).
(A) Computed tomography shows ground-glass opacities in the bilateral lung lower lobes and left upper lobe on admission. Ground-glass opacities tend to progress over time and in this case, they evolved toward retractile consolidation areas on day 5. (B) After the administration of remdesivir and dexamethasone, the patient's symptoms (fever) gradually improved. (C) Pancytopenia was present on admission and persisted after the inflammatory response improved (reference range of CRP, 0-0.14 pg/mL; and reference range of ferritin, 50-200 pg/mL). Both IL-6 (reference range, up to 7 pg/mL) and TNF-*α* (reference range, 0.75-1.66 pg/mL) levels were elevated on admission but promptly decreased.
TNF-*α*, tumor necrosis factor-*α*; IL-6, interleukin-6; CRP, C-reactive protein; WBC, white blood cells; Lymp, lymphocytes; Neut, neutrophils; Plt, platelets; Hb, Hemoglobin.

Table 1. Laboratory findings on admission.

	Reference range, adults	On admission
Hemoglobin (g/dL)	13.7-16.8	11.9
Hematocrit (%)	40.7-50.1	32.5
WBC (per μL)	3,300-8,600	1,800
Differential count (per μL)		
Neutrophils	1,620-6,540	1,020
Lymphocytes	960-3,100	450
Monocytes	110-600	270
Eosinophils	0-520	10
Basophils	0-150	0
Platelet count (per μL)	158,000-348,000	87,000
Urea nitrogen (mg/dL)	8-20	10
Plasma creatinine (mg/dL)	0.65-1.07	0.82
Sodium (mmol/L)	138-145	134
Potassium (mmol/L)	3.6-4.8	4.2
Chloride (mmol/L)	101-108	98
Calcium (mg/dL)	8.8-10.1	9.1
Total protein (g/dL)	6.6-8.1	7
Albumin (g/dL)	4.1-5.1	4.1
Lactate dehydrogenase (U/L)	124-222	146
Alanine aminotransferase (U/L)	13-30	21
Aspartate aminotransferase (U/L)	10-42	28
High-sensitivity troponin T (ng/L)	0-0.014	0
Creatine kinase (U/L)	59-248	37
C-reactive protein (mg/dL)	0-0.14	11.21
Ferritin (ng/mL)	50-200	641.4
D-dimer (μg/mL)	< 1.0	1
Fibrinogen (mg/dL)	200-400	780
Soluble interleukin-2 receptor (pg/mL)	205-587	8,374
Interleukin-6 (pg/mL)	< 7.0	60.5
Tumor necrosis factor-α (pg/mL)	0.75-1.66	3.07

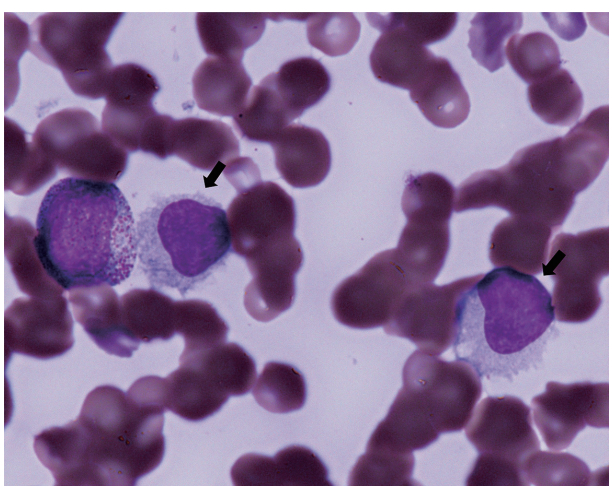

Fig. 2. Pathological findings of the bone marrow aspirate (May-Giemsa staining, × 1,000).
Bone marrow smear shows characteristic 'hairy' cells with cytoplasmic projections (arrows).

case, serum IL-6 levels were high (60.5 pg/mL), but were still much lower than those in the other two cases. Although a single factor may not explain everything, this difference in IL-6 levels may be one of the reasons underlying low disease severity. Japanese people reportedly have lower steady-state IL-6 levels compared with individuals of other ethnicities (Coe et al. 2011). Coe et al. (2011) reported that the mean IL-6 level was 1.70 pg/mL in 382 middle-aged Japanese individuals, 2.71 pg/mL in 976 Caucasian-American individuals, and 4.50 pg/mL in 233 African-American individuals. This observed effect of ethnicity on IL-6 levels remained highly significant even after analyzing body mass index as a covariate (Coe et al. 2011). The G/C polymorphism of the IL-6 gene may influence the prognostic risk for poor outcomes across ethnic groups in some types of cancer (Berger 2004). A limitation of this report is that the time from the onset to hospitalization and the type of treatment might have affected the severity of the disease. In the previous two cases, treatment was started

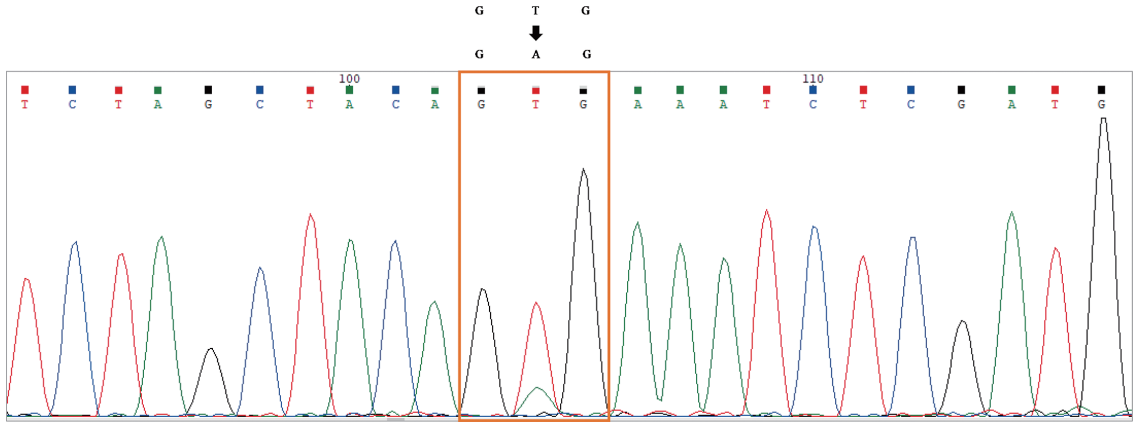

Fig. 3. *BRAF* V600E mutation analysis.
Direct DNA sequencing data from the bone marrow specimens shows a T to A substitution at nucleotide position 1799 (arrow) in exon 15 of *BRAF.*
BRAF, v-raf murine sarcoma viral oncogene homolog B1.

Table 2. COVID-19 in hairy cell leukemia patients.

		Patient 1	Patient 2	Our case
Age, Sex		58, male	54, male	52, male
Race		N/A	N/A	Japanese
BMI (kg/m^2)		N/A	26.9	26.9
Additional risk factors			Hyperuricemia, Obesity	Obsesity
Time from onset of illness to hospitalization (days)		7	10	4
SpO_2 on admission (%)		70	87	90
Invasive positive pressure ventilation		+	+	−
Symptom	fever	+	+	+
	fatigue	−	−	+
	cough	+	+	+
	shortness of breath	−	−	+
	diarrhea	−	+	+
WBC (× 10^3/μl)		2,600	3,400	1,800
Neutrophils (× 10^3/μl)		1,800	N/A	1,020
Lymohocytes (× 10^3/μl)		N/A	170	450
Hemoglobin (g/dL)		12.0	11.8	11.9
Platelates (× 10^3/μl)		85	277	87
CRP (mg/dL)		N/A	22.7	11.2
IL-6 (pg/mL)		1,843	393.9	60.5
TNF-α (pg/mL)		N/A	N/A	3.07
D-dimer (μg/mL)		73.37	N/A	1.00
Ferritin (ng/mL)		2,166	N/A	641
Treatment		hydroxychloroquine (400 mg) 7 days azithromycin (500 mg) 7 days tocilizumab (400 mg) 1 day methylprednisone (40 mg) 5 days intravenous immunoglobulin (0.4 g/kg) 5 days	favipiravir N/A beta lactam antibiotic N/A intermediate corticosteroid 5 days	remdesivir (200 mg/100 mg) 1 day/4 days dexamethason (6 mg) 10 days
Duration of hospital stay (days)		N/A	29	14
Duration of supplementary oxygen treatment (days)		N/A	24	13
Outcome		N/A	Cure	Cure
Reference		(Kohla et al. 2020)	(Bellmann-Weiler et al. 2020)	our case

BMI, body mass index; SpO_2, oxygen saturation; WBC, white blood cells; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; N/A, not applicable.

7-10 days after the onset of symptoms, but in the present case, treatment was started on the fourth day. The fact that remdesivir was administered early might also have favorably impacted the clinical outcome. Further investigation will be needed to elucidate the mechanisms involved in the severity of COVID-19 in patients with HCL.

In conclusion, this is the first Japanese case of COVID-19 with HCL. HCL is a rare disease and the precise clinical course of COVID-19 in patients with HCL is unclear. Although the previous two reports were of critical

cases, not all patients with COVID-19 with HCL experience severe disease, depending on their ethnicity. Moreover, if a patient with COVID-19 demonstrates pancytopenia in the laboratory data and splenomegaly on CT, clinicians should carefully consider HCL as a differential diagnosis of pancytopenia.

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Conflict of Interest

The authors declare no conflict of interest.

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