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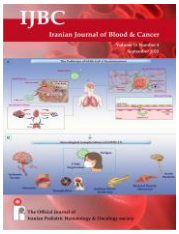

Case Report

# From viral encounter to leukemic challenge: a case of isolated molecular relapse in a child with Acute Promyelocytic Leukemia after SARS-CoV-2 infection

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## Abstract

**Background:** Acute promyelocytic leukemia (APL) is a type of aggressive acute myeloid leukemia (AML), characterized by the presence of abnormal promyelocytes in the bone marrow and bloodstream. The abnormal promyelocytes found in APL can lead to severe complications such as bleeding and blood clot formation.

**Case presentation:** A 7-year-old boy diagnosed with APL encountered a unique occurrence of isolated molecular relapse following a recent episode of SARS-CoV-2 infection while undergoing routine monitoring for treatment response. The relapse was confirmed by the detection of the PML/RARalpha gene abnormality in both the peripheral blood and bone marrow samples. Notably, during relapse, the boy displayed symptoms indicative of a cerebral ischemic stroke; however, effective management was achieved through the administration of low molecular weight heparin (LMWH) and corticosteroids. Subsequently, the patient underwent an allogenic bone marrow transplantation. Of note, throughout an 18-month period of close monitoring, no complications were reported.

**Discussion:** The detection of the PML-RARA transcript in peripheral blood can serve as a valuable tool for detecting isolated molecular relapse in pediatric APL. In cases where patients are undergoing immunosuppressive chemotherapy, the presence of neurological signs and symptoms may be the sole indicator of APL relapse, and it can be thoroughly investigated through the use of MRI with or without diffusion-weighted imaging (DWI). The administration of LMWH is a safe treatment strategy until D-dimer levels return to normal. It has been observed that COVID-19, as seen with other respiratory viruses, may potentially contribute to the relapse of pediatric APL, highlighting its significance in disease progression.

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## 1. Introduction

Acute promyelocytic leukemia (APL) is a specific type of acute myeloid leukemia (AML) characterized by the abnormal proliferation of hypergranular promyelocytes in both the bone marrow and peripheral blood [1]. Patients with APL commonly experience issues related to bleeding and coagulation abnormalities [1]. While disseminated intravascular coagulation (DIC) with excessive bleeding is a hallmark of APL, thrombosis is infrequent [2]. However, cases of thrombotic events, such as cerebral stroke, acute myocardial infarction, peripheral vascular thrombosis (e.g., deep vein thrombosis or DVT), and hepatic venous thrombosis, have been documented in APL patients [3]. Typically, thrombotic events are more prevalent during the primary stage of the disease and are rarely observed during the maintenance phase or relapse [4]. The presence of the fusion gene PML/RARalpha resulting from a translocation between chromosomes 15 and 17 serves as a diagnostic marker for APL [5]. Interphase fluorescence in situ hybridization (FISH) is one of the diagnostic techniques employed to identify the rearrangement of PML/RARalpha [6]. The early detection of APL can be aided by utilizing the PML/RARalpha transcript as a diagnostic marker, and it is recommended to conduct screenings for APL patients at intervals of approximately 4-6 months [7]. In this report, we present a child with APL who experienced a cerebral ischemic stroke. Notably, the stroke occurred in the context of an isolated molecular relapse subsequent to a SARS-CoV-2 infection. The importance of this report becomes even more evident as a wealth of research has been published on the neurological complications of COVID-19. In order to offer a concise overview of the neurological damages caused by SARS-CoV-2, we have included a schematic figure illustrating pathways of SARS-CoV-2 neuroinvasion and potential mechanisms causing neurological damage (**Figure 1**).

## 2. Case presentation

In October 2020, a 7-year-old boy diagnosed with APL was admitted to Madani hospital in Lorestan, Iran, due to left-sided weakness and difficulty speaking clearly. For the preceding seventeen months, the boy had been receiving maintenance chemotherapy as part of his treatment. Notably, three weeks prior to admission, he had tested positive for COVID-19 through real-time polymerase chain reaction (PCR), although he did not exhibit any symptoms of the infection. It is worth mentioning that other members of his family had also contracted SARS-CoV-2 infection.

During the neurological examination, the patient exhibited right-sided weakness, scoring 2 out of 5 on the Van Allen's scoring scale for motor power. The reflexes in the right biceps, brachioradialis, and patellar tendons were all diminished. The patient experienced difficulty performing tasks such as pincer grasp, quick pronation-supination, finger-to-nose coordination, and piano-playing with the right hand. Abnormal speech and an unsteady gait were also noted, while no sensory loss was observed.

Upon admission, the patient's white blood cell (WBC) count was 2700/mm3, with neutrophils and lymphocytes accounting for 48% and 52%, respectively. Hemoglobin levels measured 12.2 g/dL, and the platelet count was 273,000/μL. The patient's coagulation profile indicated a low fibrinogen level of 0.7 g/L and an elevated D-dimer level of 4980 mg/L. Other biochemical tests yielded normal results. Hemocoagulation markers such as the partial prothrombin time (PTT), prothrombin

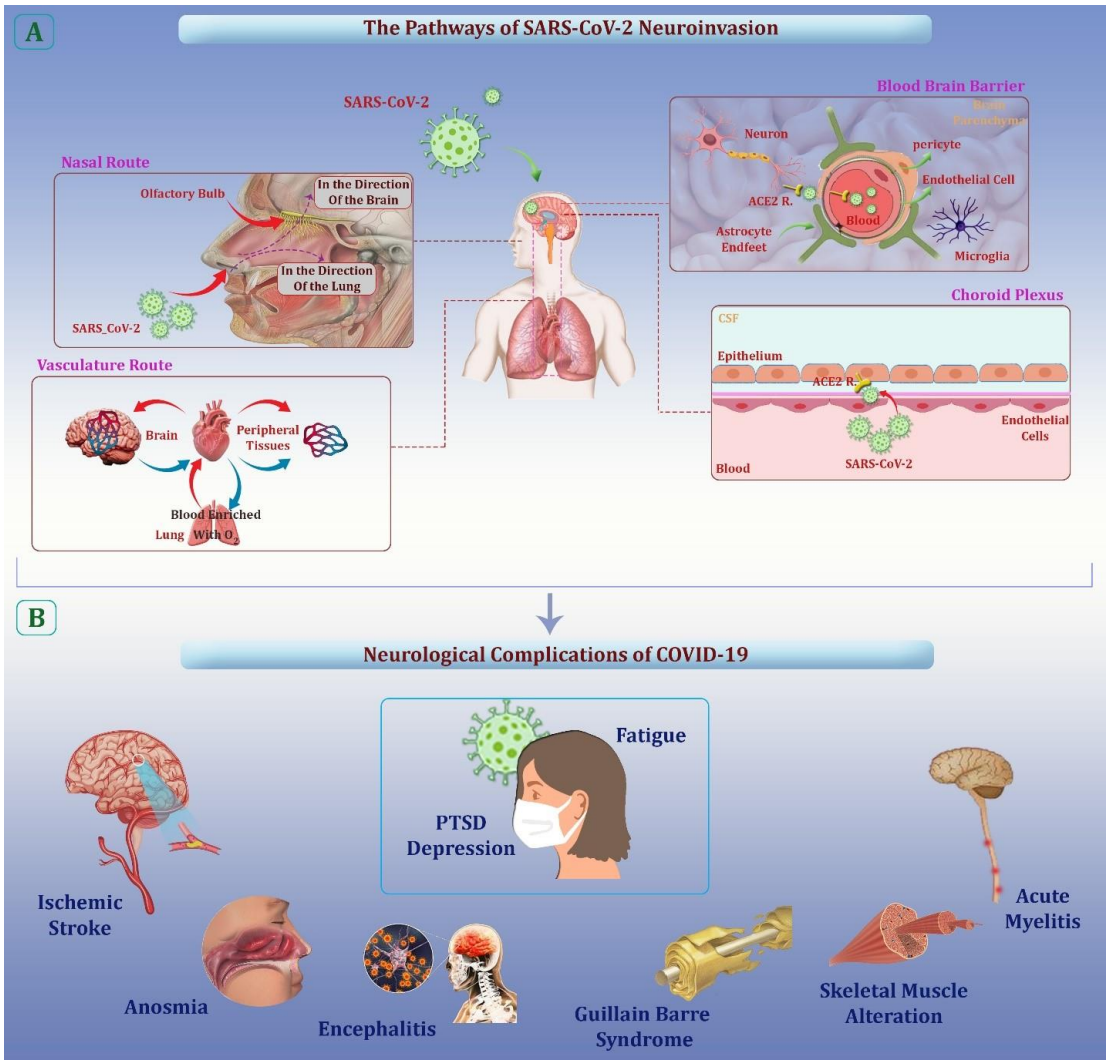


**Figure 1. The main pathways of SARS-CoV-2 neuroinvasion and potential mechanisms causing neurological damage.** **A)** The virus can enter the central nervous system (CNS) through the olfactory pathway, infecting the olfactory epithelium and traveling along the olfactory nerve fibers. Alternatively, it may invade the CNS through the bloodstream by infecting endothelial cells and breaching the blood-brain barrier (BBB). Additionally, the vasculature route and choroid plexus serve as potential pathways for neuroinvasion. **B)** This section provides a summary of neurological complications associated with SARS-CoV-2 neuroinvasion. These complications include but are not limited to autoimmune reactions, inflammation-mediated damages, ischemic stroke, encephalitis, myelitis, and anosmia.

time (PT), and international normalized ratio (INR) were all within the normal range.

The peripheral blood sample of the patient was analyzed for the presence of the PML/RARalpha transcript using fluorescence in situ hybridization (FISH), as part of the routine monitoring. The analysis revealed the presence of the PML/RARalpha transcript in the peripheral blood, while no additional abnormal findings were observed in other tests, including CBC and differential count. Two weeks later, a repeat analysis of the peripheral blood confirmed the molecular

relapse of the patient through the detection of the PML/RARalpha transcript. Additionally, the PML/RARalpha transcript was detected in bone marrow samples, despite the absence of a significant increase in promyelocyte count observed during the new bone marrow aspiration and biopsy. The presence of the PML/RARalpha transcript was not assessed in the cerebrospinal fluid (CSF), but no evidence of central nervous system (CNS) relapse was found in the CSF cytology examination.

No evidence of FLT3-ITD or any other cytogenetic abnormalities was found. A computed tomography (CT) scan of the brain revealed a stroke-like area characterized by an indistinct area of decreased density in the territories of the left middle cerebral artery (MCA). Reduced perfusion in the left hemisphere and extensive diffusion were observed through magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) (**Figures 2 and 3**).

The patient was initiated on dexamethasone at a dosage of 2 mg every 8 hours, followed by enoxaparin at a dose of 2000 IU (20mg/0.2ml) every 12 hours. Improvement in right-sided weakness and aphasia was noted one day after the initiation of enoxaparin. Following one week of treatment with enoxaparin and dexamethasone, the patient displayed significant improvement. Once the D-dimer levels returned to normal, the patient began receiving treatment with all-trans retinoic acid (ATRA) at a dosage of 20 mg/m2/day, arsenic trioxide (ATO) intravenously at a dosage of 0.15 mg/kg daily for 35 days, and Idarubicin at a dosage of 12 mg/m2 on days 1, 3, and 5. Enoxaparin was administered throughout the induction period until the completion of ATO therapy. The patient subsequently underwent a successful bone marrow allogenic transplant. During the follow-up period, no neurological deficits or other complications were detected.

## 3. Discussion

In this case report, we describe a pediatric patient who suffered a cerebral ischemic stroke following an isolated molecular relapse, despite not experiencing any clinical or hematological relapse, shortly after contracting COVID-19. APL presents a significant risk for thrombotic events, which can be particularly dangerous in children [2, 8]. Arterial thrombosis is a known side effect of anti-cancer medications like ATRA, although it may occur less frequently during maintenance chemotherapy [9]. Additionally, isolated relapse in the CNS is uncommon in APL and non-M3 subtypes of AML [10].

The interaction between leukemic promyelocytes and the coagulation system is exceptionally intricate in individuals with APL [11]. The release of anticoagulant substances by malignant promyelocytes plays a vital role in this process, significantly contributing to DIC and thrombohemorrhagic events [12]. Furthermore, cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1) stimulate coagulation factors in endothelial cells, promoting coagulation and the development of DIC [12]. Patients with elevated levels of D-dimer in the plasma and normal fibrinogen levels, particularly those with active disease, may be identified as having a higher risk of cerebral ischemia and DIC [13, 14]. Consequently, elevated D-dimer levels may serve as a specific laboratory marker for stroke and aid clinicians in determining the management of potential acute ischemic stroke cases. However, this has proven to be challenging in patients with leukemic stroke [15].

The reported incidence of thrombotic events in APL ranges from 5-10%. A recent study observed hemorrhagic or ischemic cerebrovascular accidents (CVAs) in 65 cases out of over 10,000 active AML patients, indicating a roughly 50-fold increased risk of thrombotic events compared to other diagnoses [16]. The clinical presentation of stroke varies depending on the underlying cause, but neuroimaging of cancer-related strokes often

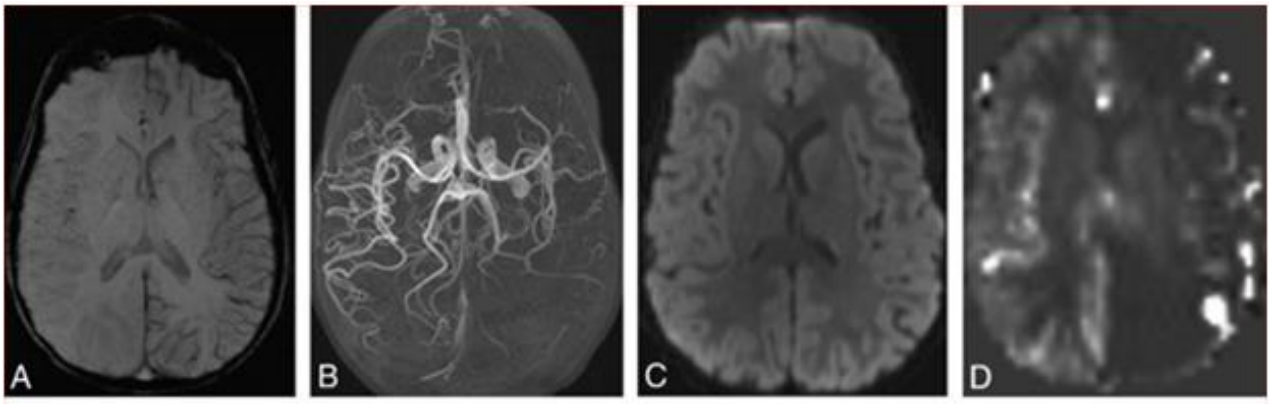


Figure 2. **The main pathways of SARS-CoV-2 neuroinvasion and potential mechanisms causing neurological damage.** **A)** The initial MR imaging conducted after admission. A) The susceptibility-weighted MRI reveals heightened visibility of the cortical veins across the left cerebral hemisphere, indicating an increase in deoxyhemoglobin on the left side. B) A collapsed maximum intensity projection from time-of-flight MR angiography displays reduced flow-related enhancement in the left anterior, middle, and posterior cerebral arteries. C) The diffusion tensor image's average trace exhibits no abnormalities in diffusion. D) The pulsed arterial spin-labeled perfusion-weighted imaging's relative CBF map demonstrates a significant decline in perfusion throughout the left cerebral hemisphere.

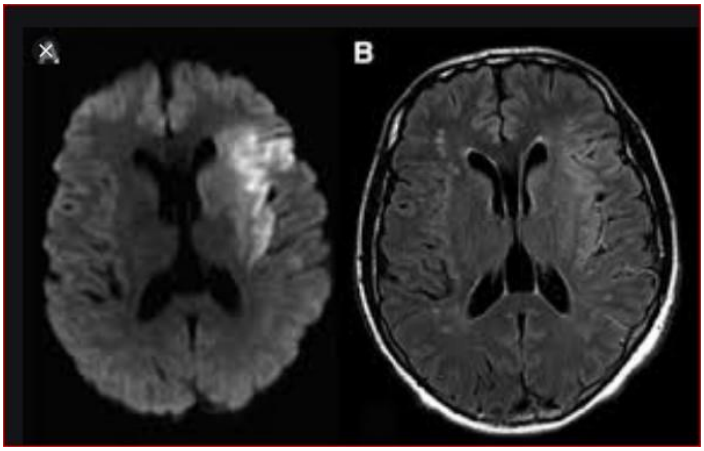


Figure 3. The utilization of diffusion-weighted imaging (DWI) and the apparent diffusion coefficient (ADC) to examine the right middle cerebral artery region. This region exhibits diminished diffusion, attributed to the presence of an acute cerebral infarction.

reveals multiple affected areas. Silent strokes, which do not cause noticeable speech or motor impairments, can occur, and many patients are unaware that they have experienced them. However, silent strokes may precede more severe strokes in the future [17].

Neuroimaging studies are necessary to confirm the diagnosis, and one commonly used MRI for evaluating acute ischemic stroke is diffusion-

weighted imaging (DWI) (**Figure 3**). DWI is highly sensitive in detecting small and early infarcts [18]. Traditional MRI such as T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI) may not reveal an infarct until up to 6 hours after its occurrence, and minor infarcts can be challenging to detect on CT scans for several days, particularly without prior imaging [19]. In patients with subacute transient ischemic attack (TIA) or silent stroke, DWI is typically beneficial [20]. Periodic DWI scans may potentially be helpful for APL patients who exhibit minor signs of relapse, elevated D-dimer levels, and increased fibrin degradation products (FDP) [21, 22].

The management of cancer patients who experience cerebral stroke is a subject of debate [21]. In the absence of documented contraindications, cancer itself should not be considered a reason to withhold thrombolysis and recombinant tissue plasminogen activator (rtPA) therapy, as the risk of hemorrhage in cancer patients has not been proven to be significantly higher than in the general population [23]. However, the use of anticoagulation warrants careful consideration. The decision to initiate anticoagulant therapy should be based on an individual assessment of each patient's risk. While new oral anticoagulants have their advantages, in cases of ischemic stroke during APL, LMWH remains the preferred choice. It is crucial for clinicians to receive adequate training in managing such patients [24].

The combination of LMWH and aspirin has been successfully employed in non-leukemic patients with ischemic stroke. Additionally, clopidogrel is recommended for the management of hypercoagulable states in leukemic children who are at an elevated risk of developing thromboembolic events due to procoagulant production from leukemia cells [25]. It is important to note that clopidogrel should not be used in combination with other medications [26].

Given the patient's young age, clopidogrel was not included in the prescribed treatment plan. Instead, aspirin was administered to prevent the formation of new arterial clots. Thrombolytic therapy was not considered for the patient due to the potential risk of intracerebral hemorrhage. However, there have been reports of successful treatment for acute stroke in cancer patients without an elevated risk of intracerebral hemorrhage or in-hospital mortality. It should be noted that our patient was admitted to the hospital after the optimal time window for thrombolytic therapy had passed.

In cases of isolated molecular relapse in APL patients where there is no evidence of hematologic relapse, chemotherapy is deemed necessary. This is because the molecular relapse is considered as minimal residual disease (MRD), which requires re-induction with intensified chemotherapy or an allogeneic hematopoietic stem cell transplantation (HSCT) [28]. Despite current recommendations for monitoring treatment response based on MRD, it may not provide sufficient time to detect molecular relapses before morphologic relapse occurs in non-M3 core-binding factor acute myeloid leukemia (CBF-AML) [30]. Typically, molecular relapse precedes hematologic relapse in AML patients with translocation (15;17) or (8;21); however, this time interval may be more extended in patients with inversion (16) and translocation (16;16) [31].

The selection of the most suitable treatment approach relies on factors such as primary cytogenetic studies, duration of remission, patient age, and donor availability. Recent retrospective studies have indicated that autologous HSCT is the preferred option for patients in their second complete remission. However, allogeneic HSCT

may be considered for patients experiencing very early relapse. It is particularly effective in advanced cases of APL and should be contemplated once relapse is diagnosed [32, 33].

The connection between respiratory viral infections, including COVID-19, and leukemia relapse is not extensively documented. Nonetheless, there have been reports of SARS-CoV-2 infection occurring in individuals with pre-existing Acute Lymphoid leukemia (ALL). In one case report, a patient with pre-existing ALL was diagnosed with COVID-19 during the initial round of chemotherapy following relapse [34]. Another study documented COVID-19 infection both at the onset of leukemia and during relapse [35].

Although thromboembolic events are well-known to be associated with COVID-19, including in asymptomatic and non-critically ill patients, cerebral thrombotic events are less commonly observed [36, 37]. However, further investigation is necessary to determine whether there is a potential link between COVID-19 and cerebral stroke, as well as its impact on disease relapse among patients with leukemia.

## 4. Conclusion

The detection of isolated molecular relapse in APL can be facilitated by examining the peripheral blood PML/RARalpha transcript. If patients undergoing immunosuppressive chemotherapy exhibit neurological signs and symptoms, it could be indicative of relapse, which can be effectively investigated using MRI with DWI. Until D-dimer levels reaches to the normal level, LMWH is a safe treatment strategy. Additionally, aspirin prophylaxis can be employed to prevent the formation of new blood clots throughout the course of treatment.

## Ethical Statement:

The research project adhered to the ethical principles and national guidelines for conducting medical research in Iran. It received approval from the "Iran National Committee for Ethics in Biomedical Research" with the approval ID: IR.LUMS.REC.1399.312 [38]. Prior to their enrollment, all individuals in the study population (or their parents) were adequately informed about the study's objectives, and written consent was obtained.

## Consent for Publication:

The legal guardian of the patient provided written informed consent for the publication of this case report, including any accompanying images. A copy of the written consent is available for the Editor-in-Chief of this journal to review.

## Competing Interest

There are no competing interests to declare.

## Funding

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## List of abbreviations

APL: acute promyelocytic leukemia
CNS: central nervous system
DVT: deep vein thrombosis
FISH: fluorescence in situ hybridization
PTT: partial prothrombin time
PT: prothrombin time
INR: international normalized ratio
CBC: complete blood count
FLT3-ITD: FMS-related tyrosine kinase 3-internal tandem duplication
CT scan: computed tomography scan
MCA: left middle cerebral artery

MRI: magnetic resonance imaging
MRA: magnetic resonance angiography
ATRA: all-trans retinoic acid
ATO: arsenic trioxide
TNF: tumor necrosis factor
IL-1: interleukin-1
CVA: cerebrovascular accident
DWI: diffusion weighted imaging
TIA: transient ischemic attack
FDP: fibrin degradation products
rtPA: recombinant tissue plasminogen activator
LMWH: low molecular weight heparin
MRD: minimal residual disease

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