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Case Report

Simultaneous Central Nervous System and Cutaneous Relapse in Acute Myeloid Leukemia

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Abstract

Introduction: Acute Myeloid Leukemia (AML) is a hematologic malignancy characterized by the clonal expansion of myeloid progenitors. While it primarily affects the bone marrow, extramedullary relapse occurs in 3–5% of cases, and it is linked to poor prognosis. Central nervous system (CNS) involvement presents diagnostic challenges due to nonspecific symptoms. CNS manifestations include leptomeningeal dissemination, nerve infiltration, parenchymal lesions, and myeloid sarcoma, occurring at any disease stage and frequently asymptomatic. Methods: A 62-year-old man with a recent history of AML in remission presented with diplopia and aching paresthesias in the left periorbital region spreading to the left frontal area. The diagnostic workup included neurological and hematological evaluation, lumbar puncture, brain CT, brain magnetic resonance imaging (MRI) with contrast, and dermatological evaluation with skin biopsy due to the appearance of nodular skin lesions on the abdomen and thorax. Results: Neurological evaluation showed hypoesthesia in the left mandibular region, consistent with left trigeminal nerve involvement, extending to the periorbital and frontal areas, and impaired adduction of the left eye with divergent strabismus in the primary position due to left oculomotor nerve palsy. Brain MRI showed an equivocal thickening of the left oculomotor nerve without enhancement. Cerebrospinal fluid (CSF) analysis initially showed elevated protein (47 mg/dL) with negative cytology; a repeat lumbar puncture one week later detected leukemic cells. Skin biopsy revealed cutaneous AML localization. A diagnosis of AML relapse with CNS and cutaneous localization was made. Salvage therapy with FLAG-IDA-VEN (fludarabine, cytarabine, idarubicin, venetoclax) and intrathecal methotrexate, cytarabine, and dexamethasone was started. Subsequent lumbar punctures were negative for leukemic cells. Due to high-risk status and extramedullary disease, the patient underwent allogeneic hematopoietic stem cell transplantation. Post-transplant aplasia was complicated by septic shock; the patient succumbed to an invasive fungal infection. Conclusions: This case illustrates the diagnostic complexity and poor prognosis of extramedullary AML relapse involving the CNS. Early recognition of neurological signs, including cranial nerve dysfunction, is crucial for timely diagnosis and management. Although initial investigations were negative, further analyses—including repeated CSF examinations and skin biopsy—led to the identification of leukemic involvement. Although neuroleukemiosis cannot be confirmed without nerve biopsy, the combination of clinical presentation, neuroimaging, and CSF data strongly supports the diagnosis of extramedullary relapse of AML. Multidisciplinary evaluation

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remains essential for detecting extramedullary relapse. Despite treatment achieving CSF clearance, the prognosis remains unfavorable, underscoring the need for vigilant clinical suspicion in hematologic patients presenting with neurological symptoms.

Keywords: acute myeloid leukemia (AML); leukemic relapse; cranial nerves; cerebrospinal fluid (CSF); leukemia cutis

1. Introduction

Acute Myeloid Leukemia (AML) is a heterogeneous group of hematologic malignancies resulting from the clonal expansion of myeloid progenitor cells [1]. While the bone marrow remains the primary site of disease activity and relapse, extramedullary involvement is uncommon and typically associated with poor prognosis and diagnostic complexity [2]. Extramedullary relapse (EMR) occurs in approximately 3–5% of AML cases and is often associated with adverse cytogenetics and molecular markers. Central nervous system (CNS) involvement, though uncommon in adult AML, poses diagnostic difficulties due to nonspecific neurologic symptoms and frequent non-informative initial cerebrospinal fluid (CSF) examination [2]. Similarly, leukemia cutis—the infiltration of the skin by leukemic cells—is rare and typically indicates systemic dissemination. The 2022 European LeukemiaNet (ELN) guidelines offer a comprehensive framework for AML risk stratification based on genetic and molecular features [1,3,4]; however, EMR remains a confounding variable not fully encompassed by the current prognostic models.

CNS involvement in AML may manifest as leptomeningeal dissemination, detectable in CSF, the infiltration of peripheral, cranial, or radicular nerves, parenchymal lesions, or as myeloid sarcoma [5–7]. It can occur at any stage of the disease, and may remain clinically silent, being detectable only through specific diagnostic procedures. Moreover, lumbar puncture is not routinely performed in AML, which contributes to variable reported incidence rates. Consequently, the incidence of CNS involvement ranges from 1.7% to 5.06% when considering only symptomatic cases, but increases to 19–32% when all newly diagnosed AML patients are systematically evaluated [7–9]. These data suggest that CNS involvement in AML is not as uncommon as traditionally thought [7]. Notably, CNS involvement is associated with poor prognosis, negatively affecting overall survival regardless of the presence or absence of neurological symptoms at the time of CSF evaluation [7,9]. The mechanisms of CNS infiltration in AML remain incompletely understood. Leukemic blasts may reach the meninges via the skull and vertebrae's bone marrow–meningeal vascular connections and cross the endothelium through adhesion molecule-mediated migration. Additional routes might include entry via the choroid plexus, direct leptomeningeal invasion from skull lesions, extension along nerve roots through the neural foramina, hemorrhage into the CNS with blood containing blasts, or iatrogenic introduction during lumbar puncture [7].

In this report, we present a patient with AML relapse presenting with cranial nerve multineuritis and cutaneous involvement, illustrating the challenges of diagnosing and managing extramedullary disease.

2. Case-Report

A 61-year-old man with an unremarkable medical history presented in May 2024 with newly diagnosed pancytopenia, discovered following an Emergency Department (ED) evaluation for asthenia and oppressive chest pain radiating to the left shoulder. Initial laboratory findings were significant for white blood cell count 1.29 $\times$ 10^9/L, absolute

neutrophil count 0.36 × 10^9/L, hemoglobin 96 g/L, and platelet count 30 × 10^9/L. A peripheral blood smear revealed 0.5% myelocytes and 0.5% metamyelocytes. Bone marrow aspiration yielded a dry tap, and subsequent trephine biopsy demonstrated interstitial fibrosis without detectable CD34+ cells. Biochemical analysis was unremarkable except for an isolated zinc deficiency, which was corrected with supplementation.

In July 2024, the patient returned to the ED with chest pain radiating to the back. A peripheral blood smear demonstrated 59% circulating blasts; a repeat bone marrow biopsy identified 68% myeloid blasts expressing the immunophenotypic markers CD13, CD15, CD33, CD36, CD38, CD45, CD56, CD65S, CD71, CD86, and HLA-DR. Additionally, cytogenetic and molecular analyses revealed trisomy 8 and mutations in NPM1, ASXL1, ETV6, and EZH2. Based on the available information, a diagnosis of Acute Myeloid Leukemia with favorable risk according to the 2022 ELN classification was established [1,3,4].

In accordance with clinical guidelines, first-line induction chemotherapy was initiated with cytarabine (100 mg/m^2/day by continuous infusion on days 1–7) and daunorubicin (60 mg/m^2/day on days 1–3), following the standard 3 + 7 protocol, resulting in complete remission, as confirmed by follow-up bone marrow aspiration. From then, the patient began to develop objective vertigo and paresthesias in the lower limbs and the left lower hemilip, attributed to chemotherapy neurotoxicity. In September 2024, the patient presented to the emergency room with objective vertigo and new-onset horizontal diplopia in primary gaze and leftward gaze, without nausea or vomiting. Additionally, he reported aching, tingling paresthesias in the left periorbital region radiating to the left frontal area. The lower limb and left lower hemilip paresthesias remained unchanged. Neurological examination revealed hypoesthesia and paresthesias in the left mandibular region, consistent with left trigeminal nerve involvement, extending to the periorbital and ipsilateral frontal areas. There was impaired adduction of the left eye with divergent strabismus in the primary position due to left oculomotor nerve palsy.

The brain CT was unremarkable for ischemic or hemorrhagic lesions. A lumbar puncture revealed elevated CSF protein (47 mg/dL) with a single large, atypical cell upon chemical–physical examination; cytology was negative for malignant cells. Given the evidence of cranial multineuritis, contrast-enhanced magnetic resonance imaging (MRI) was performed, demonstrating an equivocal thickening of the left oculomotor nerve on drive sequences, without contrast enhancement or T2 hyperintensity. The finding remained uncertain due to the subtle asymmetry compared to the contralateral nerve and the variable visualization of the nerve across imaging planes.

Due to strong clinical suspicion of CNS involvement, a second lumbar puncture was performed one week later, identifying 57% blasts on CSF immunophenotyping, confirming CNS infiltration. The isolated blast cell population tested positive for the markers CD15, CD33, CD45, CD56, and CD64, and was negative for CD4, CD11b, CD13, CD14, CD34, CD36, CD86, CD117, and HLA-DR. FISH analysis on cerebrospinal fluid was not performed. To complete the diagnostic assessment, a re-evaluation of the bone marrow was conducted, confirming the absence of bone marrow involvement in the disease.

Interestingly, the chemical–physical analysis was within the normal limits. Unfortunately, nerve biopsy—the gold standard for diagnosing leukemic infiltration—was not performed due to the high risk of permanent neurological deficits and technical challenges associated with sampling the affected cranial nerves, resulting in only a presumptive diagnosis of cranial nerve involvement secondary to possible neuroleukemiosis.

Concurrently, the patient developed nodular skin lesions on the abdomen and thorax. Histopathological examination of a skin biopsy confirmed leukemic infiltration, consistent with cutaneous relapse of AML (Figure 1).

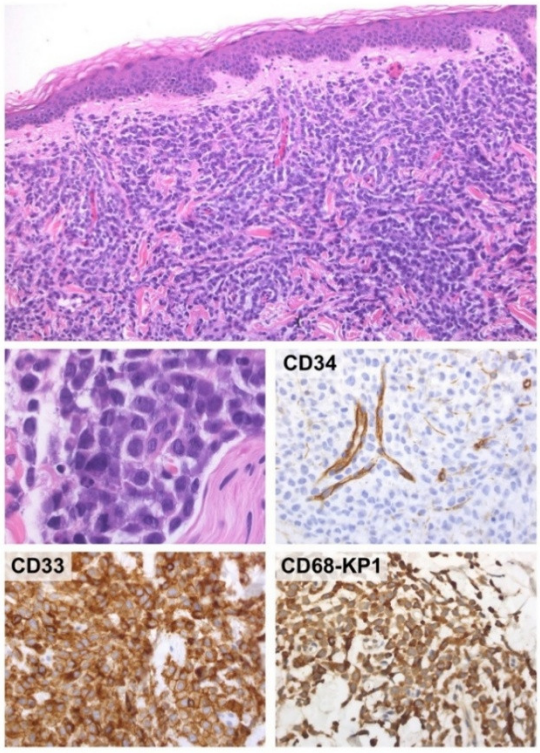


Figure 1. Histological features of the skin lesion. Histological examination of the skin lesion disclosed a diffuse dermal infiltrate of myeloid blasts with slightly irregular nuclear contours, finely disperse chromatin, and small nucleoli (**upper panel** and **mid left panel**). The neoplastic cells were negative for CD34, CD117, and MPO, with diffuse positivity for CD33 and CD68-KP1. The overall histological features were consistent with skin involvement of AML with monoblastic differentiation. (H&E and peroxidase stain; original magnification ×10, ×40 and ×63). FISH analysis on the skin lesion was not performed.

The patient was diagnosed with extramedullary AML relapse involving both the CNS and skin. Salvage chemotherapy was initiated using the FLAG-IDA-Venetoclax protocol: fludarabine (30 mg/m^2/day, days 2–6), cytarabine (2 g/m^2/day, days 2–6), and idarubicin (8 mg/m^2/day, days 4–6), in combination with venetoclax (400 mg/day, days 1–10) and intrathecal triple therapy (methotrexate, cytarabine, and hydrocortisone). Subsequent lumbar punctures showed no leukemic cells in the CSF. Post-treatment evaluation revealed hematologic complete remission, and progressive regression of the cutaneous lesions. Following therapy, neurological evaluation showed persistent tingling in the face and legs, unchanged from baseline. However, the rest of the examination was within the normal limits, with no gaze disturbances in particular. MRI control revealed new contrast-enhancing signal abnormalities in the vertebral bodies of C5, T2, T5, T8, T9, T11, T12, and the left transverse process of T4. A PET/CT scan demonstrated moderate fluorodeoxyglucose uptake (SUV max 5.9) in the left hemivertebra of T8. Targeted vertebral biopsy of the T8 lesion was negative for leukemic infiltration.

Given the high-risk profile and extramedullary disease history, the patient underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) following conditioning with craniospinal irradiation (total 12 Gy in 6 fractions) and fludarabine (30 mg/m^2/day, days −6 to −3). In October 2024, the patient received an infusion of 6×10^9/kg CD34+ stem cells from a haploidentical family donor. The post-transplant aplastic phase was complicated by septic shock and acute respiratory failure, necessitating mechanical ventilation and intensive care admission. Despite supportive measures, the patient succumbed to an invasive fungal infection.

3. Discussion

We presented a case of AML relapse manifesting with diplopia and periorbital pain, followed by sequential cranial nerve involvement. Pain and diplopia have been previously reported as early signs of CNS relapse in AML [10,11], and should be considered red flags in hematologic patients presenting with neurological symptoms [10].

While central nervous system involvement and cutaneous relapse in AML have been individually reported, the simultaneous occurrence with cranial nerve multineuritis alongside leukemia cutis is uncommon. The literature reports a few cases of acute lymphoblastic leukemia (ALL) or AML presenting with leukemia cutis and facial nerve palsy [12–15]. Our case differs from prior reports by documenting multiple cases of cranial nerve involvement, concurrent with leukemia cutis during AML relapse, a combination that is both unusual and clinically significant.

The initial lumbar puncture was negative, and MRI revealed subtle findings, consistent with reports indicating that CNS involvement in AML can occur despite normal neuroimaging [16]. Only the second CSF analysis showed cytological AML dissemination, supporting the known low sensitivity of CSF cytology and the recommendation to perform several lumbar punctures if needed. Leukemic cells may be sparse and dispersed within a large CSF volume, of which only a small sample is analyzed [9,17]. Although neuroleukemiosis cannot be definitively diagnosed without histological confirmation, the presence of myeloblasts in the CSF strongly suggests meningeal infiltration [5]. This, along with the clinical presentation of multifocal cranial neuropathies followed by cutaneous manifestations with histological evidence of AML relapse, makes one likely to consider leukemic infiltration the cause of cranial nerve multineuritis. Given that nerve biopsy is often not feasible, as in our patient, diagnosis relies on the integration of clinical evaluation, CSF analysis, radiological findings, and—when available—histological examination of other involved tissues. This comprehensive assessment is crucial to overcome the limitations of each single modality and reach a reliable diagnosis of leukemic cranial nerve involvement.

Consistent with previous reports, the patient achieved CSF clearance after treatment, suggesting that the primary site of involvement may be the nerve roots or cranial nerves rather than the peripheral nerves [10]. It has been proposed that cranial nerve dysfunction may result from leukemic infiltration and secondary inflammation, leading to nerve swelling, compression within narrow bony canals, and impaired conduction [5]. While CNS involvement in AML is not rare [7], it typically presents with isolated CSF blasts without neurological symptoms. Cranial nerve involvement, however, remains a rare and underrecognized manifestation [11].

4. Conclusions

This case underscores the clinical complexity and poor prognosis of extramedullary relapse in AML, particularly in immune-privileged sites like the CNS, which remains diagnostically challenging due to nonspecific symptoms, the need for repeated CSF evaluations, and the difficulty of obtaining a histological confirmation. A comprehensive approach—integrating clinical, radiological, and laboratory findings—is therefore essential. Similarly, cutaneous AML manifestations, though rare, can indicate systemic dissemination and therapeutic resistance. Timely diagnosis and aggressive multimodal treatment, including intrathecal therapy and stem cell transplantation, are crucial. However, outcomes remain poor, especially when complicated by infectious comorbidities during post-transplant aplasia.

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