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Case Report

Rare Presentation of Relapsed Acute Myeloid Leukemia Infiltrating Peripheral Nervous System: A Case Report

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Abstract

Acute monocytic leukemia is a subtype of acute myeloid leukemia (AML) characterized by aberrant proliferation and poor differentiation of monocytic cells and common tissue infiltration. Although very rare, AML can infiltrate peripheral nerves as an extramedullary presentation. In this case, a male patient in his 60s with a history of AML was admitted due to progressive neuropathic pain in bilateral upper extremities. Although the initial neurologic examination created a high clinical suspicion for Guillain-Barre syndrome, further testing showed an extramedullary relapse of AML with leukemia cutis and nerve and muscle invasion on a PET scan. This case highlights the unique propensity of monocytic AML to infiltrate tissue as well as the rarity of an extramedullary presentation and its associated challenges.

Keywords: Acute Myeloid Leukemia; Acute Monocytic Leukemia; Extramedullary AML; Peripheral Nerve Infiltration

Introduction

Over the last decade, the molecular and clinical heterogeneity of acute myeloid leukemia (AML) has become increasingly recognized and studied [1, 2]. AML is a type of malignancy that is distinguished by the abnormal proliferation and infiltration of cells from a hematopoietic lineage [1]. AML is morphologically categorized based on the differentiation and maturation of the hematopoietic cell by WHO 2022 classification as well as the traditional French-American-British (FAB) classification system [3]. Two categories of monocytic AML are recognized: acute myelomonocytic leukemia (M4) and acute monoblastic/monocytic leukemia (M5) [4].

Monocytic AML can uniquely infiltrate tissues due to the expression of specific receptor proteins [5]. Specifically, the leukocyte Ig-like receptor family B (LILRB) proteins are expressed on normal monocytic cells and support tumor growth by suppressing T-cell activity and facilitating leukemic cell infiltration [6, 7]. Monocytic AML exhibits a higher level of LILRB expression, thereby giving it a unique propensity to infiltrate tissue [5]. Endothelial damage has been suggested as another mechanism of tissue infiltration [8].

The infiltration of leukemia in the peripheral tissues, such as the soft tissues, the skin, and the central nervous system (CNS), is termed extramedullary AML [9]. The involvement of the peripheral nervous system (PNS), known as neuroleukemiosis, is extremely infrequent [10]. While the pathogenesis is still debated, the hematogenous spread of blast cells into the PNS is most likely part of the disease process [10]. The CNS and PNS provide a protective environment within the blood-nerve and blood-brain barriers. This allows the malignancy to thrive and provides a barrier against chemotherapies [11].

Nearly all documented cases of neuroleukemiosis present as a relapse of a previous leukemia diagnosis [11, 12]. The most common presenting signs include unresolving, progressive nerve pain, weakness, and numbness. Since the presenting symptoms are focused on neurological pain, the principal differential diagnosis should include neurotoxicity from chemotherapy, paramalignant Guillain-Barre syndrome (GBS), and an abscess from infection [10].

Extramedullary AML brings a unique challenge in diagnosis due to its vague symptoms and the rarity of the presentation [11]. The diagnosis is therefore highly reliant on clinical suspicion and supporting radiology, histology, and molecular analysis [13]. A lack of established therapeutic guidelines and the involvement of the CNS further complicates the treatment of this presentation [10, 11].

Case Presentation

A man in his 60s with a history of monocytic AML, deep vein thrombosis on Eliquis, and compensated liver cirrhosis was admitted for progressive neuropathic pain and weakness involving the bilateral upper extremities. His symptoms started two weeks prior as tingling and numbness in the left hand and gradually spread to the left upper extremity before progressing bilaterally.

His initial diagnosis of monocytic AML was made five months prior with no evidence of extramedullary disease. Cytogenetic analysis showed t (9;11) (p22;q23) translocation and deletion on chromosome 7, indicating intermediate risk. FISH studies showed results consistent with KMT2a (MLL) gene rearrangement. Next generation sequencing (NGS) showed a pathogenic KRAS mutation at 38% variant allele frequency. The patient was fit for intensive therapy and started on an attenuated dose of daunorubicin 45 mg/m2 in addition to cytarabine (7+3 regimen) due to known compensated liver cirrhosis. The patient achieved a complete remission on the evaluation of bone marrow biopsy.

Allogeneic hematopoietic stem cell transplant consolidation was deferred, given persistently elevated total bilirubin indicating worse liver cirrhosis (Child-Pugh class B). He received two cycles of intermediate-dose cytarabine consolidation with no unexpected toxicities. However, before initiating the third cycle, he presented with new onset left upper extremity pain. Initial work-up showed new left upper extremity DVT, for which the patient was treated with Eliquis. Left upper extremity pain continued to worsen over a few days, with new numbness and mild motor weakness. Similar symptoms started on the right upper extremity. MRI brain did not show any new significant findings; CT neck showed severe degenerative disc changes; and a short steroid course did not alleviate symptoms. The patient was subsequently evaluated by the neurology team, and EMG showed the possibility of brachial plexopathy. The acute bilateral presentation raised suspicion for leukemia-related neurological manifestations. Still, brachial plexus MRI was not conclusive for nerve compression (Figure 1B). New raised tender subcutaneous nodules were also noted on his upper extremities. Neurological examination showed bilateral upper extremity weakness (right>left, asymmetric and more prominent distally), sensory loss to pinprick, and temperature in all four limbs (right>left) with decreased reflexes throughout. Initial EMG showed non-specific left ulnar, median, and peroneal neuropathy, with repeated EMG showing findings more compatible with primary demyelinating polyneuropathy (thought to be related to GBS variant) vs. malignant radiculopathy. A biopsy of the skin lesions was positive for myeloid leukemia cutis. At this point, the multidisciplinary team favored paramalignant Guillain-Barre syndrome or MADSAM (asymmetric demyelinating neuropathy of motor and sensory nerves), so plasma exchange was started.

A bone marrow biopsy did not detect AML on morphology or flow cytometry. CSF exam was also negative for the presence of leukemia cells on several occasions. A PET scan was performed and showed direct tumoral invasion in several areas congruent with his neuropathic pattern (Figure 1A). MRI brachial plexus imaging was reviewed at that time with evidence of segmental regions of thickening and enhancement along the distal cords and axillary branches (right>left) compatible with leukemic involvement of the brachial plexus (Figure 1B). A diagnosis of extramedullary AML relapse was made with leukemia cutis and invasion of nerves and muscles, leading to discontinuation of plasma exchange after four sessions and starting azacytidine and venetoxlax combination in addition to intrathecal chemotherapy. The patient showed significant neurological improvements within a few weeks, with improved motor function and neuropathic pain. Repeat PET scan after completing the first cycle of azacytidine and venetoxlax showed stable disease and bone marrow biopsy remained negative for leukemia involvement. Unfortunately, the patient developed neutropenic fever and severe sepsis during the second treatment cycle with progressive multi-organ failure. The patient elected to go to hospice and eventually passed away 11 weeks after the onset of neuropathic pain and six months from the original diagnosis of AML.

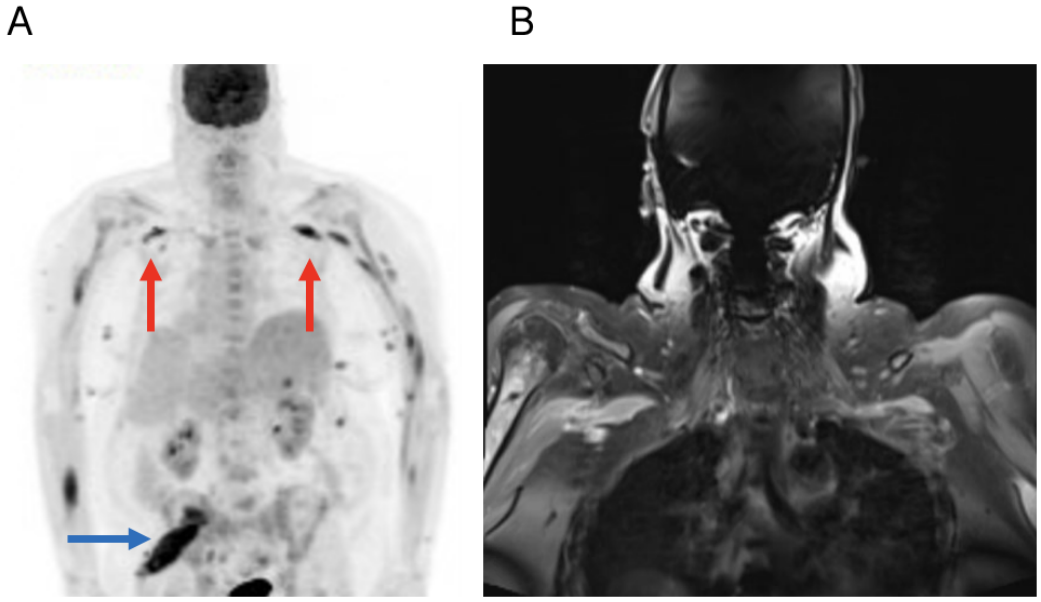

Figure 1: (A) PET scan showing small left supraclavicular and subpectoral lymph nodes (red arrows) and muscular invasion, greatest involving the left gluteus maximus (blue arrow), (B) MRI showing segmental regions of thickening and enhancement along the distal cords and axillary branches of the right brachial plexus.

Discussion and Conclusions

Acute myeloid leukemia (AML) is categorized based on hematopoietic cell type and maturity by the FAB [4]. Monocytic AML is unique in its ability to infiltrate tissues due to specific receptor proteins on monocytic cells [5, 6, 7]. This case emphasizes the heterogeneity of extramedullary AML and, in extremely rare cases, its ability to present as extramedullary infiltration of the PNS [10, 11].

The rarity of this presentation creates difficulty in diagnosis and can lead to a delay in treatment. Care is further complicated by a lack of established therapeutic guidelines [11]. Patients present with progressive motor and sensory deficits, most commonly in the setting of previously diagnosed AML [10, 11, 12]. However, chemotherapy side effects, premalignant syndromes, and other nonmalignant causes such as autoimmune diseases can present similarly. MRI and PET scans are beneficial in diagnosis and monitoring disease progression, but MRI was not conclusive in this case initially [11, 13]. The treatment is extrapolated from CNS involvement, assuming the need for antineoplastic therapy to cross the blood brain barrier in addition to systemic disease control. In this case, intrathecal chemotherapy and systemic azacytidine and venetoclax combination lead to clinical improvement and disease control on repeat PET imaging. Nonetheless, the patient eventually passed away following infectious complications related to treatment-induced neutropenia in the setting of liver cirrhosis, which underscores the treatment toxicities in patients with preexisting comorbidities.

This case highlights the rarity of extramedullary presentation of AML in the PNS and the unique ability of monocytic AML to infiltrate tissues. Given the vague presentation and complex differential diagnosis, this rare entity requires a high degree of clinical suspicion.

Data Availability Statement: The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics Statement: The studies involving human participants were reviewed and approved by University of Kansas Medical Center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

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Author Contributions: CT and HA designed the study and wrote the manuscript. JKC, AS, KB, HM, TL and JG provided data, interpretation and contributed to writing and reviewing the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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