A Case of Relapsed Acute Myeloid Leukemia Mimicking Acute Otomastoiditis

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Case Report.

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Key Clinical Message

This case illustrates the diagnostic difficulties and need for thorough evaluation in patients with extramedullary acute myeloid leukemia, especially in rare locations like the temporal bone. Although the prognostic implications and optimal management of extramedullary disease require further investigation, an accurate diagnosis through tissue biopsy and a personalized treatment approach are crucial.

Introduction

Acute myeloid leukemia (AML) is a heterogenous hematologic malignancy characterized by clonal proliferation of immature myeloid cells.[1] In rare cases, AML can manifest as myeloid sarcoma (MS), an extramedullary collection of myeloid tumor cells. MS, synonymous with extramedullary AML, is less common in adults, and occurs in approximately 2.5-9.1% of AML patients.[2] It can present concurrently with systemic disease or, rarely, as the sole manifestation before the onset of systemic disease.[2]When MS precedes systemic involvement, it may take months before the disease manifests in the blood or the bone marrow, leading to significant diagnostic challenges and delayed recognition. The prognostic significance of MS is still debated, and current treatment recommendations typically follow established protocols for systemic AML.[2–4]

Although myeloid sarcomas can develop in various tissues and organs,[5,6] there is limited data on extramedullary AML affecting the head and neck region, with most information available in the form of case reports.[7] Herein, we describe an unusual otologic case of an adult AML patient, who presented with an isolated involvement of the temporal bone after being in complete remission (CR) of systemic disease for more than a year. The clinical, radiological, and pathological features are discussed, highlighting the importance of considering differential diagnoses and implementing appropriate management strategies in similar cases.

Clinical case

A 32-year-old male without any previous medical history initially presented to our outpatient hematology department with a 1-month history of progressive weakness, dyspnea, and intermittent fever. Physical examination revealed petechiae on the upper extremities and thorax. The peripheral blood cell count showed the following results: white blood cell count (WBC), 75.8 $\times$ 10^9/l with 42% blast cells, hemoglobin level of 7.2 g/dl, and a platelet count of 54 $\times$ 10^9/l. Subsequent bone marrow aspiration revealed a hypercellular bone marrow with a significant increase in cells displaying morphological features consistent with myeloblasts (fig. 1). Larger cells with more abundant basophilic cytoplasm and scattered granules were also observed, suggestive of monocytic differentiation. A diagnosis of AML, subtype M4 (Acute Myelomonocytic Leukemia) by the French-American-British (FAB) classification, was established.

Standard induction chemotherapy was initiated with an anthracycline-based 7+3 regimen containing doxorubicin and cytarabine. After the first cycle, repeat bone marrow aspiration showed no blast cells, and the complete blood count (CBC) revealed a hemoglobin level of 10.6 g/dl, platelet count of 204 $\times$ 10^9/l, and WBC count of 6 $\times$ 10^9/l with a normal differential, indicating complete remission with hematologic recovery. Additionally, a lumbar puncture (LP) was performed due to the high WBC count at diagnosis and signs of monocytic differentiation serving as additional risk factors for CNS involvement. The cerebrospinal fluid (CSF) analysis was unremarkable for signs of disease.

Post-remission therapy consisted of three additional consolidation cycles of the same regimen, followed by monthly surveillance. After approximately 16 months of CR, the patient presented to a local otolaryngology department with complaints of left-sided otalgia, hearing loss and fever. Otoscopic examination revealed a narrowed left external auditory canal with ipsilateral hyperemia and purulent otorrhea obscuring the tympanic membrane. Examination of the right side was unremarkable, with an intact external auditory

canal and tympanic membrane. Bilateral mixed hearing loss was confirmed by audiometry. At the time, the CBC results did not show any signs of systemic AML, except for a slight leukocytosis with a left-shift deviation suggestive of an inflammatory process. Likewise, the CSF examination indicated no evidence of leukemic cells. Based on presentation and symptoms, a presumptive diagnosis of acute otitis media and externa was made, and the patient was prescribed oral antibacterial therapy. However, after one week of treatment, there was no symptomatic improvement.

A computed tomography (CT) scan was conducted (fig. 2), revealing a narrowed left external auditory canal and non-specific bilateral opacification of the middle ear cavities and the mastoid cells with increased soft tissue density, which was particularly notable on the left side. Importantly, the mastoid structure appeared intact, with no apparent areas of bone destruction and distinct masses. Taking into account the clinical presentation and imaging findings, a provisional diagnosis of acute bilateral otomastoiditis was made. Due to the worsening of the symptoms and refractoriness to conservative therapy, a left-sided mastoidectomy was performed with a curative intent (fig. 3). On visual inspection, the mastoid fragment contained no soft tissue.

The subsequent pathological review of the mastoid structure demonstrated extensive effacement with a homogeneous population of atypical cells, characterized by irregular nuclei, coarse chromatin, prominent nucleoli, and scant cytoplasm (fig. 4). Importantly, these findings were at odds with the absence of leukemic cells in the blood, bone marrow and CSF. An initial diagnosis of Burkitt's lymphoma was considered; however, further immunohistochemistry profiling showed positive staining for myeloperoxidase, CD34, TdT, CD117, CD68, and negative staining for CD3, CD20, PAX5, ALK, and Desmin. These results were consistent with the presence of blast cells of the myeloid lineage. Consequently, a final diagnosis of relapsed AML presenting as an isolated myeloid sarcoma of the temporal bone was confirmed.

Following the surgical intervention, the patient made a full recovery with significant symptom relief. Approximately 3 months have passed since the initial presentation, during which neither the CBC, nor the bone marrow examination showed signs of leukemic involvement. As such, combined treatment with local radiation (28 Gy) and intrathecal chemotherapy with cytarabine, methotrexate and dexamethasone was attempted.

However, by the end of radiation therapy, the patient presented once again with fever and progressive weakness. The CBC revealed a hemoglobin level of 12.4 g/dl, platelet count of 74×10^9/l and a WBC count of 4.2×10^9/l with 8% blast cells. Subsequent bone marrow aspiration confirmed systemic relapse, with 56% blast cells. Reinduction was attempted using the previously successful induction regimen; however, after two cycles, the patient failed to achieve remission.

Discussion

Extramedullary AML, also known as myeloid sarcoma, is characterized by the infiltration of blast cells into normal tissues, as confirmed by histological examination.[1] Although it can occur at any age, myeloid sarcoma predominantly presents in the pediatric population.[8] Myeloid sarcoma may develop either de novo or concomitantly with systemic AML. In some cases, it may precede the development of systemic disease by several months or serve as the initial manifestation of relapsed AML.[5] The most commonly affected sites are other hematopoietic organs (such as the liver, spleen, and lymph nodes), followed by skin and gingivae.[6] Localized bone involvement, particularly in the temporal bone, is rare and has only been reported in a few case studies. The underreporting of such cases could be a common issue that may be attributed to the diagnostic challenges associated with distinguishing myeloid sarcoma from other conditions, with misdiagnosis rates reported as high as 47% in recent studies.[9]

In cases similar to the one presented, several factors can contribute to an erroneous diagnosis. Patients with leukemia are prone to developing otologic symptoms, and acute leukemia patients are particularly susceptible to bacterial, fungal, or viral infections affecting the external, middle, or inner ear.[10] Less commonly, thrombocytopenic hemorrhage or direct leukemic infiltration can lead to thickening or bleeding in the external auditory canal and tympanic membrane, skin lesions, acute otitis media or externa with effusions, and various types of hearing loss, including sensorineural, conductive, or mixed.[11–14] Temporal bone in-

volvement, specifically, may often manifest as a triad of otalgia, hearing loss, and facial paralysis due to facial nerve involvement; additional symptoms may include retroauricular swelling and pain, ear fullness, and vertigo.[15–17] Finally, progressive disease can result in extensive bone erosions, permanent damage, and bacterial superinfections, contributing to the development of acute otomastoiditis.[11]

In the presented case, the patient initially exhibited two of the three symptoms of the aforementioned triad (otalgia and hearing loss), along with fever, ear effusions, and narrowing of the left external auditory canal. Still, these symptoms are non-specific. Considering the prolonged hematologic remission with no signs of systemic disease or central nervous system involvement, a provisional diagnosis of acute otitis media and externa was made.

Unsurprisingly, the subsequent conservative treatment proved ineffective. In some cases, a CT or magnetic resonance imaging (MRI) scan can aid in establishing the diagnosis. Specifically, extramedullary involvement could present as a well-defined, solid mass.[8] Imaging features are variable and site-dependent: craniospinal lesions are mostly homogenous and hyperdense on CT, iso- or hypointense on T1 and hyperintense on T2 MRI, with frequent invasion of adjacent bony structures.[7,8]Nevertheless, these features may be indistinguishable from other, more common malignancies, such as lymphoma.[8] Imaging can also demonstrate less specific findings, as was the case in our patient, posing additional diagnostic challenges. Therefore, given a patient's history, even non-specific opacification should be considered as potential evidence of neoplastic invasion mimicking a benign condition (such as otomastoiditis). Although PET/CT has demonstrated high sensitivity and specificity in identifying myeloid sarcoma,[18] it is costly and not widely available. Most importantly, its results are heterogenous when it comes to concurrent bone marrow involvement,[18] and interpretation can be even more challenging in cases of extramedullary bone disease and inflammatory complications. As such, imaging features can be insufficient for distinguishing not only between various neoplasms, but also non-malignant disorders.

Hence, a biopsy of the lesion appears to be the only definitive method for confirming a case of isolated extramedullary relapse or de novo myeloid sarcoma. Despite this, invasive procedures are frequently avoided or not feasible owing to certain frequent comorbidities, such as thrombocytopenia. As mentioned, the reported frequency of myeloid sarcoma has varied from 2.5% to 9.1%.[2] In contrast to this, a recent PET/CT-based study revealed a prevalence of 22%.[18] Likewise, a large-scale study of newly diagnosed AML patients showed an overall incidence of extramedullary disease of 23.7% based on physical examination and imaging.[6] Access to potentially affected sites (including the most typical ones, such as liver and spleen) may be challenging or life-threatening, and these are commonly not subjected to biopsy, which likely contributes to the underestimation of prevalence in previous reports, including the cases of temporal bone involvement. Finally, the morphologic appearance of blasts in myeloid sarcoma can vary and depends on the type of AML and characteristics of differentiation, presenting additional challenges. Nevertheless, immunohistochemistry, flow cytometry, and genetic analysis can usually resolve most issues when a tissue biopsy specimen is available.

When present, extramedullary involvement, whether de novo or in the context of relapse, is generally considered a negative prognostic factor.[2,19,20] In a study of newly diagnosed AML, CR rate and OS were significantly reduced for patients with EM AML (median OS of 14 months vs. 26.2 months), but event- and relapse-free survival did not differ in patients with and without extramedullary involvement.[20] Still, up to 60% of adult patients first present with EM AML during relapse, as was the case in the current report.[21] Expectedly, these patients show inferior outcomes when compared to newly-diagnosed cases, with a median overall survival (OS) of 11.6 months and 19.1 months, respectively;[21] however, the prognostic significance of EM AML in the context of relapse is still controversial. In a different study investigating extramedullary relapses among AML patients, there was no difference in survival between extramedullary and bone marrow relapse.[22] In contrast, another study showed significantly better survival rates in patients with extramedullary relapse (69% at 6 months) when compared to systemic or combined relapses (27% and 8%, respectively).[23] Overall, data are limted and show significant heterogeneity and the independent prognostic value of extramedullary disease is still debated. Despite this, the site and pattern of leukemic involvement seem to be important prognostic factors.[6,21] For instance, patients with leukemia cutis showed a significantly inferior OS when

compared to other sites of disease (median of 5.7 months vs. 21.9 months, respectively).[21,24] Interestingly, rare areas of involvement, such as the bone, may be associated with better survival rates.[6] Furthermore, a recent review reported that around 22% of temporal bone MS cases may harbor the prognostically favorable t(8;21) translocation.[17] Although genetic profiling was unavailable at our center at the time of this case, earlier data had also indicated at existing associations between myeloid sarcoma and the favorable cytogenetic abnormalities t(8;21) and inv(16); still, results are inconsistent, and several studies showed no significant associations with these core-binding factor mutations, and report a varying incidence of other molecular and genetic abnormalities.[5,20,21,25] In summary, both the prognostic significance and the genetic profile of MS may be dependent on disease site and other unexplored risk factors, and further studies are needed to investigate this possibility.

Current management of AML in eligible patients involves standard anthracycline-based multi-agent chemotherapy induction, followed by consolidation, with the possible addition of targeted therapy based on risk stratification and mutational profiling.[3] There is a lack of prospective clinical trials, and treatment of extramedullary disease, specifically, remains controversial. However, the onset of isolated extramedullary relapse frequently heralds a bone marrow relapse with a mean interval of around 7 months.[26] Accordingly, current recommendations for MS are based mainly on existing AML protocols, with or without the addition of radiation therapy and surgery.[2,3] In the present case, local treatment was attempted initially. Radiation therapy has shown excellent response rates (91-97%) and local disease control, with a median progression-free survival of 11 months, in one study.[27–29] Unsurprisingly, cases of isolated temporal bone AML relapse with prolonged responses after radiation therapy have previously been reported.[15] Regardless, survival is poor even among those achieving clinical remission with local therapy, and the majority are likely to relapse.[30] In the current case, systemic relapse occurred soon after the end of radiation therapy, possibly due to delayed recognition of the local relapse. Regrettably, management options for relapsed AML and targeted treatment are limited at our center. Despite the late relapse increasing the odds of reinduction with the previously successful regimen, subsequent chemotherapy failed to achieve CR.

Improving management strategies and outcomes in myeloid sarcoma may involve novel therapy and targeting specific molecular alterations, similar to systemic acute myeloid leukemia. For instance, a recent analysis reported a 45% CR rate among EM AML patients treated with venetoclax and hypomethylating agents, and 38% for patients in a relapsed setting.[31] However, genetic events underlying extramedullary disease are still not well understood and remain controversial.[20] Potentially targetable mutations commonly encountered in AML, such as those of NPM1, FLT3-ITD, IDH, KMT2A, as well as the presence of KIT, TET1, ASXL1, EZH3, SF3B1, NRAS alterations have been associated with extramedullary disease in several recent next-generation sequencing (NGS) studies.[20,21]In line with this, a study by Ball et al. demonstrated a complete response in three out of four patients treated with IDH inhibitors based on on-site next-generation sequencing of the MS tumor.[21] Therefore, biopsy followed by mutational analysis could be crucial for optimizing future therapy of EM AML. Furthermore, significant discordance has been observed between the molecular profiles of the myeloid sarcoma tumors and concurrent bone marrow disease, suggesting the importance of molecular alterations in the pathogenesis of extramedullary disease.[21,32] In one study, up to one third of cases showed molecular discordance, with the majority revealing discordance in prognostically important or potentially targetable alterations.[32] Importantly, patients presenting with mutational discordance were shown to have an inferior overall survival, underlining the significance of this clonal heterogeneity not only for the pathogenesis, but also prognostication and targetability of extramedullary AML.[32] In practice, obtaining sufficient material for cytogenetic and molecular analyses from MS biopsies, often available only in the form of formalin-fixed-paraffin-embedded tissues, can be challenging.[33] Utilization of novel NGS-based analyses in clinical practice may overcome this limitation, enabling proper genetic risk assessment and precision-based treatment.[33] Nonetheless, due to the low prevalence and varying presentation of myeloid sarcoma, our understanding of optimal management strategies is limited, and more prospective trials are necessary to evaluate the novel treatment approaches for extramedullary AML.

Conclusions

Myeloid sarcoma of the temporal bone is a rare finding that can occur either independently or in the context of relapsed acute myeloid leukemia. It is a diagnostic challenge and can often mimic other disorders, such as otologic infections, presenting with non-specific clinical and imaging findings. Therefore, it is crucial to maintain a high level of suspicion, particularly in patients with a history of neoplastic disease. Biopsy, followed by immunohistochemistry, flow cytometry and molecular analyses, should ideally be performed in every patient with myeloid sarcoma, whether it is isolated or concurrent with systemic disease. These diagnostic procedures are not only essential for an accurate differential diagnosis, but may also aid in proper risk stratification, identification of mutational discordance and optimization of treatment strategies.

Figures and legends

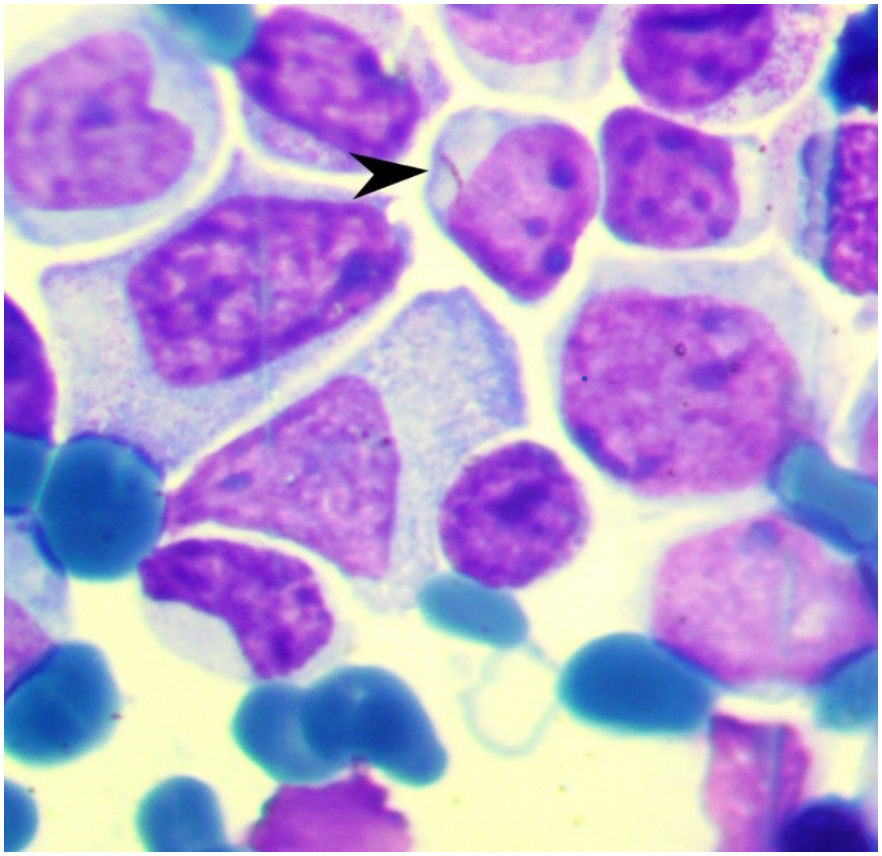

Figure 1. Bone marrow aspirate.

Bone marrow examination reveals the presence of blast cells of the myeloid lineage. A characteristic Auer rod (arrowhead) can be seen.

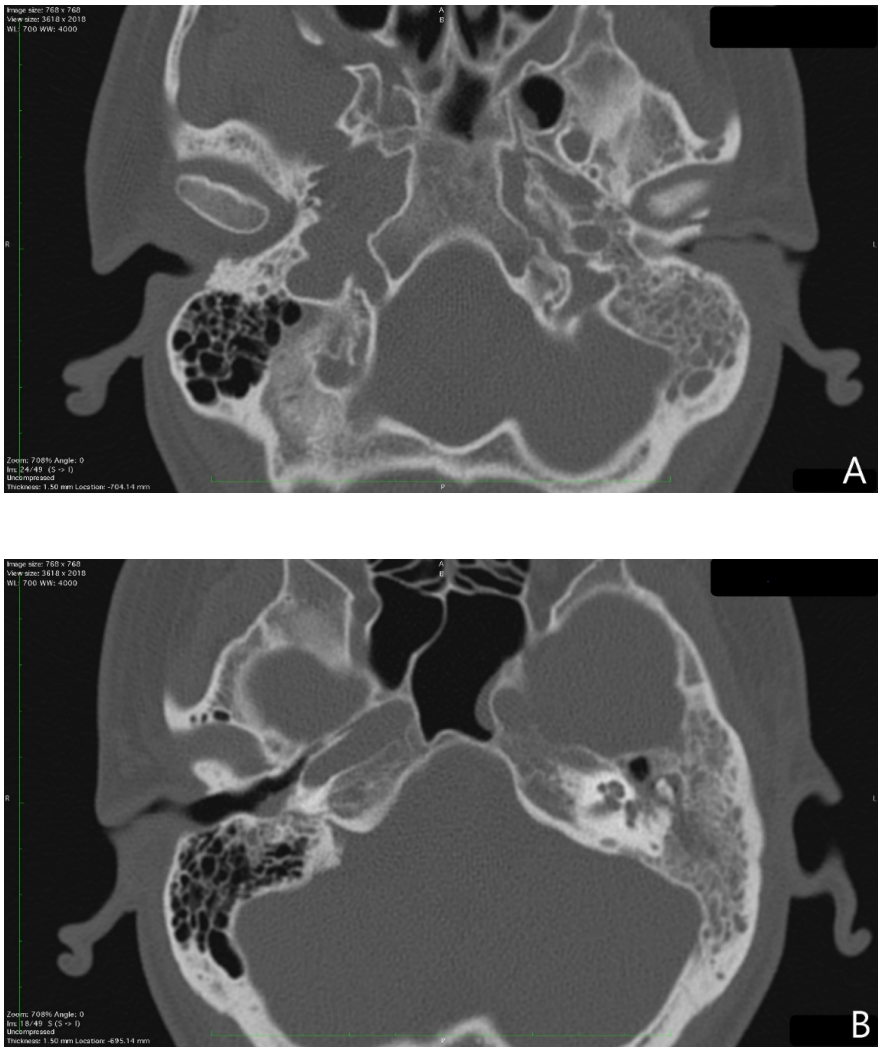

Figure 2. Head computed tomography.

Computed tomography reveals a complete homogenous left-sided and partial right-sided opacification of the mastoid cells and the middle ear with a relatively intact bony structure. A significant narrowing of the left external auditory canal (A) is shown, compared to the right external auditory canal (B).

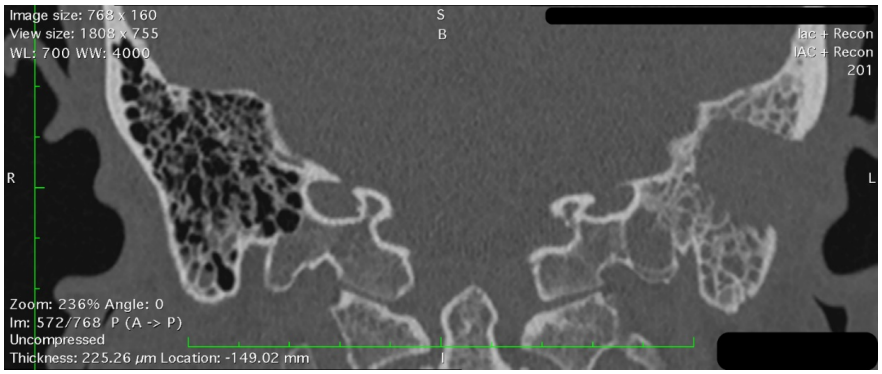

Figure 3. Head computed tomography, post-mastoidectomy.

Following left-sided mastoidectomy, computed tomography reveals persistent opacification in the remaining mastoid cells on the left and partial opacification of the right mastoid cells, around 3 months after initial imaging.

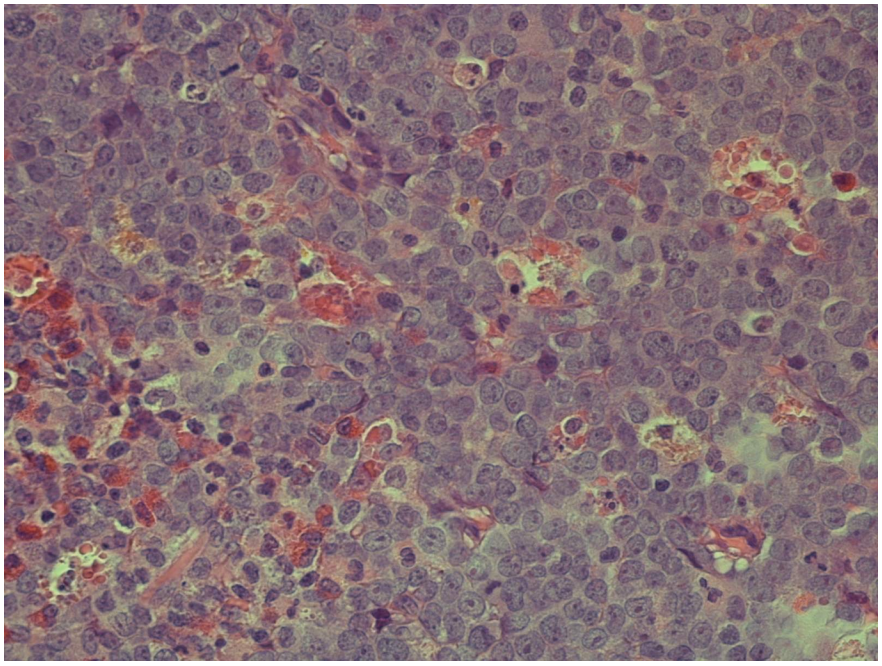

Figure 4. Histology of the left mastoid bone.

Histologic evaluation shows diffuse infiltration with medium- and large-sized cells with irregularly shaped nuclei and scant cytoplasm. Subsequent immunohistochemistry showed positive staining for myeloperoxidase, CD34, TdT, CD117 and CD68, indicative for the presence of myeloblasts.

Author Contributions

Ivan Negara: Conceptualization; Writing – original draft; Writing – review and editing.

Inga Chemencedji: Investigation.

Natalia Dobrovolschi: Investigation.

Natalia Sporis: Supervision; Validation.

Sanda Buruiana: Supervision; Validation; Writing – original draft.

Igor Vinogradov: Investigation; Supervision; Validation; Writing – review and editing.

References

1. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 4th ed Lyon: International Agency for Research on Cancer. 2017.

2. Bakst RL, Tallman MS, Douer D, Yahalom J. How I treat extramedullary acute myeloid leukemia. *Blood* . 2011;118(14):3785-3793. doi:10.1182/blood-2011-04-347229

3. Heuser M, Ofran Y, Boissel N, et al. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up+. *Annals of Oncology* . 2020;31(6):697-712. doi:10.1016/j.annonc.2020.02.018

4. Fu L, Zhang Z, Chen Z, Fu J, Hong P, Feng W. Gene Mutations and Targeted Therapies of Myeloid Sarcoma. *Curr Treat Options in Oncol* . 2023;24(4):338-352. doi:10.1007/s11864-023-01063-6

5. Pileri SA, Ascani S, Cox MC, et al. Myeloid sarcoma: clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients. *Leukemia* . 2007;21(2):340-350. doi:10.1038/sj.leu.2404491

6. Ganzel C, Manola J, Douer D, et al. Extramedullary Disease in Adult Acute Myeloid Leukemia Is Common but Lacks Independent Significance: Analysis of Patients in ECOG-ACRIN Cancer Research Group Trials, 1980-2008. *JCO* . 2016;34(29):3544-3553. doi:10.1200/JCO.2016.67.5892

7. Noh BW, Park SW, Chun JE, Kim JH, Kim HJ, Lim MK. Granulocytic Sarcoma in the Head and Neck: CT and MR Imaging Findings. *Clin Exp Otorhinolaryngol* . 2009;2(2):66-71. doi:10.3342/ceo.2009.2.2.66

8. Singh A, Kumar P, Chandrashekhara SH, Kumar A. Unravelling chloroma: review of imaging findings. *Br J Radiol* . 90(1075):20160710. doi:10.1259/bjr.20160710

9. Yilmaz AF, Saydam G, Sahin F, Baran Y. Granulocytic sarcoma: a systematic review. *Am J Blood Res* . 2013;3(4):265-270.

10. Andrès E, Kurtz JE, Maloisel F, Dufour P. Otological manifestations of acute leukaemia: report of two cases and review of literature.*Clinical & Laboratory Haematology* . 2001;23(1):57-60. doi:10.1046/j.1365-2257.2001.00358.x

11. Almadori G, Del Ninno M, Cadoni G, Di Mario A, Ottaviani F. Facial nerve paralysis in acute otomastoiditis as presenting symptom of FAB M2, T8;21 leukemic relapse. Case report and review of the literature.*Int J Pediatr Otorhinolaryngol* . 1996;36(1):45-52. doi:10.1016/0165-5876(95)01323-7

12. Leite da Silveira P, Gonçalves Silva V, Rizzato Paschoal J, Nizam Pfeilsticker L. Bilateral peripheral facial palsy and mastoid infiltration as symptoms of relapsed acute myeloid leukemia.*European Annals of Otorhinolaryngology, Head and Neck Diseases* . 2015;132(1):41-43. doi:10.1016/j.anorl.2013.09.003

13. Cankaya H, Ugras S, Dilek I. Head and neck granulocytic sarcoma with acute myeloid leukemia: three rare cases. *Ear Nose Throat J* . 2001;80(4):224-226, 228-229.

14. Howell J, Segel J, Jajosky R, et al. Acute facial paralysis and otomastoiditis as presenting symptoms of myeloid sarcoma. *Otol Neurotol* . 2015;36(4):e104-106. doi:10.1097/MAO.0000000000000490

15. Jung DJ, Lee HJ, Kwak JH, Lee KY. A Case of Myeloid Sarcoma Mimicking Otomastoiditis with Retroauricular Abscess. *Journal of Clinical Otolaryngology Head and Neck Surgery* . 2019;30(1):77-82. doi:10.35420/jcohns.2019.30.1.77

16. Murakami M, Uno T, Nakaguchi H, et al. Isolated recurrence of intracranial and temporal bone myeloid sarcoma–case report.*Neurol Med Chir (Tokyo)* . 2011;51(12):850-854. doi:10.2176/nmc.51.850

17. Zheng HD, Abdel-Aty Y, Taylor C, et al. Myeloid Sarcoma of the Temporal Bone: A Unique Cause of Hearing Loss, Otalgia, and Facial Nerve Weakness. *Otol Neurotol* . 2022;43(4):e435-e441. doi:10.1097/MAO.0000000000003478

18. Stölzel F, Lüer T, Löck S, et al. The prevalence of extramedullary acute myeloid leukemia detected by 18FDG-PET/CT: final results from the prospective PETAML trial. *Haematologica* . 2020;105(6):1552-1558. doi:10.3324/haematol.2019.223032

19. Cornelissen JJ, Gratwohl A, Schlenk RF, et al. The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach.*Nat Rev Clin Oncol* . 2012;9(10):579-590. doi:10.1038/nrclinonc.2012.150

20. Eckardt JN, Stölzel F, Kunadt D, et al. Molecular profiling and clinical implications of patients with acute myeloid leukemia and extramedullary manifestations. *Journal of Hematology & Oncology* . 2022;15(1):60. doi:10.1186/s13045-022-01267-7

21. Ball S, Knepper TC, Deutsch YE, et al. Molecular annotation of extramedullary acute myeloid leukemia identifies high prevalence of targetable mutations. *Cancer* . 2022;128(21):3880-3887. doi:10.1002/cncr.34459

22. Shimizu H, Saitoh T, Hatsumi N, et al. Prevalence of extramedullary relapses is higher after allogeneic stem cell transplantation than after chemotherapy in adult patients with acute myeloid leukemia. *Leukemia Research* . 2013;37(11):1477-1481. doi:10.1016/j.leukres.2013.08.017

23. Solh M, DeFor TE, Weisdorf DJ, Kaufman DS. Extramedullary relapse of acute myelogenous leukemia after allogeneic hematopoietic stem cell transplantation: better prognosis than systemic relapse. *Biol Blood Marrow Transplant* . 2012;18(1):106-112. doi:10.1016/j.bbmt.2011.05.023

24. Ball S, Knepper TC, Deutsch YE, et al. Molecular annotation of extramedullary acute myeloid leukemia to identify prevalence of targetable mutations. *JCO* . 2021;39(15_suppl):7024-7024. doi:10.1200/JCO.2021.39.15_suppl.7024

25. Kaur V, Swami A, Alapat D, et al. Clinical characteristics, molecular profile and outcomes of myeloid sarcoma: a single institution experience over 13 years. *Hematology* . 2018;23(1):17-24. doi:10.1080/10245332.2017.1333275

26. Byrd JC, Weiss RB. Recurrent granulocytic sarcoma. An unusual variation of acute myelogenous leukemia associated with 8;21 chromosomal translocation and blast expression of the neural cell adhesion molecule. *Cancer* . 1994;73(8):2107-2112. doi:10.1002/1097-0142(19940415)73:8<2107::AID-CNCR2820730815>3.0.CO;2-W

27. Bakst R, Wolden S, Yahalom J. Radiation therapy for chloroma (granulocytic sarcoma). *Int J Radiat Oncol Biol Phys* . 2012;82(5):1816-1822. doi:10.1016/j.ijrobp.2011.02.057

28. Oertel M, Elsayad K, Haverkamp U, Stelljes M, Eich HT. Radiotherapy for extramedullary leukaemic manifestation (Chloroma). *Strahlenther Onkol* . 2018;194(2):164-173. doi:10.1007/s00066-017-1236-4

29. Hall MD, Chen YJ, Schultheiss TE, Pezner RD, Stein AS, Wong JYC. Treatment outcomes for patients with chloroma receiving radiation therapy. *J Med Imaging Radiat Oncol* . 2014;58(4):523-527. doi:10.1111/1754-9485.12172

30. Cunningham I, Kohno B. 18FDG-PET/CT: 21st century approach to leukemic tumors in 124 cases. *American Journal of Hematology* . 2016;91(4):379-384. doi:10.1002/ajh.24287

31. Otoukesh S, Zhang J, Nakamura R, et al. The efficacy of venetoclax and hypomethylating agents in acute myeloid leukemia with extramedullary involvement. *Leukemia & Lymphoma* . 2020;61(8):2020-2023. doi:10.1080/10428194.2020.1742908

32. Werstein B, Dunlap J, Cascio MJ, et al. Molecular Discordance between Myeloid Sarcomas and Concurrent Bone Marrows Occurs in Actionable Genes and Is Associated with Worse Overall Survival. *The Journal of Molecular Diagnostics* . 2020;22(3):338-345. doi:10.1016/j.jmoldx.2019.11.004

33. Kashofer K, Gornicec M, Lind K, et al. Detection of prognostically relevant mutations and translocations in myeloid sarcoma by next generation sequencing. *Leukemia & Lymphoma* . 2018;59(2):501-504. doi:10.1080/10428194.2017.1339879