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Sudden Hearing Loss in a Young Patient with Chronic Myelogenous Leukemia

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ABSTRACT

Hyperleukocytosis is a typical presentation of chronic myelogenous leukemia (CML). It sometimes induces leukostasis, the symptoms of which include visual change, headache, tinnitus, dizziness, and occasional disturbance of consciousness. In the present study, a 26-year-old male patient visited a general physician, who observed marked hyperleukocytosis and referred the patient to our hospital. The patient was diagnosed with CML and treated with a tyrosine kinase inhibitor and hydroxycarbamide. On the fourth day after admission, the patient suddenly complained of left-sided hearing loss. An audiogram revealed profound left sensorineural hearing loss. Magnetic resonance imaging of the head showed no lesions in the inner ear, cerebellum, or brain stem; therefore, we diagnosed sudden hearing loss due to leukostasis. Subsequently, his hearing did not improve, despite a decrease in leukocytes. The pathophysiology of leukocytosis involves increased leukocytes and thrombi, which induce high blood viscosity in the microcirculation. Leukostasis-related infarction and hemorrhage can lead to occlusion of the labyrinthine artery, causing deafness. Physicians should be aware that deafness can develop when diagnosing marked leukocytosis because such deafness is irreversible in most cases.

Key words: *Chronic myelogenous leukemia*, *Hyperleukocytosis*, *Sudden hearing loss*, *Adolescents and young adults*

INTRODUCTION

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder in which the granulocyte count increases. Although nearly 50% of patients with CML are asymptomatic, some complain of fatigue, malaise, weight loss, and anemia at presentation. Hyperleukocytosis is variably defined as a total leukemic cell count greater than 100×10^9/L. It can sometimes induce leukostasis, the symptoms of which include visual changes, headache, tinnitus, dizziness, and altered level of consciousness. Symptoms of leukostasis are sometimes seen in acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL)[1,3)], but are rare in the chronic phase CML [1,4)]. In the present report, we describe a case of CML in which sudden hearing loss and vertigo due to hyperleukocytosis were present at diagnosis.

CASE

A 26-year-old man presented with vertigo and nausea in early March in 202X. He visited the hospital at the end of March. The doctor checked the laboratory reports and found marked hyperleukocytosis. The doctor immediately referred the patient to our hospital for a detailed examination. Physical examination revealed that the edge of the spleen was palpable 8 cm below the navel. The gaze-nystagmus test revealed right horizontal beating in the right direction and slight vertical left beating in the upward and left directions, respectively (Figure 1a). The non-gaze-nystagmus test revealed right horizontal fixed beating in all directions (Figure 1b). No other abnormal neurological findings were observed. The patient's white blood cell (WBC) count was markedly increased with various stages of granulocyte maturation. Table 1 shows laboratory data at the first visit. Bone marrow examination revealed hypercellular marrow with marked myeloid lineage proliferation (Figure 2). No cellular dysplasia was observed, and myeloblasts accounted for fewer than 5% of the marrow cells. Chromosomal G-band metaphase analysis revealed t(9;22)(q34;q11.2) but no additional chromosomal abnormalities. BCR-ABL1 mRNA showed a high copy number

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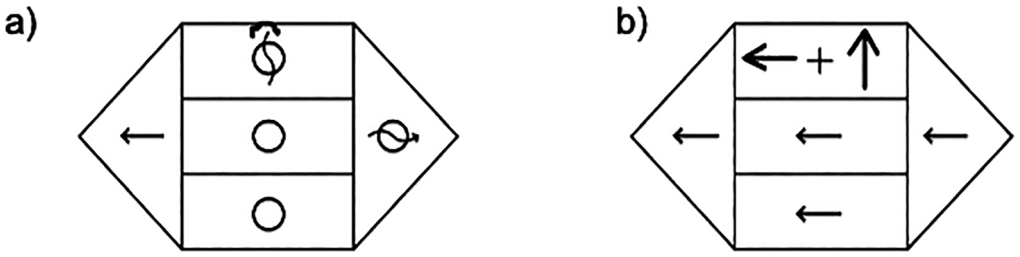

Figure 1 Nystagmus pattern. (a) Gaze-nystagmus test reveals right horizontal beating in the right direction and slight vertical left beating in the upward and left directions, respectively. (b) Non-gaze-nystagmus test reveals right horizontal direction fixed beating in all directions. Slight upbeating is also noted in the upward direction.

Table 1 Laboratory data at the first visit.

WBC	627.37 × 10^3 /μl	PT	15.3 sec	Na	142 mEq/l
myel-blast	1 %	APTT	39.9 sec	K	3.9 mEq/l
promyel.	8.5 %	Fib	313.2 mg/dl	Cl	103 mEq/l
myel.	21.5 %	FDP	< 2.5 μg/ml	Ca	10.1 mg/dl
metamyel.	17 %	TP	7.5 g/dl	BUN	14.4 mg/dl
stab.	16 %	Alb	4.4 g/dl	Cr.	1.25 mg/dl
seg.	27.5 %	T-bil	0.5 mg/dl	e-GFR	60 ml/min.
lym.	0.5 %	D-bil	0.2 mg/dl	UA	8.3 mg/ml
mo.	3.5 %	AST	48 U/ml	CRP	1.73 mg/ml
eo.	2 %	ALT	36 U/ml	Glu	66 mg/ml
baso.	2.5 %	LDH	1712 U/ml	Ferritin	297.1 ng/ml
Eryth	1 %	ALP(IFCC)	128 U/ml	Fe	110 μg/dl
RBC	244 × 10^4 /μl	GGTP	126 U/ml	BCR-ABL(IS)	128.669 %
Hb	8.2 g/dl	CK	38 U/ml	BCR	871901
Ht	23.7 %	AMY	70 U/ml	ABL1	758944
Plt	226 × 10^3 /μl				
Reti	5.83 %				

variation (Table 1). Head magnetic resonance imaging (MRI) revealed several hematomas in the subcortical regions of the anterior and occipital lobes. However, no lesions were observed in the inner ear, cerebellum, or brainstem (Figure 3a, b). Therefore, the patient was diagnosed with chronic phase CML. We administered 100 mg of dasatinib and hydroxycarbamide. However, we tried leukapheresis but had to stop due to severe vomiting and vertigo. On the fourth day after admission, the patient suddenly complained of left-sided hearing loss. The tympanic membrane was normal. An audiogram showed severe sensorineural hearing loss in the left ear (> 90 dB hearing level [HL] by 4-tone average) and normal hearing in the right ear (7.5 dB HL by 4-tone average; Figure 4). We diagnosed sudden hearing loss and immediately began treatment with prednisolone (60 mg per day for 2 days, followed by tapering off for 10 days). One month after dasatinib administration, the WBC counts were within the normal range, and immature cells in the peripheral blood disappeared. However, the patient's hearing did not improve after 3 months.

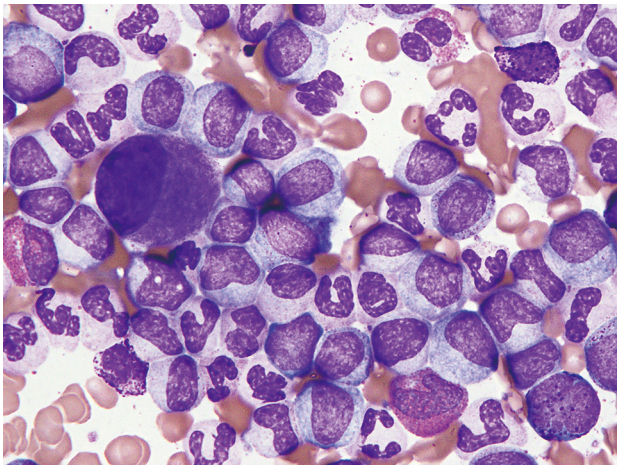

Figure 2 Bone marrow aspiration reveals hypercellular bone marrow and a marked increase in myeloid cells at various stages of maturation. Excess myeloblast proliferation is not noted. Smaller megakaryocytes than normal, with hypolobated nuclei, are also observed.

DISCUSSION

Hyperleukocytosis is typically observed in hematological malignancies such as AML, ALL, and CML. It is associated with an increased risk of early mortality, especially in AML and ALL. Hyperleukocytosis induces leukostasis, which is a medical emergency. Symptoms of leukostasis are usually respiratory (dyspnea, tachycardia, and hypoxia) and neurological (visual change, headache, dizziness, tinnitus, and altered level of consciousness). In CML, cell concentrations greater than 300 × 109/L tend to produce such complications. Such manifestations are reversed by cytoreduction, and poor outcomes are less common than in AML[8]. In leukosta-

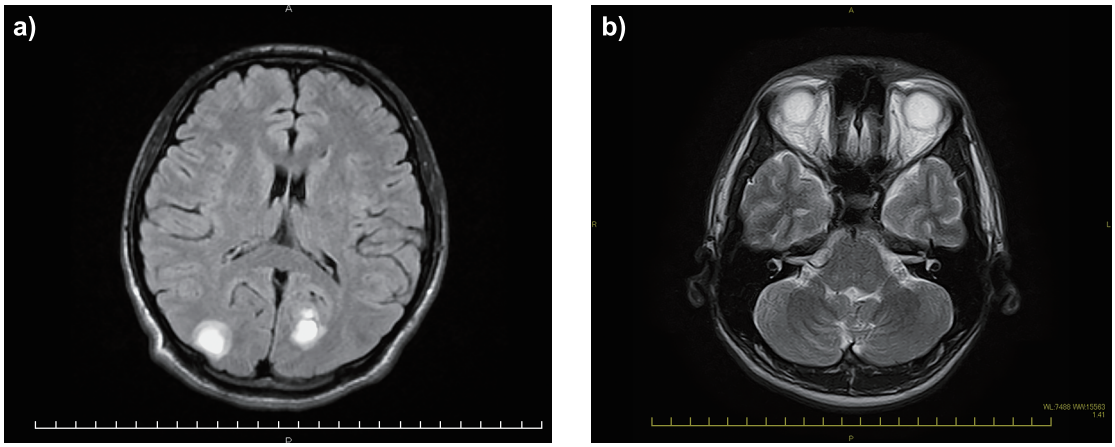

Figure 3 Head magnetic resonance imaging (MRI). (a) There are several high-intensity lesions in the occipital lobes in the T2/flair image. The lesions suggest hematomas. (b) No abnormal lesions are observed in the inner ear, cerebellum, or brain stem on the T2-weighted image.

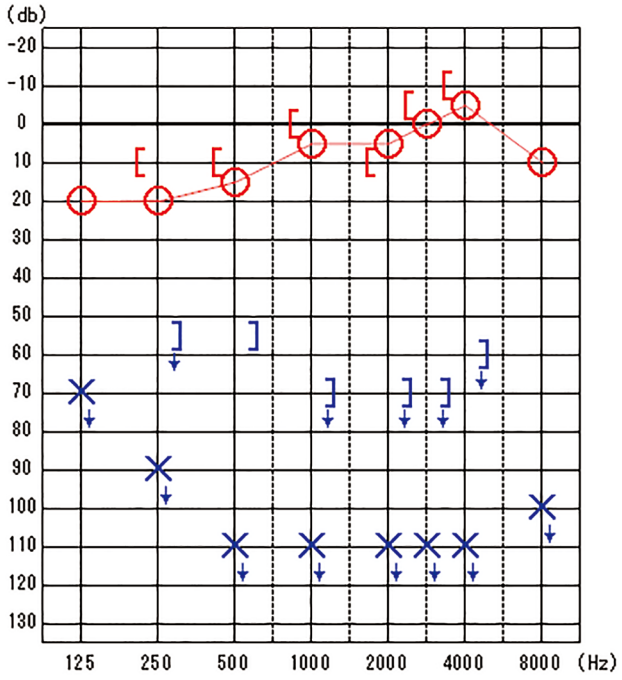

Figure 4 Audiogram at the first examination. An audiogram shows profound sensorineural hearing loss in the left ear (> 90 dB hearing level [HL] by 4-tone average) and normal hearing in the right ear (7.5 dB HL by 4-tone average).

sis, extreme proliferation of immature cells, which are poorly deformable, causes a high fractional volume of leukocytes and increased blood viscosity. This decreases microvascular blood flow and causes occlusion of the labyrinthine artery, leading to deafness, tissue infarction, or hemorrhage[4]. In the present patient, the MRI findings showed several lesions in the anterior and occipital lobes, which suggested subcortical hemorrhage associated with CML-related leukocytosis. There were no intracranial space occupying lesions on MRI; therefore, they were unlikely to be responsible for the deafness. Therefore, we reasoned that occlusion of the labyrinthine artery, which supplies the cochlea and vestibule, may have caused the deafness. Unfortunately, most patients have irreversible deafness despite rapid cytoreduction, according to previous reports[1,4,9,10,13].

The clinical characteristics and management of CML differ between adults and adolescents/young adults (AYAs)[2], who tend to have more aggressive clinical characteristics than adults[5,12]. Sakurai et al. reported that AYAs presented with higher WBC counts than adults in a Japanese cohort[14]. Splenomegaly, a poor prognostic factor in CML, is more frequent in AYAs than in adults[12]. Furthermore, response rates to tyrosine kinase inhibitors (TKIs) and event-free survival are inferior in AYA patients[5,12]. This is because the ASXL1 mutation that causes non-response to TKIs[3,7] is more frequent in pediatric and young adult patients than in adults[6], and because these age groups have poorer adherence to therapy[11] and less access to healthcare and medical insurance[12]. In addition to dealing with persistent deafness, our patient must undergo long-term treatment for CML, necessitating medical and sociological support.

In conclusion, we report a case of sudden hearing loss caused by CML-associated leukocytosis. In most cases, deafness is irreversible. Therefore, physicians should be aware that deafness can develop when diagnosing marked leukocytosis.

Conflict of interest

We have no conflicts of interest.

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REFERENCES

1. Acar, G.O., Acioğlu, E., Enver, O., Ar, C. and Sahin, S. 2007. Unilateral sudden hearing loss as the first sign of chronic myeloid leukemia. Eur. Arch. Otorhinolaryngol. 264(12): 1513–1516.
2. Athale, U., Hijiya, N., Patterson, B.C., et al. 2019. Management of chronic myeloid leukemia in children and adolescents: recommendations from the Children's Oncology Group CML Working Group. Pediatr. Blood Cancer. 66(9): e27827.
3. Baer, C.R., Kern, W., Haferlach, C. and Haferlach, T. 2017. Mutation screening at diagnosis reveals a high

frequency of ASXL1 mutations in CML patients who fail to achieve molecular remission criteria after one year of TKI treatment. Blood. 130; Suppl 1: 1585–1596.
4. Cass, N.D., Gubbels, S.P. and Portnuff, C.D.F. 2018. Sudden bilateral hearing loss, tinnitus, and vertigo as presenting symptoms of chronic myeloid leukemia. Ann. Otol. Rhinol. Laryngol. 127(10): 731–734.
5. Castagnetti, F., Gugliotta, G., Baccarani, M., et al. 2015. Differences among young adults, adults, and elderly chronic myeloid leukemia patients. Ann. Oncol. 26(1): 185–192.
6. Ernst, T., Busch, M., Rinke, J., et al. 2018. Frequent ASXL1 mutations in children and young adults with chronic myeloid leukemia. Leukemia. 32(9): 2046–2049.
7. Imatiki, O., Ishida, T., Kubo, H., et al. 2020. A case of tyrosine kinase inhibitor resistant chronic myeloid leukemia, chronic phase with ASXL1 mutation. Case Rep. Oncol. 13(1): 449–455.
8. Kaushansky, K., Prchal, J.T., Burns, L.J., Lichtman, M.A., Levi, M. and Linch, D.C. Williams Hematology 10th ed. New York: McGraw-Hill; 2021.
9. Kayhan, F.T., Kaya, H., Yazici, Z.M., Göksoy, H., Biskin, S. and Erdur, Ö. 2010. Bilateral sudden sensorineural hearing loss as a first sign of chronic myeloid leukemia. J. Int. Adv. Otol. 6: 288–290.
10. Lossos, I.S., Berger, S., Gomori, M., Leibovich, G. and Matzner Y. 1996. Hearing loss and leukocytosis. Postgrad. Med. J. 72(845): 183–185.
11. Marin, D., Bazeos, A., Mahon, F.X., et al. 2010. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. J. Clin. Oncol. 28(14): 2381–2388.
12. Pemmaraju, N., Kantarjian, H., Shan, J., et al. 2012. Analysis of outcomes in adolescents and young adults with chronic myelogenous leukemia treated with upfront tyrosine kinase inhibitor therapy. Haematologica. 97(7): 1029–1035.
13. Ruggiero, A., Rizzo, D., Amato, M. and Riccardi, R. 2016. Management of hyperleukocytosis. Curr. Treat. Options Oncol. 17(2): 7.
14. Sakurai, M., Mori, T., Karigane, D., et al. 2015. Unfavorable outcome of chronic myelogenous leukemia in adolescent and young adults treated with tyrosine kinase inhibitors. Int. J. Hematol. 102(3): 342–348.