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*by Paulus Budiono Notopuro*

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# Sensorineural Hearing Loss in Juvenile CML: A Rare Case Report in Surabaya, Indonesia

Ihda Kartika Syamsuddin<sup>1</sup>, Paulus Budiono Notopuro<sup>2</sup>

<sup>1</sup>Department of Clinical Pathology, Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia; <sup>2</sup>Department of Clinical Pathology, Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Indonesia

Correspondence: Paulus Budiono Notopuro, Email paulus-b-n@fk.unair.ac.id

**Abstract:** Chronic myeloid leukemia (CML) is a type of myeloproliferative neoplasm (MPN) in which granulocytes are the primary proliferating cells. CML in pediatric patients (juvenile CML) is an uncommon MPN, representing 2–3% of children newly diagnosed with leukemia. Sensorineural hearing loss that progresses rapidly is an uncommon early sign of a hematological disorder in patients with CML. This article presents the case of a 10-year-old patient with complaints of bilateral hearing loss for 2 weeks. Pure-tone audiometry indicated sensorineural hearing loss of the left ear and mixed hearing loss of the right ear. After an in-depth evaluation of a bone marrow smear and positivity for the BCR-ABL fusion gene, it was concluded that the patient had chronic-phase juvenile CML. However, hearing loss recovery after hydroxyurea therapy could not be observed because the patient died after suffering an uncontrolled seizure on day 14 of hospitalization.

**Keywords:** sensorineural hearing loss, chronic myeloid leukemia, BCR-ABL, pediatric, cancer

## Introduction

Juvenile chronic myeloid leukemia (CML) is an uncommon myeloproliferative neoplasm (MPN) that represents 2–3% of newly diagnosed leukemias in children. Around 95% of children with CML are in the chronic phase (CML-CP).<sup>1,4,11</sup> CML is a type of MPN in which granulocytes are the primary proliferating cells. This proliferation causes neoplastic cells of the myeloid lineage to infiltrate the blood, bone marrow, spleen, and liver. Most patients are diagnosed in the chronic phase (CP), which usually has an insidious onset. Nearly 50% of newly diagnosed cases are asymptomatic and are discovered when elevated white blood cell (WBC) count or splenomegaly is observed during a regular medical examination.<sup>2</sup>

Leukemia patients with otologic manifestations are seen in 15–40% of cases.<sup>3,5,8</sup> Unilateral or bilateral sensorineural hearing loss (SNHL), tinnitus, dizziness, and facial nerve paresis are among the symptoms.<sup>3,18</sup> Hearing loss has been linked to acute leukemias; however, it is uncommon in patients with CML,<sup>3,5,6,17,18,20</sup> especially in childhood;<sup>15</sup> it may develop later in the disease course than in acute leukemia.<sup>5</sup> This rarity is supported by a study that reported ocular symptoms and priapism as the most common leukostasis symptoms in juvenile CML.<sup>20</sup> Previous reports have demonstrated SNHL in adult patients with CML (aged 21–100 years),<sup>3,5–10,21–23</sup> and only a few cases of SNHL in juvenile CML have been reported.<sup>16–20</sup>

## Case Report

A 10-year-old male reported to a pediatric outpatient facility with a 3-month history of generalized weakness, stomach pain, and a 2-week history of bilateral hearing loss. There was no ear pain, no exposure to loud noise, no ear damage, no history of foreign bodies in the ear, and no facial pain. Furthermore, there was no history indicative of nasal symptoms, and there was no exposure to ionizing irradiation.

The examination revealed a conscious and responsive pediatric patient who was pale, anicteric, acyanosed, and not dehydrated. All of the vital signs were within normal ranges. The liver was not palpable; however, the spleen was palpable (Schuffner 5).

Laboratory data showed hemoglobin 7.3 g/dL, hematocrit 18.6%, WBC count  $780.72 \times 10^9/L$  ( $780.720 \text{ cells/mm}^3$ ), and platelet count  $457 \times 10^9/L$ . CML-CP was observed on the peripheral blood film, with myeloblasts accounting for 7% of the total WBCs. Furthermore, thrombocytosis was present and the bone marrow aspiration results were compatible with a diagnosis of CML-CP (Figure 1). The marrow was found to be hypercellular with a 45:1 myeloid: erythroid ratio, and erythropoiesis was considerably decreased. However, myelopoiesis was significantly increased, and there was sequential maturation throughout the myeloid series, with 8% myeloblasts. The result of a qualitative study of chromosomal breakpoints p210 BCR-ABL was positive.

Pure-tone audiometry (PTA) indicated moderate-to-severe SNHL of the left ear and severe mixed hearing loss of the right ear during examination by an otorhinolaryngologist (Figure 2). Hearing aids are considered when hearing loss is not corrected after 3 months.

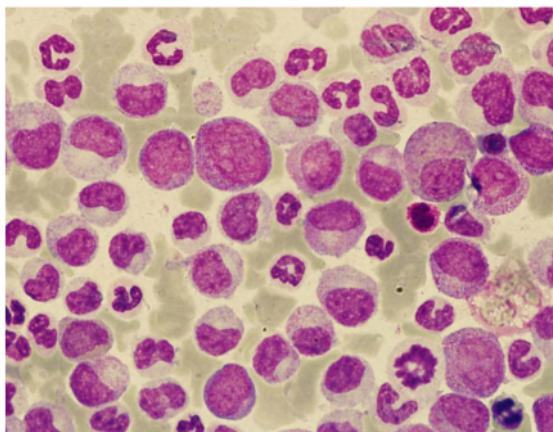
Because of hyperleukocytosis, the patient was admitted to the pediatric ward. After intravenous fluid hydration, hydroxyurea therapy (20 mg/kg/day) was administered. However, the recovery of hearing impairment could not be observed because the patient died immediately after an uncontrolled seizure on day 14 of hospitalization.

## Discussion

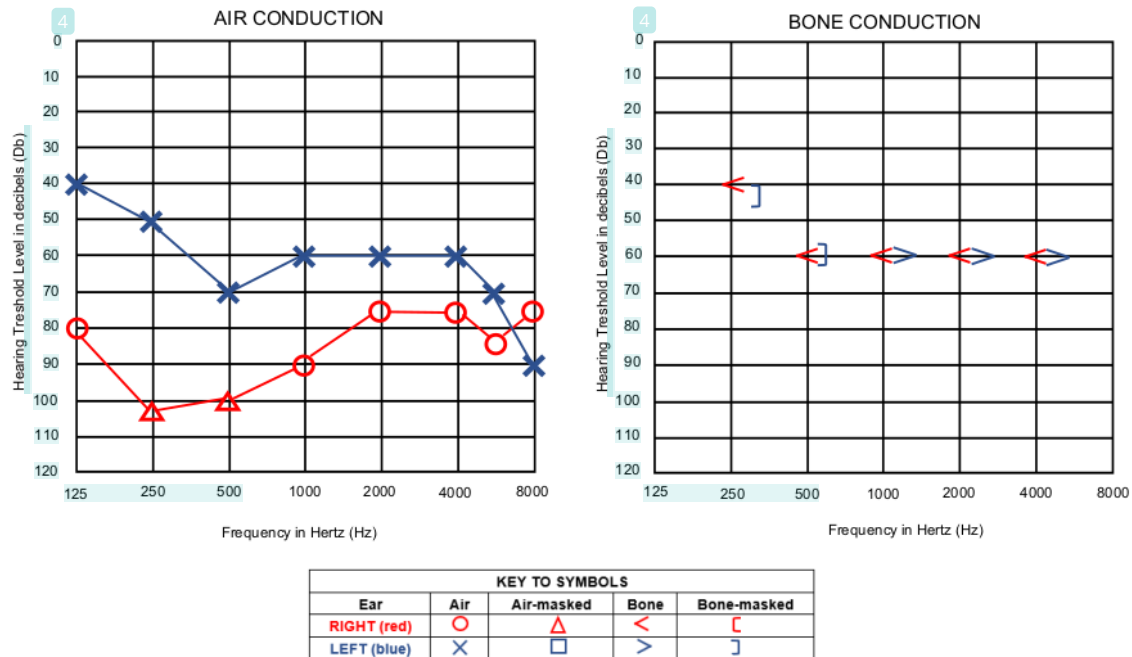
Hearing loss as a primary symptom of CML is uncommon.<sup>3,5,6,17,18,20</sup> Hearing loss in CML could be unilateral or bilateral SNHL, or it may begin as unilateral then progress to bilateral.<sup>18</sup> There have been only a few cases of juvenile CML in which SNHL was reported in previous studies.<sup>16–20</sup> Furthermore, acute myeloid leukemia (AML) causes more pronounced leukostasis than CML, acute lymphoblastic leukemia (ALL), and chronic lymphocytic leukemia (CLL) because blasts generally withstand deformation better than well-differentiated leukocytes. Furthermore, myeloblasts (the dominating cells in AML) are bigger than lymphoblasts (the dominating cells in ALL) and lymphocytes (the dominating cells in CLL).<sup>3,20</sup>

The multifactorial pathogenesis of SNHL involves leukostasis, leukemic infiltration of the cochlea, hyperviscosity syndrome, thrombohemorrhagic complications, and infections.<sup>5,6,8,10,17,22</sup> According to Kayode et al, hyperleukocytosis with leukostasis in the labyrinthine artery and other minor arteries of the vertebrobasilar area causes bilateral deafness in CML patients.<sup>5</sup>

Hyperleukocytosis is a condition in which the WBC count is  $\geq 100 \times 10^9/L$ .<sup>25</sup> Patients with a WBC count higher than  $300 \times 10^9/L$  and a spleen size larger than 10 cm are more likely to develop leukostasis complications.<sup>7,19,20</sup> A previous



**Figure 1** Bone marrow examination using Wright's stain (1000 $\times$  magnification) showing hypercellular marrow with 8% myeloblasts.



**Figure 2** Pure-tone audiometry results.

study on leukostasis in children and adolescents with CML reported a significantly higher median WBC concentration in leukostasis cases than in non-leukostasis cases:  $458.5 \times 10^9/L$  versus  $151.8 \times 10^9/L$ , respectively.<sup>20</sup> The reported cases of SNHL as an initial manifestation in juvenile CML have also revealed high WBC concentrations of  $167\text{--}733 \times 10^9/L$ .<sup>17–19</sup> In our case, the patient had an extremely high WBC count of  $780.72 \times 10^9/L$  and splenomegaly Schuffner 5. These data suggest that, among the multifactorial pathogenesis of CML,<sup>5,6,8,10,17,22</sup> the most notable in our case was hyperleukocytosis.

Hyperleukocytosis can cause leukostasis and partial obstruction of the small-calibre labyrinthine artery (terminal branch of the basilar artery) that feeds the cochlea and vestibular system.<sup>3,6,7,18,23,24</sup> The theory of leukemic-cell adhesion to endothelial cells explains the mechanism of leukostasis. Leukemic cells may secrete cytokines (TNF- $\alpha$  and IL-1) that activate endothelial cells to express specific adhesion receptors (selectins and VCAM-1). This enables leukemic cell adhesion and leads to leukostasis.<sup>25</sup> In addition, the high oxygen consumption of those leukemic cells competes for this scarce resource in the microcirculation, worsening the local tissue hypoxia and ischemia and resulting in tissue infarction. Furthermore, this temporary stasis may induce irreparable inner ear neuronal and vascular damage.<sup>3,6,23</sup> Brief periods of ischemia may cause hearing loss due to the lack of redundant blood supply to the cochlea.<sup>12</sup> The inner ear ischemia caused by leukostasis may lead to irreversible hearing loss.<sup>3,6–9,18,20,22</sup> A case series of six adult (26–56 years old) CML patients with sudden onset of hearing and visual loss reported persistent hearing loss in five patients (one patient was lost of follow-up) despite receiving cytoreduction therapy.<sup>6</sup>

Some reported cases of SNHL in CML have shown hearing improvement after the patients received a combination of leukapheresis and chemotherapy.<sup>8,18,22,23</sup> This improvement indicates a reversible hearing loss and an association with hyperviscosity syndrome.<sup>18,23</sup>

Leukapheresis is an invasive technique that has a rapid cytoreductive impact. It is promptly considered when leukostasis symptoms like respiratory distress, priapism, severe retinopathy/papilledema, or central nervous system (CNS) symptoms suggestive of ischemic or hemorrhagic stroke are reported.<sup>1</sup> However, leukapheresis was not routinely

performed as a primary procedure in our facility. In other reports, effective leukoreduction did not improve mortality and, in some studies, hearing recovery varied following disease management.<sup>6,9,15,17</sup>

Cytoreduction and chemotherapy may lead to improvement in certain cases of SNHL in CML. In our case, the recovery of hearing impairment was not observed because the patient died after a seizure on day 14 of hospitalization.

Seizures in CML patients have been associated with extramedullary blast crisis that affects the CNS. Infiltration of the CNS by blast cells is highly uncommon.<sup>14</sup> CNS blast crisis is often associated with meningitis- or encephalitis-related clinical and radiological characteristics, including headache, ataxia, aphasia, seizures, and meningismus, and localized neurological symptoms and signs like.<sup>13,21</sup> Myeloid or lymphoid blasts are detected in the cerebrospinal fluid (CSF) and, in certain cases, molecular testing of the CSF reveals typical BCR-ABL oncogenes.<sup>13</sup> Unfortunately, in our patient, the presence of myeloblasts and the BCR-ABL oncogene in the CSF had not been established.

## Conclusion

SNHL as the earliest sign of CML is relatively uncommon. SNHL was diagnosed when our patient's WBC count increased to  $780.71 \times 10^9/L$ , which was greater than  $300 \times 10^9/L$ , indicating that hyperleukocytosis was a possible cause. Therefore, rapid and accurate diagnosis and treatment of CML is needed to minimize the sequelae and complications of hyperleukocytosis, especially in patients with SNHL.

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## Disclosure

The authors declare that they have no conflicts of interest.

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