Secondary pseudotumor cerebri syndrome in a child with chronic myeloid leukemia: Report of a case and review of previous cases

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June 11, 2022

Abstract

Chronic myeloid leukemia (CML) is a rare disease in children and adolescents and clinical presentations are variable. Symptoms are often attributable to anemia and splenomegaly. We present a case of secondary pseudotumor cerebri syndrome as the presenting feature in a pediatric patient with CML and a review of previous cases. Through these cases, we discuss this rare but important manifestation of chronic myeloid leukemia in pediatric CML, its cause and management. We conclude that pseudotumor cerebri is an important differential diagnosis in these patients as it may result in permanent visual loss if not addressed appropriately.

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by uncontrolled proliferation of myeloid cells and defined by a chromosomal translocation resulting in the Philadelphia chromosome containing the BCR-ABL1 fusion gene.¹

CML is a rare disease in children and adolescents accounting for approximately 2-3% of newly diagnosed leukemia’s and often debuting in the chronic phase.²

Clinical presentations for children and adolescents are highly variable from asymptomatic to more severe symptoms attributable to anemia and splenomegaly. A subset of patients may present with symptoms attributable to hyperviscosity.¹,³ Children and adolescents are reported to have more pronounced clinical features such as a relatively larger spleen size, and higher white blood cell counts at the time of diagnosis as compared to adults.¹,³

We present a pediatric patient with hyperleukocytosis and symptoms possibly attributable to hyperviscosity syndrome.⁴ The diagnostic work-up revealed her to have CML and further evaluation of her ophthalmological and radiological signs confirmed a diagnosis of secondary pseudotumor cerebri syndrome.

Through this case and a review of previous cases with pseudotumor cerebri syndrome as the presenting feature in patients with CML we discuss this rare but important manifestation of pediatric CML, its cause and management.

CASE REPORT

A previously healthy 13-year-old girl presented at our emergency room with severe headache, dysarthria and paresthesia of the right hand. Prior to these symptoms, she had experienced pulse synchronous tinnitus, extremity pains and missed periods for the last four months. Neurological examination was normal. Her blood pressure was 106-97/60-56 mmHg, her pulse was 90 beats per minute, and she was afebrile. Physical evaluation revealed palpable splenomegaly.
Her blood count revealed an elevated white blood cell count (WBC) of $416 \times 10^9/L$, thrombocytosis at $522 \times 10^9/L$ and anemia $4.7 \text{ mmol/L}$. Because of her symptoms, an elevated lactate dehydrogenase $1170 \text{ U/L}$ and elevated uric acid of $0.41 \text{ mmol/L}$ she was started on hyperhydration by means of intravenous fluids $3000 \text{ ml per square meter per day}$ and cytoreductive treatment with hydroxurea. Peripheral blood and bone marrow evaluation were consistent with chronic myeloid leukemia in the chronic phase. Cytogenetics confirmed the Philadelphia chromosome and she was started on imatinib mesylate.

At the time of diagnosis, visual acuity was normal in both eyes. Both pupils were equal sizes and with no relative afferent pupillary defect (RAPD). A dilated fundus examination revealed bilateral papilledema (Fig. 1). There were no sign of vitritis, retinitis or choroiditis. The optical coherence tomography of both eyes showed increased retinal nerve fiber layer (RNFL) thickness with no detectable macular edema.

Her headaches worsened and she complained of horizontal diplopia. Repeated ophthalmological evaluation revealed slight sixth cranial nerve palsy. Visual fields (by automated perimetry), showed enlarged blind spot on the left eye. Visual acuity remained normal.

MRI revealed partial empty sella, bilateral papilledema, bilateral transverse venous sinus stenosis and flattening of posterior globes. Fig. 1 depicts ophthalmological and neuroradiological findings.

Oral acetazolamide therapy was initiated for the presumptive diagnosis of idiopathic intracranial hypertension (IIH) and the patient underwent a lumbar puncture demonstrating an elevated cerebrospinal fluid (CSF) pressure at $290 \text{ mm H}_2\text{O}$. The CSF composition was normal and showed negative cytology.

Her symptoms considerably improved. Acetazolamide was weaned after normalization of ophthalmological manifestations. She has recovered without sequelae and her CML has shown continuous complete hematological and major molecular response after 6 month of treatment.$^{2,5}$

A literature review yielded additional six cases with an association between CML and pseudotumor cerebri in children$^6$ and adults.$^7-11$

**DISCUSSION**

Chronic myeloid leukemia is a rare disease in children and adolescents and clinical presentations are highly variable.$^1,3$ Pseudotumor cerebri is equally a rare syndrome that most commonly presents with headache, vision changes, and papilledema.$^12$

The diagnosis of pseudotumor cerebri is established by demonstrating an elevated lumbar puncture opening pressure $\geq 280 \text{ mm CSF}$ in children with normal CSF composition and neuroimaging study that shows no other etiology for intracranial hypertension.$^{13}$ Common radiological features are empty sella, flattening of the posterior sclera, increased perioptic subarachnoid spaces, with or without optic nerve tortuosity, transverse sinus stenosis and optic nerve head protrusion.$^{13,14}$

In children, the condition can be either primary or secondary to medications or associated medical conditions.$^{12,14}$

Secondary pseudotumor cerebri in pediatric oncology and hematology is uncommon.$^{15}$ If it occurs, it is often associated with medications, most commonly corticosteroid and all-trans-retinoic acid in the treatment of acute promyelocytic leukemia.$^{16}$ The clinical hallmarks of pseudotumor cerebri may also occur with anemia, stress, as a side effect to chemotherapy or due to neurological complications such as metastatic disease, CNS involvement, intracranial hemorrhage, venous sinus thrombosis or infections.$^{15}$ In some cases, CML patients may present with ophthalmological manifestations either from direct or indirect infiltration of neoplastic cells or from secondary causes.$^{17}$ Accordingly, timely multidisciplinary evaluation involving neuroimaging and ophthalmological evaluation are warranted in these children and pseudotumor cerebri is an important differential diagnosis as it may result in permanent visual loss if not addressed appropriately.$^{15,18}$

The association of pseudotumor cerebri and chronic myeloid leukemia is rare and to our knowledge, only one previous case has been reported in a child.$^6$ Only six previous cases have been reported in total.$^6-11$ All
six cases had headaches and most had visual disturbances. Reported cases, including the present case, were relatively young individuals with a median age of 19 years, range 13-32 years. WBC at presentation ranged between 142–730 x 10^9/L (median 416 x 10^9/L). All patients had lumbar puncture opening pressure [?] 270 mm H2O (range 270 to 650 mm H2O, median of 400 mm H2O). In five cases treatment with acetazolamide was initiated.6-8,10,11 All cases reported resolve or improvement of symptoms and/or ophthalmological findings. Tabel 1 shows a summary of clinical, radiological and ophthalmological characteristics of the current and previous cases.

The mechanisms leading to increased intracranial pressure (ICP) in pediatric IIH are not entirely clear, but it is suggested that alterations in CSF dynamics cause increased intracranial pressure.12,14 Cases of increased ICP in CML may be caused by reduced absorption of CSF into the patent sinuses due to increased resistance to outflow secondary to hyperleukocytosis.7,9 Accordingly, increased viscosity may lead to increased resistance to flow of CSF from the arachnoid villi into the sinuses as proposed earlier.7,9,11 Leukopheresis is an effective treatment modality, especially in cases of hyperviscosity syndrome in patients with CML when rapid cytoreduction is needed. However, the decision should be based on symptoms of leucostasis and risk of end organ injury rather than the presenting WBC count.2,5 Leukopheresis may have been a viable option in the present case. However, the symptoms resolved hyperhydration, hydroxyurea, imatinib and acetozolamide.

The current case and literature review establishes pseudotumor cerebri as an important differential diagnosis in the evaluation of patients with CML and clinical signs of increased intracranial pressure in a pediatric context.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

INFORMED CONSENT

Informed consent was obtained from the legal guardians of the patients prior to publication. Both the patient and the legal guardians had the opportunity to comment on the article prior to publication.

REFERENCES


**FIGURES AND TABLES**
FIGURE 1 Ophtalmological and neuroradiological findings. (A+B) Fundus photography showing bilateral papilledema at the initial presentation of the right and left eye, respectively. (C+D) Optical coherence tomography of both eyes showed increased retinal nerve fiber layer (RNFL) thickness of the right and left eye, respectively. (E) Contrast enhanced venography showing bilateral transverse venous sinus stenosis. (F) Axial T2 weighted image showing optic nerve head protrusion. (G) Axial T2 weighted image showing increased subarachnoid space around optic nerves (only visible on the right side on this image). (H) Sagittal T1 weighted image showing posterior globe flattening. (I) Sagittal Fluid attenuated inversion recovery (FLAIR) showing partial empty sella.

TABLE 1 Review of previous cases with pseudotumor cerebri syndrome as the presenting feature in patients with chronic myeloid leukemia

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Age, Sex</th>
<th>WBC $10^9$/L</th>
<th>ICP mm H$_2$O</th>
<th>Symptoms</th>
<th>Ocular findings</th>
<th>PTC treatment</th>
<th>CML treatment</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Falardeau, 2001$^{11}$</td>
<td>27, F</td>
<td>697</td>
<td>650</td>
<td>Frontal headaches; blurred vision; pulse syn-chronous tinnitus; binocular horizontal diplopia</td>
<td>Bilateral papilledema; multifocal Roth spots; mild ab-duction deficit; reduced visual acuity; enlarged blind spot</td>
<td>Acetazolamide; hydroxyurea; furosemide; prednisone</td>
<td>Hydroxyurea; leukopheresis; imatinib</td>
<td>Resolved without long-term sequelae</td>
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<tr>
<td>Pavithran, 2002$^{10}$</td>
<td>32, F</td>
<td>205</td>
<td>270</td>
<td>Headache; blurred vision;</td>
<td>Bilateral papilledema; Visual acuity 6/18; enlarged blind spots</td>
<td>Acetazolamide; hydroxyurea; diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guymer, 1993$^9$</td>
<td>19, M</td>
<td>730</td>
<td>&gt;400</td>
<td>Near collapse</td>
<td>Papilledema; dilated tortuous veins</td>
<td>No treatment</td>
<td>Hydroxyurea; leukopheresis</td>
<td>Reduction of ICP to 270 mmH$_2$O; ophthalmological manifestations improved</td>
</tr>
<tr>
<td>Author, year</td>
<td>Age, Sex</td>
<td>WBC $10^9$/L</td>
<td>ICP mm H$_2$O</td>
<td>Symptoms</td>
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<td>Gasparian*, 2021$^8$</td>
<td>18,F</td>
<td>12.9-141.9</td>
<td>210 - 350</td>
<td>Headaches; right eye pain; nausea; vomiting</td>
<td>Unilateral-bilateral papilledema; transient vision loss; peripapillary hemorrhages; retinal hemorrhages</td>
<td>Acetazolamide; Hydroxyurea; bosutinib</td>
<td></td>
<td>Resolved without long-term sequelae</td>
</tr>
<tr>
<td>Sharma, 2018$^7$</td>
<td>28,F</td>
<td>240</td>
<td>650</td>
<td>Headache; blurred vision</td>
<td>Bilateral papilledema</td>
<td>Acetazolamide; Imatinib; Dasatinib; Nilotinib; Bosutinib; Leukopheresis</td>
<td></td>
<td>Resolved</td>
</tr>
<tr>
<td>Abbott, 2008$^6$</td>
<td>15,M</td>
<td>480</td>
<td>480</td>
<td>Headache; lower back and neck pain; blurred vision; priapism</td>
<td>Bilateral papilledema; Visual acuity 20/30</td>
<td>Acetazolamide; Leukopheresis; Resolved without long-term sequelae</td>
<td></td>
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<tr>
<td>Present case</td>
<td>13,F</td>
<td>416</td>
<td>290</td>
<td>Headache; dysarthria; paresthesia; pulse synchronous tinnitus; extremity pains; diplopia</td>
<td>Bilateral papilledema; slight sixth cranial nerve palsy; enlarged blind spot on the left eye</td>
<td>Acetazolamide; Hydroxyurea; hydration; imatinib</td>
<td></td>
<td>Resolved without long-term sequelae</td>
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Abbreviations: CML, chronic myeloid leukemia; ICP, intracranial pressure; PTC, pseudotumor cerebri; WBC, white blood cells. * Progression over the course of a few months with ophthalmology follow-up