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Case Report

Subarachnoid Hemorrhage in a Newly Diagnosed Chronic Myelogenous Leukemia Patient: A Diagnostic Challenge

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Abstract:
Chronic Myelogenous Leukemia (*CML) is a myeloproliferative neoplasm with a prevalence of 1 to 2 cases per 100,000 adult population. In chronic myelogenous leukemia (CML), central nervous system (CNS) manifestations are reported in the advanced phase of the disease due to leukostasis, thrombosis, bleeding, infection, and CNS infiltration. However, CNS manifestations are uncommon in the chronic phase (CP) of CML, and an alternate diagnosis should be considered for symptomatic patients. We report a ruptured aneurysmal subarachnoid hemorrhage (SAH) as an initial presentation in a previously undetected CML patient.*

Keywords*: Chronic Myelogenous Leukemia, Chronic phase, Subarachnoid Hemorrhage*
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Introduction

CML is a myeloproliferative neoplasm characterized by a clonal proliferation of mature and maturing myeloid lineage cells [1]. The prevalence of CML is 1 to 2 cases per 100,000 adult populations, and the median age at diagnosis is 55 [2].The annual mortality of CML has been reduced to 2% from 10% to 20% after the introduction of tyrosine kinase inhibitors (TKIs) [2, 3]. CML pathogenesis is primarily driven by the BCR-ABL1 chimeric gene product, which constitutively expresses tyrosine kinase activity [4]. There are no population based prevalence studies in Ethiopia, but a hospital based study found CML in 57.8% cases of leukemia [5].

CML patients usually present chronic phase of the disease which is asymptomatic in up to 90% of cases, and symptoms from splenomegaly to cell count derangements, such as anemia, thrombocytosis, or leukocytosis. The advance phases of the disease are characterized by progressive enlargement of splenic size, fever, constitutional symptoms, cytopenias, increased blast count, and treatment-refractory leukocytosis [6-8].

CNS manifestations in CML include leptomeningeal infiltration (metastasis), both ischemic and hemorrhagic cerebrovascular involvements such as coagulopathy, thrombocytopenia, vasculitis, and infectious complications [9-16].

SAH is acute bleeding into subarachnoid space. Excluding trauma, ruptured aneurysm accounts for 80% of SAHs. Intracranial aneurysm is a cerebrovascular disorder in which the vessel walls are weakened and causes dilation and ballooning. Aneurysms grow over time and portend risk of rupture. Prevalence of unruptured aneurysm in general population is 3.2%. Incidence of aneurysmal SAH is 2 to 16 per 100,000 with median age at diagnosis is 55 years [17-19].

There are several risk factors and conditions associated with increased intracranial aneurysm including hypertension, tobacco smoking, adult polycystic kidney diseases (ADPKD), connective tissue diseases, endocarditis, and cocaine use. Most aneurysms are asymptomatic and symptoms depend on the location of the aneurysm. Severe headache is the commonest manifestation of ruptured aneurysmal SAH. Brain noncontrast CT scan is a highly

sensitive imaging modality for the diagnosis of SAH and CT-angiography visualizes the aneurysm [20-22]. In the present study, we report a case of ruptured aneurysmal SAH as initial presentation in a newly diagnosed CML patient in CP.

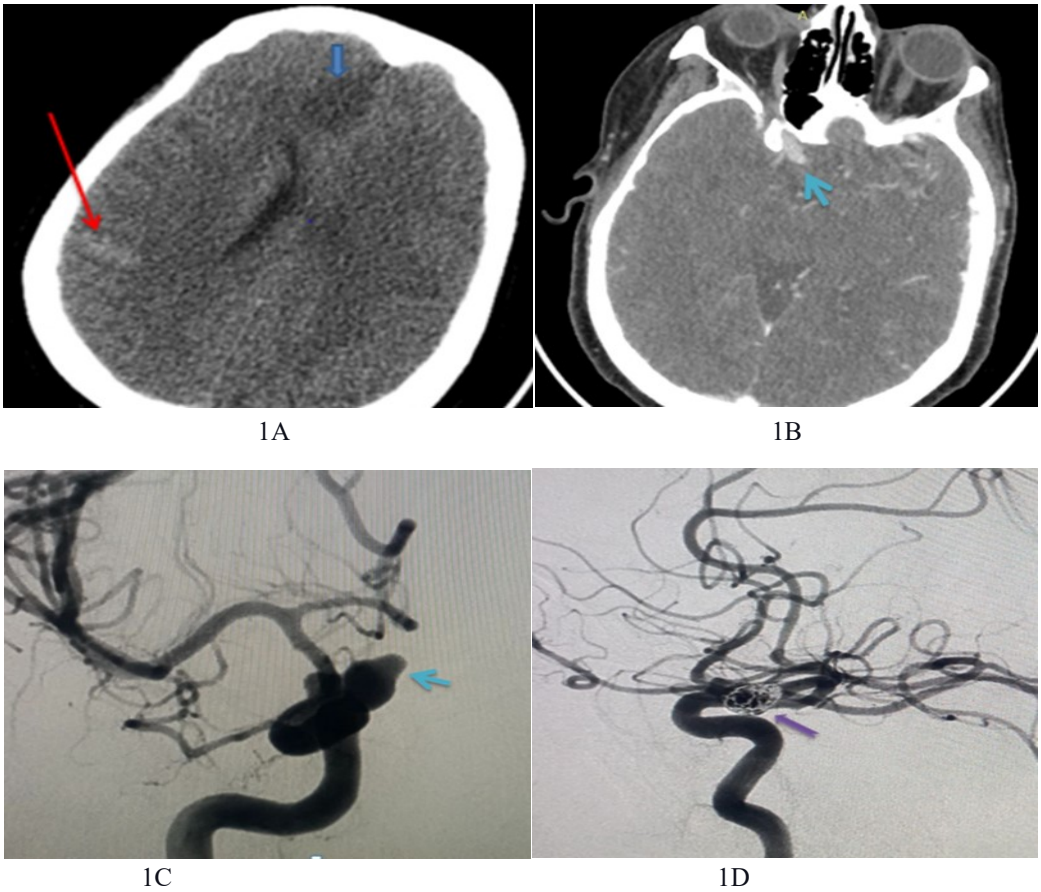
Case Presentation

A 62-year-old woman referred to our hospital in February 2023 G.C. with a gradual onset of severe unilateral throbbing type headache with associated blurring of vision and photophobia for 4 days. She did not report having nausea, vomiting, weakness of the extremities, or abnormal body movement. There was no current or previous history of trauma to the head, or bleeding tendencies from other sites. She was not known to be hypertensive, nor did she have other chronic illnesses. At presentation, she was in pain, otherwise physical examination was unremarkable.

Complete blood count showed white blood cell (WBC) count of 176,000/mm3 with 95% granulocytes, hemoglobin of 14 g/dl and platelet count of 444,000/mm3, and other blood workups including coagulation profile were normal. The peripheral blood smear revealed granulocytes at all stages of maturation and elevated platelet count.

She was admitted and started on cytoreductive therapy with hydroxyurea and a gadolinium-enhanced brain magnetic resonance imaging (MRI) with MRV was done to look for the possible causes of her CNS symptoms. The MRI was non-revealing. Subsequently, lumbar puncture was done and grossly the cerebrospinal fluid (CSF) was bloody. The CSF analysis also showed RBC count 2400x106/L and cytology showed sheets of PMNs on a hemorrhagic background.

The next day, she developed a sudden onset of left upper and lower extremity weakness and unilateral vision loss ipsilateral to the weakness. She was started on SAH management and brain Computed Tomography (CT) angiography was done, which showed a right distal ICA (clinoid-supra clinoid segment) aneurysm abutting the right optic canal with possible optic nerve compression and effaced the basal cisterns, especially the supra-sellar and para sellar regions, with iso-dense attenuation and subtle linear hyper-dense attenuation with loss of gray-white matter differentiation over the bilateral cerebral high frontal and parietal lobe region.



1A 1B

1C 1D

Figure 1: Subarachnoid hemorrhage (subacute) in the sulci shown on noncontrast Brain CT scan (red arrow).

Right ICA territory acute infarct is also depicted (blue arrow) [1A]. Right distal ICA [Clinoid-supraclinoid segment] aneurysm abutting the right optic canal with optic nerve compression shown on CT angiography [1B] and on Digital Subtraction Angiography (DSA)[1C] (green arrows). 1D shows the status after endovascular coiling of the aneurysm (notched purple arrow).

She was then referred to neurosurgical center and treated with endovascular coiling and a 21-day regimen of nimodipine. Thereafter, further workup of CML was done, with bone marrow showed hypercellular marrow with myeloid hyperplasia and 5% blasts, and fluorescence in situ hybridization (FISH) for BCR-ABL was positive. A diagnosis of BCR-ABL-positive CML in CP was made and imatinib 400 mg QD was initiated. At 2-month evaluation after initiation of imatinib, the patient had achieved complete hematologic response and her neurologic symptoms (body weakness and vision loss) were improved.

Discussion

CML causes CNS manifestations through direct and indirect mechanisms. Meningeal metastasis, the formation of intraparenchymal mass lesions, and cerebrovascular complications are commonly identified as direct mechanisms of CNS involvement. Meningeal metastasis is the commonest direct mechanism, and patients typically present with non-localizing symptoms of encephalopathy, neuropathy, radiculopathy, or myelopathy. Features of increased intracranial pressure ((ICP) can also occur from leptomeningeal involvement [10, 11]. Both ischemic and hemorrhagic cerebrovascular involvements are identified in both acute and chronic leukemias [13]. The possible indirect mechanisms that cause cerebrovascular complications in leukemias include coagulopathy directly from leukemia or its treatment, thrombocytopenia, vasculitis, or paraneoplastic complications [14, 15]. Infectious complications can cause CNS manifestations in leukemias. Infections are due to a dysregulated host immune response due to the direct leukemic effect or indirect effect of immunosuppressive therapies [9, 16].

Herein, we reported an occurrence of ruptured aneurysmal SAH in previously undetected CML in the chronic phase as an initial presenting event. To our best knowledge, there is no report of SAH as an initial manifestation of CML. Generally, the occurrence of ICH in CML is rare as compared to acute leukemias [23]. ICH is more frequently linked to the accelerated and blast crisis phases of CML. In accelerated and blast crisis phases, malignancy or treatment-related coagulopathy, thrombocytopenia, and hyperleukocytosis are the underlying processes. Although patients with CML-CP rarely experience ICH, hyperleukocytosis with leukostasis is thought to be the underlying mechanism of ICH [24, 25]. Leukocytosis can predispose to the development of hemorrhage and thrombosis. It may cause increased blood viscosity and blood stagnation in small cerebral blood vessels, which in turn raises intravascular pressure and causes rupture, resulting in ICH. Additionally, coagulopathy and thrombocytopenia may be related to it [26]. Other than hemorrhage, leukocytosis in CML can lead to development of cerebral venous thrombosis (CVT). In CP of CML, the median WBC count at diagnosis is 100,000/mm3 and leukostasis is uncommon [27].

The rarity of ICH/SAH in CP of CML should not prevent treating physicians from considering its uncommon occurrence in this phase, since delayed diagnosis and treatment of both SAH and ICH result in significant morbidity and mortality. So far, no studies have been conducted to determine whether CML increases the risk of saccular aneurysm rupture. Future reports and studies could shed some light on this question.

Conclusion

In chronic myelogenous leukemia (CML), central nervous system (CNS) manifestations are reported in the advanced phase of the disease due to leukostasis, thrombosis, bleeding, infection, and CNS infiltration. However, CNS manifestations are uncommon in the chronic phase (CP) of CML and an alternate diagnosis should be considered for symptomatic patients. Hence, physicians should thoroughly evaluate and investigate for other possible causes of CNS manifestations before attributing it to CML. Further studies are needed to determine the impact of leukostasis (due to CML or other causes) on the risk of saccular aneurysm rupture.

Ethical Approval

Written informed consent was obtained from the patient for publication of this case. Approval from the Ethics Committee of Lancet General Hospital was not required to publish this case report, but Institutional review board (IRB) wavier was obtained from Addis Ababa Health Bureau.

Author Contribution

ZD and NZ: Data collection and manuscript writing
BA and FT: Reviewing and editing the manuscript

Data Availability Statement

Data for this case report would be available upon reasonable request to the authors.

Financial support and sponsorship

None

Conflict of Interest

All authors declare no competing interests of any kind in this publication.

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