Case Report

No PL in APL: No Perception of Light in Acute Promyelocytic leukemia

Dina N. Laimon[1], Mohammed Gad[1], Basma Atef [2], Doaa H. Sakr [3], Noha Badawy [2], Raghda Ibrahim [2], Noreen M. Bayomi [2], Yasmine Shaaban [2] ✉

[1] *Mansoura University Ophthalmic Center, Faculty of Medicine, Mansoura University, Mansoura, Egypt;* [2] *Clinical Hematology Unit, Internal Medicine Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt;* [3] *Medical Oncology Unit, Internal Medicine Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt*

Abstract

Background: Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia with a favorable prognosis. Hemorrhagic manifestations in APL at presentation are usually due to thrombocytopenia, consumptive coagulopathy, and fibrinolysis. Central nervous system (CNS) hemorrhage carries a risk for CNS relapse and early death in APL patients.

Case Presentation: A 23-year-old male presented with sudden bilateral visual loss and headache. The ocular examination revealed a massive exudative retinal detachment in the right eye and bilateral dense vitreous hemorrhage. APL diagnosis was confirmed through peripheral blood and bone marrow examination, along with cytogenetic and molecular testing. The patient received 7+3 induction chemotherapy combined with All-trans-retinoic acid. After achieving complete remission, he underwent pars plana vitrectomy and silicone oil injection in the right eye. Intrathecal chemotherapy was considered for CNS prophylaxis after induction. Later, he had a medullary relapse which was managed with salvage therapy and autologous stem cell transplantation.

Conclusion: Although APL has a favorable prognosis, its management can be complicated. It may present with retinal detachment or intraocular hemorrhage. Managing intraocular and intracranial hemorrhage is challenging due to the risks of hemorrhage and coagulopathy. This complexity is further heightened by poor visual prognosis, high risk of CNS infiltration, and potential for medullary relapse.

Keywords: Acute promyelocytic leukemia, CNS hemorrhage, Retinal detachment, Retinal hemorrhage, Vitreous hemorrhage

Introduction

Acute myeloid leukemia (AML) is the most common leukemia among adults. It is characterized by clonal infiltration by blast cells in the peripheral blood and bone marrow resulting in its suppression [1]. Acute promyelocytic leukemia (APL) APL, also known as AML-M3, accounts for 10- 15% of adult AML cases [2]. In APL, The peripheral blood is typically dominated by promyelocytes and myelocytes, with some myeloblasts present [3].

Acute promyelocytic leukemia is caused by the chromosomal translocation t(15;17) in 98% of cases, which involves 2 genes: promyelocytic leukemia (PML) and retinoic acid receptor alpha (RARA). This translocation leads to the expression of the PML/RARA fusion oncoprotein, which drives leukemogenesis by deregulating retinoic acid-dependent cell differentiation pathways and enhancing the self-renewal of myeloid progenitors [4]. Additionally, PML/RARA expression is linked to defective p53 activation, leading to senescence deregulation and increased self-renewal [5].

Bleeding tendencies in APL can occur secondary to thrombocytopenia due to bone marrow failure or alterations in the hemostatic system. Laboratory abnormalities consistent with disseminated intravascular coagulation with excess fibrinolysis activation are commonly present at the initial presentation of APL [6]. Clinical manifestations range from diffuse life-threatening bleeding caused by the consumption of coagulation factors and platelets to localized venous or arterial thrombosis, necessitating proper management [7].

Previous studies have shown that hemorrhage, especially intracranial and pulmonary hemorrhages, is the leading cause of death in APL patients [8, 9]. Patients who survive intracranial hemorrhage are more likely to develop a central nervous system (CNS) relapse [10]. A previous multivariable analysis concluded that a high white blood cell count (WBC) at presentation is a risk factor for CNS relapse [11]. Immediate initiation of all-trans-retinoic acid (ATRA) once APL is suspected, along with prophylactic platelet transfusions to maintain a platelet count at or above 50 x10^9/L, is highly recommended [7]. The use of antifibrinolytic agents is recommended only for patients with retinal, intracranial, or other life-threatening hemorrhages [12].

The ophthalmic manifestations of leukemia can result from direct leukemic infiltration of the ocular tissues or indirectly from anemia, thrombocytopenia, hyperviscosity, or chemotherapy. Leukemic retinopathy is the most common ocular manifestation of this condition and can present as white-centered hemorrhages (Roth's spots), cotton-wool spots, retinal, subretinal and vitreous hemorrhages, and perivascular choroidal infiltration, which may lead to exudative retinal detachment. Other manifestations include anterior segment hemorrhage and opportunistic ocular infections [13].

Case Presentation

Herein, we report the case of a 23-year-old male who developed sudden loss of vision in both eyes as the initial presentation of APL. On November 22, 2022, he presented with sequential sudden painless visual loss in the right eye, followed by the left eye five days later. There was no history of trauma, pre-existing ocular disorders, or previous visual complaints. His only complaint was intermittent frontal and occipital headache.

On admission the patient complained of bleeding from the gums, nosebleeds, and rectal bleeding, along with symptoms of upper respiratory tract infection. He did not complain of constitutional symptoms, there was no relevant medical or family history of any ocular abnormality. On physical examination, few purpuric eruptions and areas of ecchymosis were observed. There were no organomegaly or signs of neurological insult.

On ophthalmological examination, visual acuity (VA) was no perception of light (PL) in both eyes. Bilateral subconjunctival hemorrhage was noted, and fundus examination revealed a right subtotal retinal detachment with retinal hemorrhage, along with bilateral dense vitreous hemorrhage, which was denser in the left eye, obscuring the fundus view (Figure 1). B-scan ultrasonography was performed (Figure 2). Electrophysiological tests showed markedly reduced visual evoked responses.
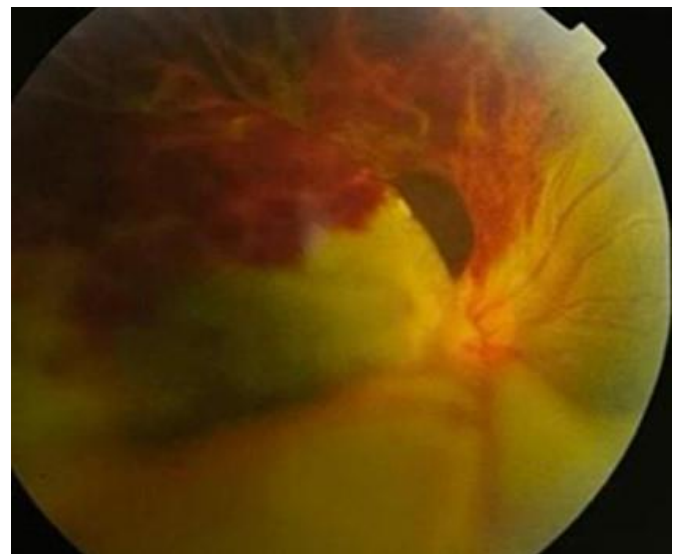

Figure 1. A fundus photo depicting a right-sided massive exudative retinal detachment with leukemic retinal infiltration, accompanied by intraretinal, epiretinal, and vitreous hemorrhages

A computed tomography scan of the orbit and brain showed hyperdensity at the vitreous bilaterally, likely indicative of vitreous hemorrhage (Figure 3). Additionally, there was a left occipital hyperdense lesion with surrounding edema at the posterior horn of the lateral ventricle, measuring 15.76 x 15.53 mm, likely a parenchymal hematoma (Figure 4).
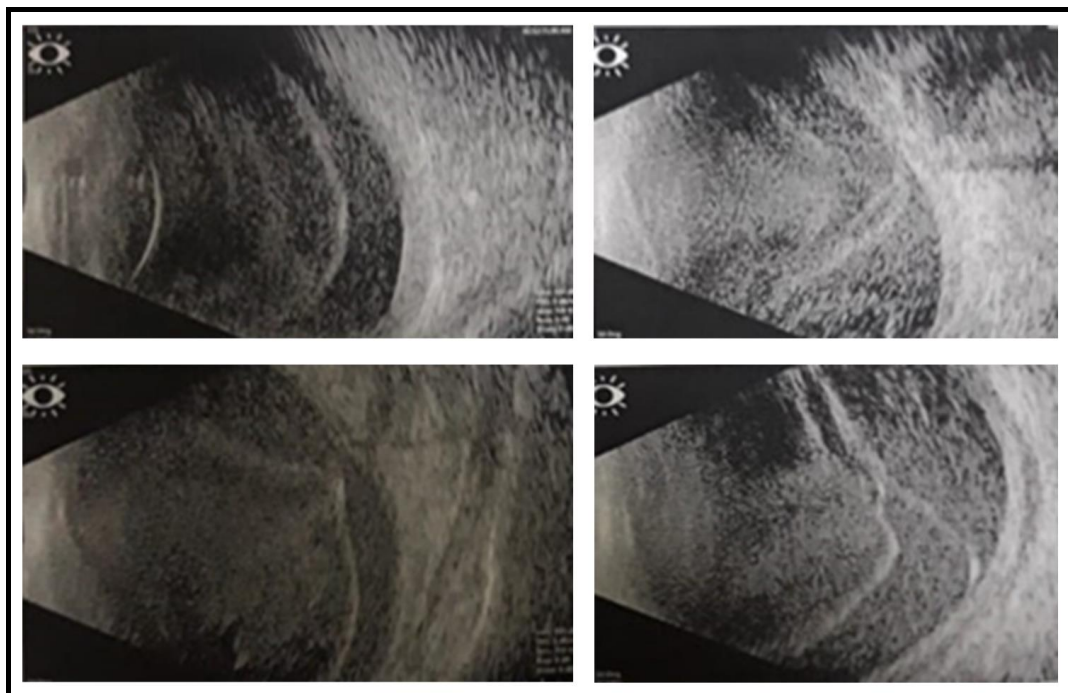
Figure 2. B-scan ultrasonography of the right eye shows dense vitreous hemorrhage, epiretinal hemorrhage, subtotal retinal detachment, and choroidal thickening

Figure 3. A computed tomography scan of the orbit and brain shows bilateral hyperdensity in the vitreous, indicative of vitreous hemorrhage

A complete blood count revealed normocytic normochromic anemia and thrombocytopenia, with a white blood cell count (6.14 k/uL). Peripheral blood smear and bone marrow examination revealed features consistent with APL. The bone marrow was hypercellular for age, with marked suppression across all cell series, showing 91% promyelocytes and 6% blasts. Immunophenotyping was done by gating on 70% mononuclear cells that expressed high side scatter and positive expression for bright CD33, CD13, CD117 and CD81 while being negative for HLA-DR, CD34, cCD79a, cCD22, TdT, cCD3, CD10, CD19, CD20, CD38, CD7, CD14, CD36, CD15, and CD64. Chromosomal translocation t(15;17) was positive using fluorescence in situ hybridization analysis. The patient was diagnosed with low-risk APL (WBC count was <10.000/mcL at presentation). However, with bilateral optic neuropathy caused by leukemic infiltration and edematous compression, the patient was recognized as a high-risk case.

The patient's coagulation profile revealed slightly elevated prothrombin time (14.3 seconds) and normal activated partial thromboplastin time (26.7 seconds) and elevated international normalized ratio (1.23). D-dimer and fibrinogen levels were within normal. He received fresh frozen plasma transfusion to maintain PT and aPTT at normal values and platelet transfusion to keep a platelet count ≥50.000/mcL.
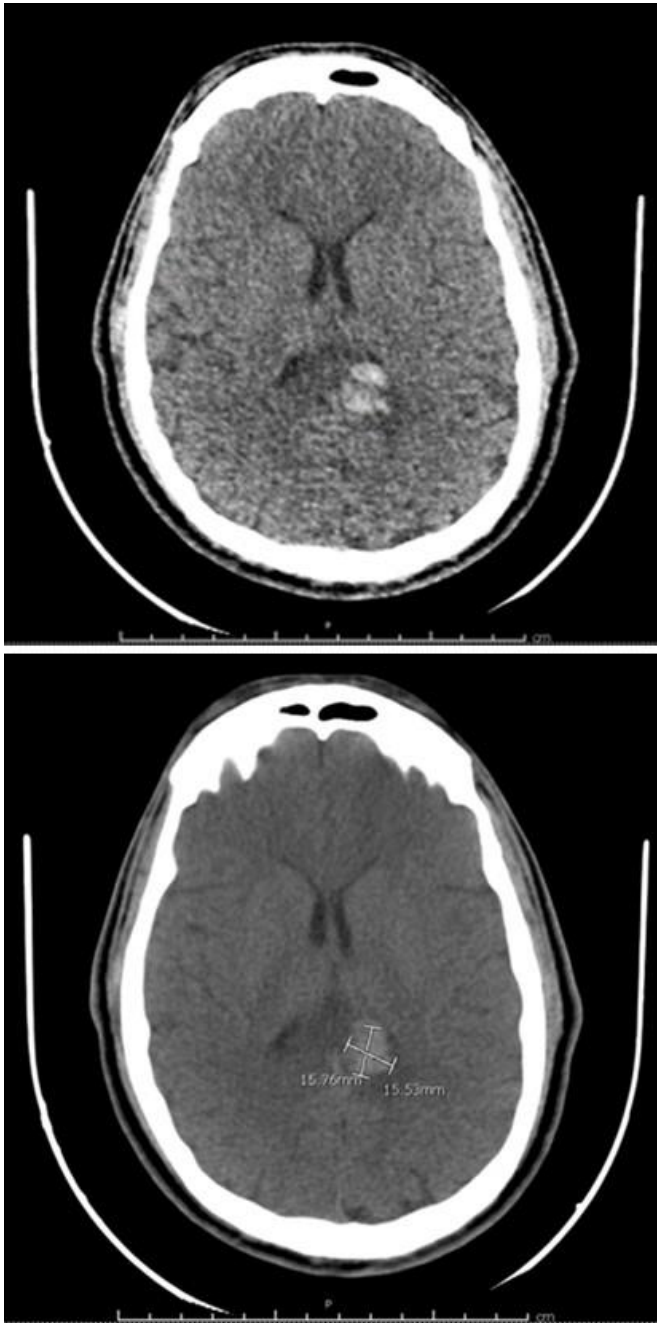
Figure 4. A computed tomography scan of the brain and orbit shows a left occipital hyperdense lesion with surrounding edema at the posterior horn of the lateral ventricle, measuring 15.76 x 15.53 mm, likely indicating a parenchymal hematoma

Intensified standard induction chemotherapy (7+3; standard dose cytarabine 200mg/m^2 continuous infusion for 7 days with daunorubicin 60mg/m^2 for 3 days) together with ATRA at a dose of 45mg/m^2 in 2 divided doses was started as per our institution guidelines on November 27, 2022. The patient was closely observed for any signs of differentiation syndrome. The patient achieved complete hematological remission, confirmed by bone marrow aspiration and biopsy, and negative

interphase fluorescence in situ hybridization test for t(15;17) on December 18, 2022. His post-chemotherapy coagulation profile was within normal ranges, except for D-dimer level (1.16 ng/ml, reference range 0.0-0.5). A post-contrast computed tomography scan of the orbits and brain after the first cycle of chemotherapy showed a regression of the previously described hematoma, with decreased density and surrounding edema (Figure 5). The patient continued with consolidation regimens, and molecular remission was confirmed with a negative RT-qPCR assay for PML/RARA fusion transcript on December 29, 2022.

Figure 5. A computed tomography scan of the brain after the first cycle of chemotherapy shows regression of the hematoma with decreased density and surrounding edema

However, there was no visual improvement in either eye after the first cycle of chemotherapy. The patient complained of right periocular pain for one week, and ophthalmological follow-up revealed perception of light (PL) vision in the right eye and no PL vision in the left eye, with persistent vitreous hemorrhage in both eyes. Subsequently, the right eye underwent pars plana vitrectomy (PPV) and silicone oil injection under general anesthesia performed by Dr. Mohamed Abdallah Gad, Professor of vitreoretinal surgery, and his team at Mansoura Ophthalmology Center (MOC) on January 2, 2023. Two weeks postoperatively, there was an improvement in visual acuity (VA) from PL to 1/60. Fundus examination showed a flat retina with

residual scattered retinal and epiretinal hemorrhage, few fibrous bands, and diffuse attenuation of the retinal pigment epithelium (RPE) (Figure 6). Six months later, the patient developed silicone-induced cataract and underwent phacoemulsification, posterior chamber intraocular lens (PCIOL) implantation, and silicone oil removal at MOC on April 24, 2024, following stabilization of his general condition. His postoperative VA remained at 3/60 and has been maintained since. The patient is scheduled for PPV in the left eye.

Consolidation therapy commenced on January 11, 2023, with daunorubicin 60mg/m^2 for 3 days plus cytarabine 200mg/m^2, followed by cytarabine 2gm/m^2 every 12 hours for 5 days in the subsequent cycle starting on February 28, 2023, alongside continued ATRA therapy. Our patient, classified as high-risk for CNS involvement in APL due to initial intracranial and ophthalmological hemorrhage with significant impact on vision, faced an elevated risk of CNS relapse. Consequently, lumbar puncture and intrathecal chemotherapy were scheduled for cerebrospinal fluid analysis and CNS prophylaxis post-hematological recovery during consolidation cycles. CSF cytology indicated no leukemic blast infiltration.

Unfortunately, the patient experienced a medullary relapse on March 29, 2023. Subsequently, salvage chemotherapy (HAM protocol) combined with ATRA was administered on April 3, 2023, resulting in a second complete remission documented on May 9, 2023, with maintained molecular remission status. The medical panel decided on autologous stem cell transplantation (ASCT). Consolidation chemotherapy with high-dose cytarabine (HiDAC) continued while awaiting ASCT, which was successfully performed on January 10, 2024, at our Bone Marrow Transplant Unit. The patient continues to maintain medullary and molecular remission, with blood counts within normal ranges and ongoing monitoring of his chemistry profile.

Discussion

Acute promyelocytic leukemia presenting with a WBC count ≤10 x 10^9/L is categorized as a low-risk condition. Recognized as a hematological emergency, immediate hospitalization is crucial upon suspicion of APL to prevent early mortality. Treatment typically includes chemotherapy combined with ATRA and supportive measures to manage coagulopathy and correct bleeding tendencies. Confirmation of the diagnosis involves genetic testing, specifically molecular detection of the PML-RARA fusion gene [14].
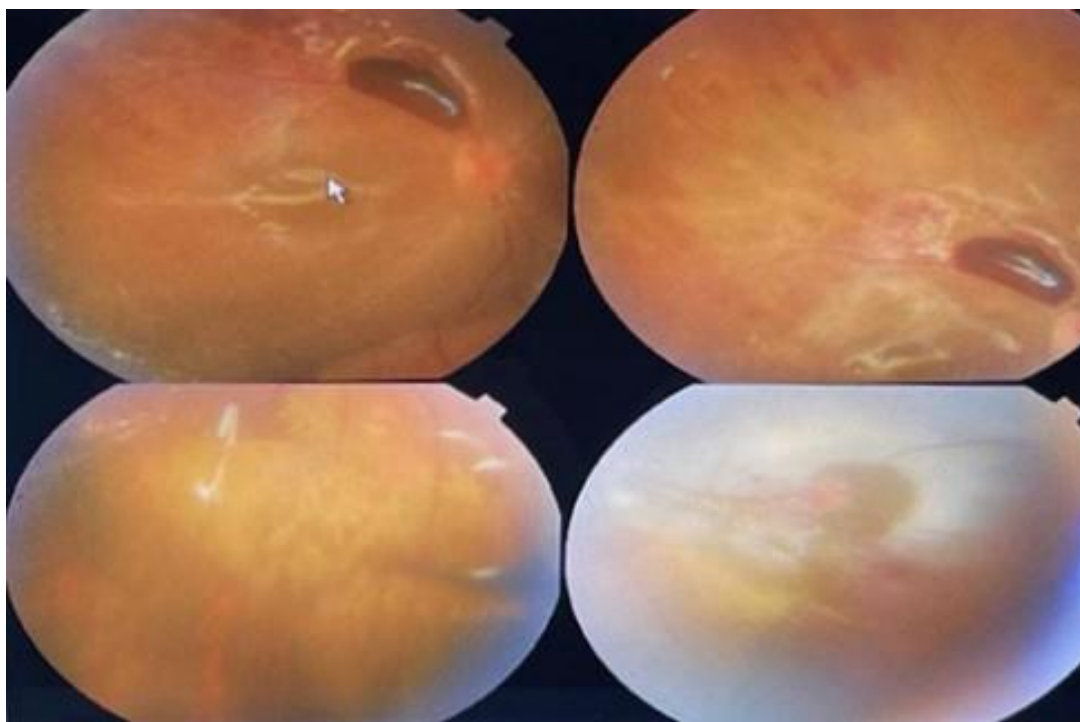

Figure 6. Postoperative fundus image of the right eye shows flat retina with juxtapupillary preretinal hemorrhage, fibrous bands, and areas of diffuse atrophic retinal pigment epithelium (RPE) and retinal infiltration

Transfusion support includes platelets and fresh-frozen plasma immediately to maintain fibrinogen concentration > 100-150 mg/dL, platelet count between 30-50 × 10^9/L, and INR < 1.5. Daily monitoring of the coagulation profile and platelet counts is essential, continuing until all clinical and laboratory signs of coagulopathy resolve [14].

Disseminated intravascular coagulation (DIC) in APL is characterized by consumptive coagulopathy, accompanied by primary and secondary fibrinolysis. Intracranial and pulmonary hemorrhages are the leading causes of death, occurring frequently before and shortly after initiating treatment. Thrombotic complications are rare at APL presentation [14].

Patients with acute promyelocytic leukemia (APL) commonly present with hemorrhagic symptoms [16]. Studies have identified elevated white blood cell (WBC) counts, abnormal coagulation profiles, and thrombocytopenia as significant risk factors for bleeding and its complications in APL [17]. Central nervous system hemorrhages in APL carry an increased risk of CNS relapses, so these patients could be entitled to CNS prophylaxis. However, lumbar punctures should be postponed until patients achieve complete remission to minimize bleeding risk [10, 18, 19]. Current guidelines recommend the consideration of a lumbar puncture before consolidation therapy in high-risk APL [20].

Isolated leukemic vitreous infiltration is uncommon due to the protective barrier of the internal limiting membrane, which typically prevents blast cells from entering the vitreous. However, leukemic infiltrates may breach this membrane either near the optic nerve head or alongside vitreous hemorrhage. Infiltrating leukemic cells can increase protein content, leading to condensation and clouding of the vitreous. Additionally, they may cause liquefaction and detachment [21].

Retinal detachment is a rare ophthalmological manifestation of acute leukemia and is rarely observed as an initial presentation [22, 23]. It occurs due to dense choroidal leukemic infiltrates that can disrupt blood flow in the choriocapillaris, leading to ischemia of the retinal pigment epithelium (RPE) and subsequent disruption of tight junctions, resulting in serous retinal detachments [24]. Leukemic retinopathy is often associated with abnormal hematologic parameters and coagulopathy [25].

A previous case report highlighted that hemorrhagic retinal detachment can occur as a presentation of APL, underscoring the importance of prompt surgical intervention [22]. However, the thrombocytopenia and coagulopathy inherent in APL can sometimes delay or complicate surgical procedures, potentially impacting visual outcomes. Other case reports have documented initial ophthalmic neuropathies in APL presentations, such as papilledema, hemorrhagic bilateral optic disc edema, and left homonymous hemianopia associated with occipital lobe hemorrhage. These cases achieved complete remission following appropriate APL treatment [26].

Recommendations and conclusions

We stress the importance of routine fundus examinations for all acute leukemia cases. Early detection of ophthalmic manifestations, particularly in APL, significantly impacts outcomes by enabling timely diagnosis and appropriate management.

The challenging presentation of APL as an ophthalmic emergency highlights the necessity of a multidisciplinary approach to patient care. Collaboration among ophthalmologists, hematologists, and other specialists is crucial for accurate diagnosis and optimal treatment outcomes.

For APL patients with CNS bleeding, we recommend CSF examination post-stabilization and induction chemotherapy. Utilizing flow cytometry for CSF analysis enhances diagnostic precision compared to conventional cytology, guiding effective treatment strategies.

Recent studies advocate early consideration of HiDAC for CNS prophylaxis, especially for patients not receiving intrathecal chemotherapy. This strategy may better suit APL patients presenting similarly to the case discussed herein.

In conclusion, APL can mimic inflammatory conditions with retinal detachment. Tailored diagnostic and management approaches are pivotal for optimizing outcomes in challenging leukemia cases with ophthalmic involvement. Continued interdisciplinary collaboration and advanced diagnostic tools are essential for delivering comprehensive care throughout the treatment journey.

Authors' contribution

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