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Case Report

Acute Philadelphia Chromosome Positive Biphenotypic Leukemia Presenting with Bilateral Orbital Chloroma: A Rare Case Report

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Abstract

Introduction: Chloromas are characteristically formed by the extramedullary soft tissue infiltration by the immature myeloid malignant cells. Such extramedullary masses are most commonly seen in acute myeloid leukemia usually in the M2, M4, M5 subtypes of the AML FAB classification. However, it has been reported to rarely present only in pediatric patients with acute lymphoblastic leukemia.

Presentation of the case: We encountered an unusual case of a young male, who presented with proptosis of both eyes followed by fever and fatigue. On evaluation, he was diagnosed to have bilateral orbital chloroma which was due to infiltration by leukemic cells of acute leukemia. Flowcytometry revealed features confirming an acute biphenotypic leukemia. Subsequently, cytogenetic evaluation revealed the leukemic cells to be Philadelphia chromosome positive.

Conclusion: To our knowledge, this is the first case of bilateral orbital choloroma due to Philadelphia positive biphenotypic acute lymphoblastic leukemia.

Keywords: biorbital chloroma; philadelphia positive; biphenotypic acute leukemia
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Introduction

A chloroma, also known as granulocytic sarcoma, is characteristically formed by the extramedullary soft tissue infiltration by the immature myeloid cells. Such extramedullary masses are described to either precede or present simultaneously with a myeloproliferative disorder [1]. The greenish color of chloroma is due to the myeloperoxidase (MPO) enzyme in the cells of granulocytic lineage. Since all such extramedullary leukemic deposits were not green, these deposits were also called Granulocytic sarcoma [1]. Chloromas may arise in the skin, subcutaneous tissue, orbits, bones such as the ribs, sternum, pelvis, brain and spine, lymph nodes, gums, paranasal sinuses, the thyroid gland, the pleural and peritoneal cavities, the breasts, the thyroid, salivary glands, the small bowel, the lungs, or various pelvic organs [2]. Orbital chloromas are most commonly seen in acute myeloid leukemia (AML) and needs to be differentiated from other malignancies such as rhabdomyosarcoma, metastatic neuroblastoma, African Burkitt's lymphoma and idiopathic inflammatory pseudo tumor. Up to 30 % of pediatric AML and up to 2-5 % of adult AML may have associated chloromas [3]. It is more common to have chloromas in the pediatric age group than adults, with a majority of patients being younger than 15 years [4].

Chloromas commonly present with either before the onset or simultaneously with a new onset AML. After treatment of AML, chloroma may also be the first sign of a relapse [1, 5]. An FNAC or a biopsy usually confirms the histotype; immunohistochemical studies are helpful in determining the correct diagnosis. Even though chloromas are more commonly seen in the AML FAB classification M2, M4, M5 subtypes, they are also seen less commonly in acute lymphoblastic leukemia (ALL) [6]. Herein, we report a rare case of a young man presenting with proptosis of both eyes who was subsequently diagnosed to have bilateral orbital chloroma due to Philadelphia chromosome positive acute biphenotypic leukemia (BAL). To our knowledge, this is the first case report of Philadelphia (Ph) chromosome positive acute biphenotypic leukemia with bilateral orbital chloroma.

Case Summary

A 21 year old previously healthy man presented with a history of rapidly progressing bilateral proptosis over a period of 2 months. Patient initially presented to an ophthalmologist who found marked proptosis and chemosis of both eyes with bilateral exposure keratitis (**FIGURE 1a, 1b**). Vision in the both eyes was markedly diminished with only projection of light positivity in the left eye. Plain MRI of the orbits revealed bilateral moderate proptosis with both globes anterior to the inter-zygomatic line and significant retro-orbital soft tissue prominence. (**Figure 2a, 2b**) During

evaluation, he developed recurrent fever with chills and fatigue. Hemogram revealed a total white leukocyte count of 150,000 cells per microlitre with normal red blood cell profile and platelet counts. The peripheral blood smear study revealed 80 % blasts with high nuclear: cytoplasmic ratio, 1-3 prominent nucleoli with few blasts showing presence of cytoplasmic granules. Bone marrow aspiration study showed 80 % blasts. On flowcytometry, the blasts showed positivity for TdT, CD34, HLA-DR, CD 19, CD79a, CD 14, CD 64, MPO with dim CD 33 and CD117; the blasts were negative for CD 3, CD 5, CD 7 and CD 13. (**Figure 3**) This was suggestive of homogeneous expression of both myeloid and B lymphocyte markers by all the blasts. Cytogenetics revealed a karyotype 46 XY, t (9:22) (q34:q11.2). BCR-ABL real time polymerase chain reaction (RQPCR) assay showed international standardized transcript ratio of 100 % p190 Kda molecular weight BCR ABL1 protein. A final diagnosis of Philadelphia chromosome positive acute biphenotypic leukemia was made. Patient underwent bilateral tarsorraphy. Patient was subsequently started on Tablet Imatinib 800 mg OD with concurrent induction phase of BFM 95 acute lymphoblastic leukemia treatment protocol. Patient had marked reduction in the proptosis at day 26 of induction phase and had regained his vision significantly in the left eye; he was able to count fingers at 10 meters and had projection of light positivity in the right eye also with a leucoma in the right eye. (**Figure 4**) However, patient expired due to septic shock on day 36 of Induction phase.

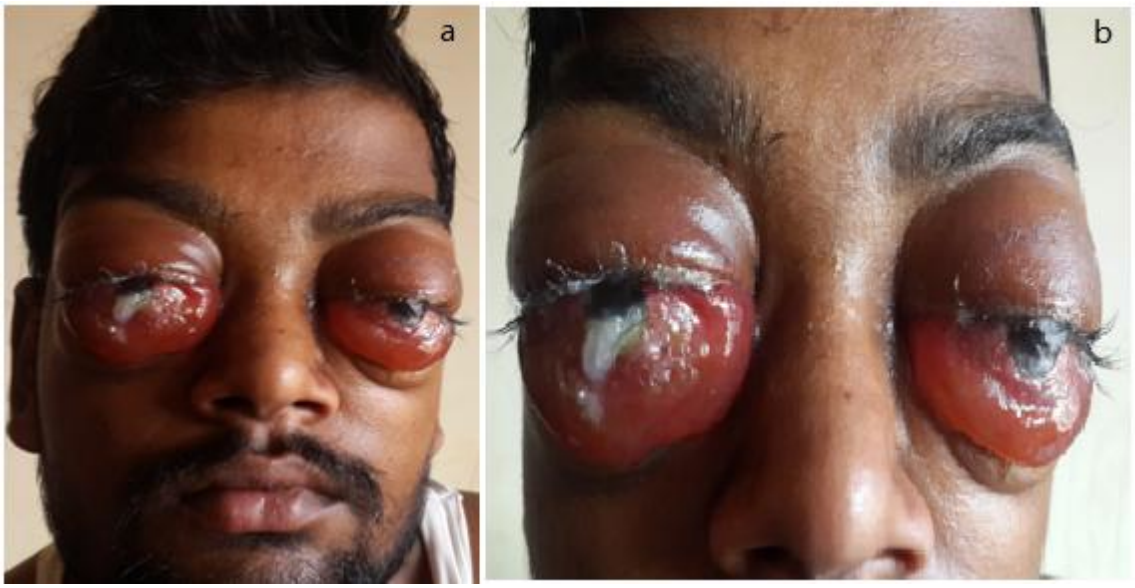

Figure 1 (a) Bilateral proptosis at presentation. (b) Bilateral proptosis at presentation

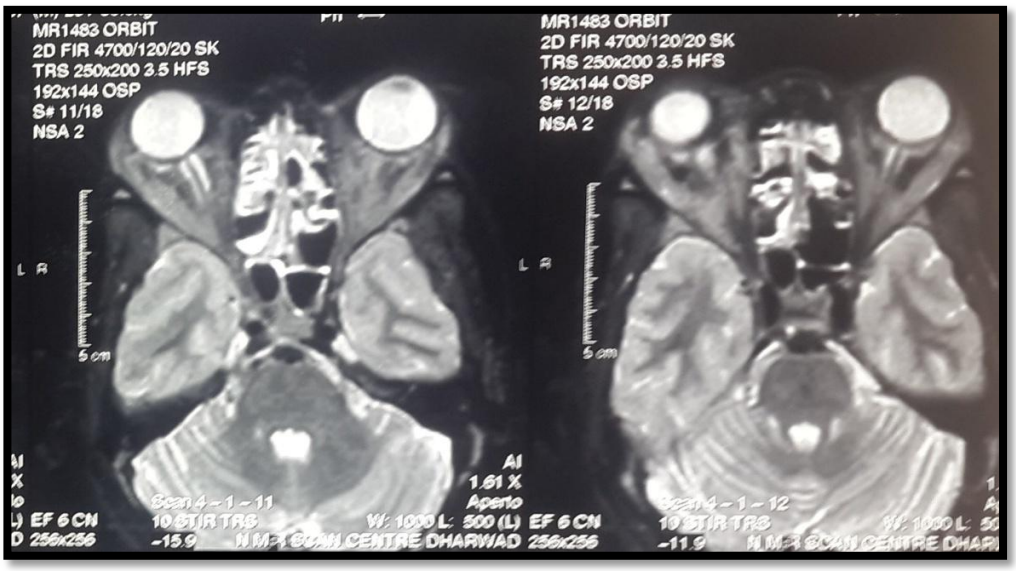

Figure 2a MRI plain showing bilateral Orbital iso-intense lesions

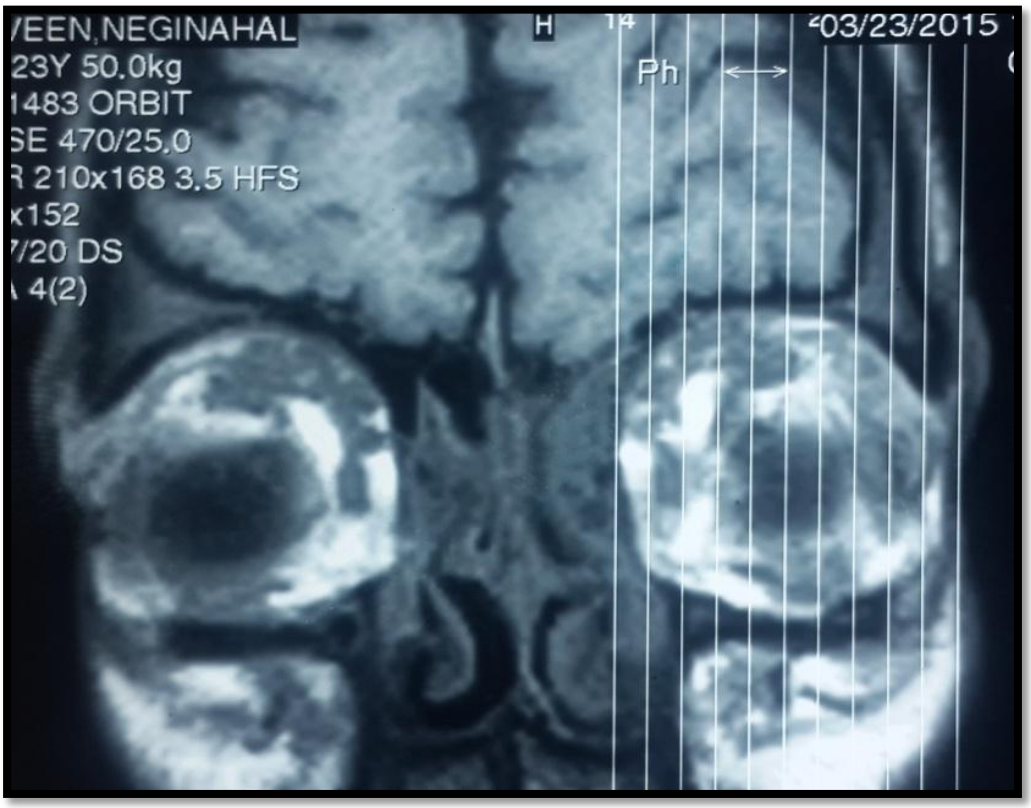

Figure 2 b MRI plain showing bilateral Orbital iso-intense lesions

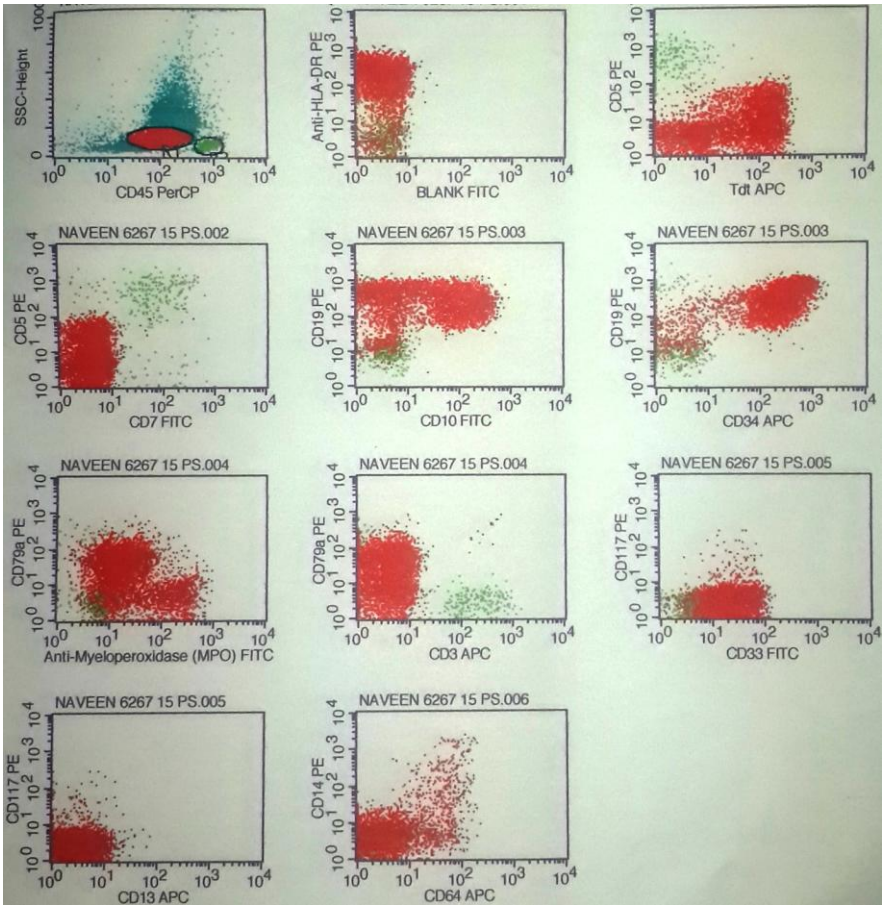

Figure 3 Flowcytometry shows the gated blasts to be positive for TdT, CD34, HLA-DR, CD 19, cCD79a, CD 14, CD 64, MPO with dim CD 33 and CD117; the blasts were negative for cCD 3, CD 5, CD 7 and CD 13

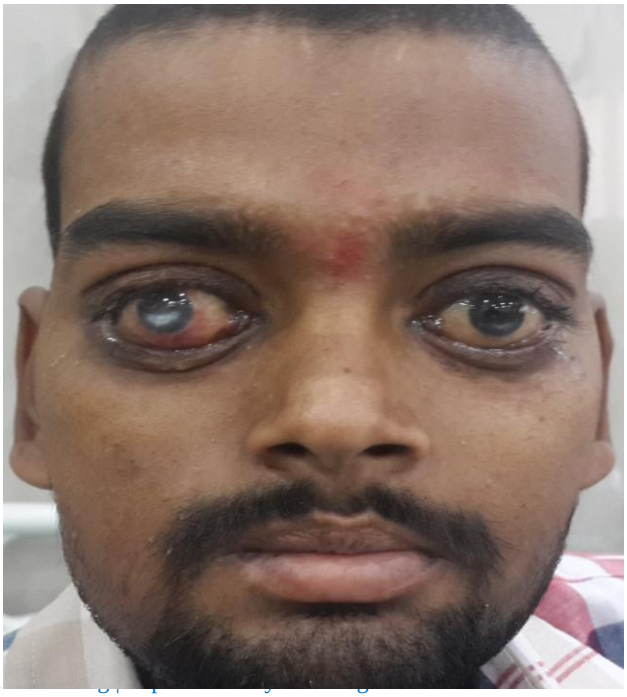

Figure 4 Resolution of bilateral proptosis after chemotherapy

Discussion

Acute biphenotypic leukemia (BAL) is a rare subtype of acute leukemia which expresses both the myeloid and lymphoid markers simultaneously. BAL comprises 2-5% of all acute leukemias. In 2008, the World Health Organization classification of hematopoietic and lymphoid tumors proposed a simpler diagnostic algorithm, which relies on fewer and more lineage-specific markers to define BAL [6]. As per the WHO 2008 hematological classification system, BAL is diagnosed when the leukemic cell expresses a combination of antigens of different lineages. However, AML with t (8:21), t (15:17) and inv 16 can also express lymphoid-specific antigens but should still be classified as AML with recurrent genetic abnormalities. While the defining criterion for AML is the presence of $\geq$ 20% myeloblasts in peripheral blood or bone marrow, diagnosis of BAL is made when the total number of leukemic blasts (including the myeloblasts and non-myeloblasts populations) is 20 % or more taken together. If there is only a single lineage of blasts present that otherwise meets the criteria for B-ALL or T-ALL, the presence of MPO positivity as per flowcytometry, immunohistochemistry or cytochemistry confirms a so-existing myeloid lineage. Patients with chronic myelogenous leukemia (CML) in blast crisis, AML with myelodysplasia-related changes and therapy-related AML should be classified and managed as their respective entities even if they have leukemic cells of mixed phenotype [6]. Although cases of CML in blast crisis can show blasts of mixed lineage, these cases often have a presence of background of CML with leukocytosis and basophilia [7]. Studies by Yen et al and Manola, showed that 15-25 % of all BAL's with B phenotype are positive for Ph chromosome and should be specifically treated with Tyrosine Kinase Inhibitors (TKI's). The clinical manifestations of BAL are similar to other acute leukemias but have a worse outcome when compared to AML or ALL [8-10]. There is no standard therapy regimen that has been proven to be of benefit in BAL [6]. Several studies have suggested that patients with acute leukemia of mixed phenotype have a worse clinical outcome when compared with matched controls with acute myeloid leukemia or acute lymphoblastic leukemia. In the study by Shimizu et al, addition of Imatinib to intensive ALL treatment regimen for treatment of BAL conferred a prognosis similar to that seen with treatment of B- ALL [11]. Further studies are needed to confirm the significance of BAL as currently defined, to determine a standardized treatment approach and to better understand the biological and clinical aspects of this disease [12, 13].

Our patient is a rare case of Philadelphia chromosome positive BAL. Chloromas are most commonly seen with AML. Sometimes, if there is minimal myeloid differentiation in histology, it may be difficult to differentiate a chloroma from lymphoblastic leukemia, lymphomas and other small round cell tumors. A complete immunophenotyping (IPT) study using lineage specific markers such as helps to determine the exact histology of chloroma. Myeloid origin of the chloroma can be determined in most cases by using specific markers such as MPO, CD 34, CD68, CD33, CD 99 and HLA DR whereas the B and T cell IHC markers CD 2, CD 3, CD 4, CD 7, CD45, CD20, UCHL-1, and CD30 help in confirming a lymphoid origin.

Orbital involvement by AML is relatively rare among orbital tumors. Orbital Chloromas may present intraconally or extraconally and may be bilateral in a few cases. However, in the setting of bilateral

orbital tumors in children, myeloid sarcoma is the most likely diagnostic possibility. Although orbital involvement by chloroma with or without concurrent AML is well described in the literature, similar presence of ALL of either precursor T-cell or B-cell lineage is very rare, particularly in the adult population. There have been rare published case reports of a leukemic infiltration of the orbit secondary to ALL (14-18). The most commonly known AML cytogenetic abnormality seen in granulocytic sarcoma is t (8:21) [14-19].

Conclusion

To conclude, bilateral orbital chloroma due to Philadelphia chromosome positive biphenotypic acute leukemia has not been previously reported in literature. Whereas effective management of Ph positive BALs is not well understood, TKIs concurrent with ALL based treatment protocols are the currently used. However, prognosis currently remains poor, as seen in this patient.

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