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Case Report

Chronic Myelogenous Leukemia Presenting with Oculomotor Nerve Palsy: A Case Report and Review of Literatures

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Abstract

Introduction: Chronic myelogenous leukemia (CML), the most common sub-type of leukemia, usually presents with anorexia, fatigue, weight loss, splenomegaly, infection, and bleeding diasthesis. Cranial nerve palsy is a rare occurrence with myelo-proliferative disorder. Though prior literatures reported cranial neuropathies with different myelo-proliferative disorders, commonly acute leukemias and lymphomas, this is the first case of CML presenting with oculomotor nerve palsy.

Presentation of case: We report a 55-year old African American male presented in emergency department with features of third cranial nerve palsy, including unilateral ptosis, diplopia, and downward-outward deviation of eyeball without involvement of pupil. Clinical suspicion of CML, based on preliminary routine laboratory investigation, was confirmed by bone marrow biopsy and genetic testing of marrow aspirate. Patient was treated with Imatinib and regularly followed up with complete blood count.

Conclusion: CML may present with lone cranial nerve palsy as the first clinical finding. Hence, we emphasize to consider leukemia as one of the possible differential diagnoses in suspected patients presenting with isolated oculomotor palsy, if no other cause is evident.

Keywords: Chronic Myelogenous Leukemia; CML; Oculomotor Nerve; Palsy

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Introduction

Chronic myelogenous leukemia (CML) is a myelo-proliferative neoplasm caused by the translocation between break point cluster region (BCR) gene on chromosome 22 and Abelson 1 (ABL1) on chromosome 9 leading to BCR-ABL1 gene fusion (Philadelphia chromosome), and producing constitutive activation of ABL1, a gene coding for tyrosine kinase [1,2]. Being the common type, CML constitutes 10-15% of all leukemias [3]. The annual incidence of CML is approximately 1-1.5 in 100,000 population worldwide, with an estimated 6,650 new cases in the year 2015 [4,5]. Moreover, the prevalence is increasing due to increased survival with the advancement of BCR-ABL tyrosine kinase inhibitors [6].

Of the chronic, accelerated, and blast crisis phases of CML, most of the cases (85-95%) are diagnosed in chronic phase [3,7], and up to 50% of patients are asymptomatic at the time of diagnosis [8]. Central nervous system (CNS) involvement of chronic leukemia, cranial nerve in particular, is very rare. An autopsy study conducted on 100 subjects who died of active leukemia suggested that CNS involvement is more common in acute than chronic leukemia. In the study, 81% of acute lymphoblastic leukemia (ALL) and 46 % of acute myelogenous leukemia (AML) cases revealed CNS infiltration in autopsy, while eight of sixteen cases with chronic lymphocytic leukemia (CLL) and a single case with CML evidenced CNS involvement [9].

We performed a meticulous literature search in various databases, such as Pubmed/Medline, Google Scholar, and the references from review articles, to identify the cases that have reported oculomotor nerve (CN III) palsies associated with myelo-proliferative disorders (Table 1). However, to the best of our knowledge, this is the first case that describes CN III palsy as the sole presentation of CML.

Case Presentation

A 55-year old African American male presented to the emergency department with diplopia and drooping of left eyelid for nine days. Patient reported sudden onset of double vision, and downward and outward deviation of his left eyeball which was followed by left eyelid drooping after three days. He mentioned that the diplopia resolved on persistently closing the affected eye. Patient denied any history of weight loss, fever, anorexia, fatigue, chest pain, limb or facial weakness, and photophobia. There was no any discharge, pain, swelling, or redness of his eyes. The patient had past medical history of diabetes mellitus (DM), and chronic back pain. Prior to admission, his medications were fentanyl and oxycodone for his back pain; glipizide, insulin glargine, insulin lispro protamine, and sitagliptin-metformin for his DM. He had undergone right knee joint replacement surgery in 2004. Patient had been chronic smoker (7-8 cigarettes per day) for the last 20 years, but denied the use of alcohol or illicit drugs.

On examination, patient was well oriented to time, place and person. He was morbidly obese with BMI of 51.9. Physical examination showed temperature of 37.2 C (98.9 F), pulse 80 per min, blood pressure 132/94 mmHg, and respiratory rate 14 breaths per minute. Complete ptosis of the left eye was evident with outward and downward deviation of eyeball on lid retraction. When the patient was asked to open the affected eye, the contra-lateral eye deviated laterally. Funduscopic examination revealed early signs of diabetic retinopathy in both eyes with more severe retinopathy in the unaffected right eye. Notably, pupil in the affected eye was not reactive to light. The features were suggestive of CN III palsy with pupillary involvement. Neither lymph node nor liver/spleen was palpable. Physical examination of the heart and lungs were unremarkable. The abdomen was soft, non-tender and bowel

sounds were appreciated. The neurological exam was otherwise unremarkable.

Baseline laboratory data revealed blood glucose of 285 mg/dL, and a hemoglobin A1c of 11.4%. The complete blood count was significant for a white blood cell count of 35.7 K/uL, with red blood cell MCV of 80.1 fl. The hemoglobin was 11.9 mg/dL, hematocrit was 38.7 %, and platelet count was 228,000/UL. Complete blood count showed a distribution of 74.8% granulocytes, 15.1 % lymphocytes, 7.2% monocytes, 3.5% basophils, and 1.5% eosinophils. The absolute numbers of all blood cells were increased except for eosinophil. The liver function test was unremarkable except for alkaline phosphatase of 115 units/L and lactate dehydrogenase of 545 units/L.

Peripheral blood smear showed a left shift with 20% myelocytes, basophilia, neutrophilia, and no blast cells. Head CT showed no tumors or aneurysms impeding on CN III. HIV testing, blood culture, urine culture, and CSF cultures were all negative. On admission, laboratory results revealed an unexceptional complete metabolic panel with sodium of 139 mmol/L, potassium of 4.2 mmol/L, chloride of 102 mmol/L, bicarbonate of 25 mmol/L, blood urea nitrogen of 22 mg/dL, and creatinine of 1.1 mg/dL. The remaining liver function tests showed a total bilirubin of 0.3 mg/dL, alanine aminotransferase of 27 units/L, and aspartate aminotransferase of 31 units/L, while total protein and albumin were 6.8 g/dL and 2.9 g/dL respectively.

The patient's initial differential diagnoses were leukemoid reaction secondary to infection and CML. As a precaution, the patient was started on doxycycline to treat for possible Lyme disease. Antibiotics were discontinued after ruling out Lyme disease by a negative Lyme panel. The bone marrow yielded no abnormal findings on flow cytometry. However, bone marrow biopsy revealed granulocytic hyperplasia. A FISH for BCR-ABL1 translocation of the bone marrow aspirate was positive. The patient was immediately treated with Imatinib 400mg/day. The patient was advised for outpatient follow-up where the response to treatment was monitored with complete blood count.

Discussion

We describe the unique presentation of left oculomotor palsy in a patient who was later diagnosed with CML. Prior to this report, two different cases were reported on CML presenting with CN palsy [11,12]. One study reported a case of 53-year old male with signs of hyperemia and slight edema in funduscopy (CN II involvement), without any presenting symptoms [11], while the other reported 61 year-old male diagnosed with CML presented with unilateral diplopia and lateral rectus muscle palsy (CN VI). Furthermore, there were 16 different articles with 17 patients of CN III palsy associated with different myelo-proliferative disorders, of which majority [7,13-19] was associated with different types of Non-Hodgkin's lymphoma (n=9), followed by ALL (n=3) [20-22]. Remaining five cases were associated with each of AML [23], Hodgkin's lymphoma [24], infectious mononucleosis [25], leukemic meningitis [26], post-transplant lympho-proliferative disorders [27] (Table 1). However, none of the CML case was associated with CN III palsy suggesting latter as a very rare presentation of CML.

Due to the patient's body habitus, an MRI could not be performed. As an alternative to MRI, CT angiography of the head with contrast and CSF exam was performed on our patient; both showed no abnormalities suggesting that normal findings in neuroimaging and CSF do not rule out the possibility of CN involvement in leukemic patients. This finding is replicated in another study [20], which showed no abnormalities in either brain MRIs with or without intravenous gadolinium, or magnetic resonance venography in a patient with T-cell acute lymphoblastic leukemia and right oculomotor palsy. Additionally, CSF studies in this patient demonstrated normal results.

The patient's history of uncontrolled diabetes puts him at great risk for diabetic mono-neuropathy which was the first and the most important differential to be considered in our patient. Ophthalmoplegia is associated with 0.4% of diabetic patients and isolated CN III palsy accounted for 59.3% of such cases [28]. The clinical presentation of oculomotor nerve palsy in a diabetic patient is acute-onset diplopia and ptosis without involvement of pupil. Sparing of pupil is an important distinction between diabetic neuropathy and other ophthalmoplegias such as aneurysms, tumors, masses or infiltrative processes [29]. Hence, absence of pupillary reaction to light (pupillary involvement), and abnormality in the routine white blood cells count urged us to rule out diabetes and consider leukemia as the most likely diagnosis which was later confirmed with further investigation. Diabetic cranial nerve neuropathy affects somatic fibers and not parasympathetic fibers. While isolated III cranial nerve palsy is rare in diabetic patients, it cannot be excluded from our differentials, which includes hematologic infiltration, infectious etiologies, and diabetic mono-neuropathies. The pathogenesis for involvement of the left oculomotor nerve in CML is not clear. However, we believe that infiltrative myelogenous cells may induce inflammation or compression of the nerve fibers leading to the presenting symptoms.

Conclusion

To the best of our knowledge, this is the first case report of CN III palsy presenting as the only clinical feature of CML. However, there have been isolated cases of oculomotor palsy due to other hematological neoplasia. Based on our report, we emphasize that clinician should consider the possibility of CML in an unexplained, suspected cases of cranial nerve palsy.

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Table 1 Summary of case/case-series reports of cranial nerve palsies associated with myelo-proliferative disorders.

References	Year	Age/ Sex	CN Palsy	Type of MD	Clinical Features and/or findings	Conclusion
Bhatt VR et al.	2012	28/F	**III**	ALL	Sudden onset R CN III palsy, normal neuro-radiography and CSF studies	T-ALL involving CN III despite normal neuro-radiography and initial CSF studies.
Oz O et al.	2011	48/M	**III**	ALL	L CN III palsy, ptosis, diplopia, lymphoblastic infiltration of both cavernous sinuses on MRI	First case of ALL presenting with CN III palsy
Al-Mujaini AS et al.	2009	25/M	**III**	AML	U/L CN III palsy	AML presenting as acute CN III palsy
Tabata M et al.	1998	53/M	**III**	AML	Diplopia, R blepharoptosis, MRI: B/L enlargement of CN III; partial remission with intrathecal MTX & CA	MRI can be helpful in early diagnosis of leukemia.
Kiratli H et al.		10/M	**III**	BAL	R Superior rectus palsy, proptosis	Leukemic infiltration of extraocular muscles in BAL.
Levy J et al.	2006	34/M	**III**	BL (NHL)	Headache, L eye pain, diplopia, complete ptosis for several hours, pupillary involvement	BL should be considered in any patient presenting with diplopia or ophthalmoparesis.
Park YM et al.	2007	53/F	**III**	DLBCL (NHL)	Headache, diplopia, ptosis, mydriasis, outward positioning of eyeball,CD_{20} positive, CD_3 negative	Complete CN III palsy as a presenting feature of Large BCL
Sato H et al.	2011	71/M	**III**	DLBCL (NHL)	Diplopia, mild ptosis, complete L CN palsy, no pupillary involvement	Isolated CN III palsy is associated with Large BCL
		89/F	**III**	DLBCL (NHL)	Diplopia, L ptosis, no pupil or visual acuity affected	
Tsai CH et al.	2013	51/F	**III**	DLBCL (NHL)	Dropped eyelid, blurred vision, anisocoria, complete CN III paresis	CN III palsy can occur in patient with DLBCL
Meireles J et al.	2014	69/F	**III**	HL	Ptosis, diplopia	HL presenting as isolated CN III palsy.

References	Year	Age/ Sex	CN Palsy	Type of MD	Clinical Features and/or findings	Conclusion
Erben Y et al.	2007	19/M	**III**	IM	R headache, sub-acute diplopia	IM presenting as isolated CN III neuritis
Bhatti MT et al.	2005	45/M	**III**	DLBCL (NHL)	Isolated CN III palsy, involvement of pupil, HIV positive	CNS lymphoma presenting as isolated CN III palsy.
Celebisoy N et al.	2008	56/M	**III**	LM	R diplopia and ptosis, intermittent frontal headache, BM findings consistent with myelofibrosis.	CNS leukemia presenting as isolated CN III palsy
Chen CS et al.	2008	58/M	**III**	NKTL (NHL)	Proptosis of R eye, complete R CN III palsy	CN III palsy can be caused by intracranial extension of a sino-orbital NKTL
Manabe Y et al.	2000	-	**III**	NHL	Eyelid lifting, vertical gaze palsy; normal Lateral gaze, no involvement of pupil	Partial CN III palsy could occur as the first sign of NHL
Metellus P et al.	2002	64/M	**III**	NHL	CN III palsy, diplopia, Headache, mass in sphenoidal sinus on MRI	CN III involvement with NHL
Kraus TS et al.	2014	8/M	**III**	PTLD	Heart transplant patient with CN III palsy, features of angioblastic T-Cell lymphoma	CN III palsy associated with monomorphic T cell PTLD in heart-transplant patient.

Note: ALL=Acute Lymphoblastic Leukemia; ALL=Acute Myeloblastic Leukemia; BAL=Biphenotypic Acute Leukemia; BL=Burkitt's Lymphoma; B/L=Bilateral; BM=Bone Marrow; CD=Cluster Differentiation; CN=Cranial Nerve; CNS=Central Nervous System; CSF=Cerebrospinal Fluid; CA=Cytosine Arabinoside; DLBCL=Diffuse Large B-Cell Lymphoma; F=Female; HL=Hodgkin's Lymphoma; L=Left; LM=Leukemic Meningitis; IM=Infectious Mononucleosis; M=Male; MD=Myeloproliferative Disorder; MRI=Magnetic Resonance Imaging; MTX=Methotrexate; NHL= Non-Hodgkin's Lymphoma; NKTL=Natural Killer/T-Cell Lymphoma; PTLD=Post-transplant Lympho-proliferative Disorder; R=Right; L=Left; U/L=Unilateral.