CASE REPORT

Bilateral Facial Nerve Palsy in Acute B Cell Lymphoblastic Leukemia: A Case Report and Review of the Literature

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Abstract Acute lymphoblastic leukemia (ALL) is a haematological malignancy that can involve the central nervous system (CNS). Less than 10 % of patients with ALL have CNS involvement at presentation. The cranial nerve most commonly affected is cranial nerve VII although bilateral involvement is rare. Management and outcomes of these patients are not well understood. Moreover bilateral Bells palsy as a presenting symptom of ALL is extremely uncommon. We report a very unusual presentation of ALL with bilateral facial nerve palsy, and discuss the management strategies and outcomes for patients with ALL that present with cranial nerve palsies.

Keywords Acute lymphoblastic leukemia · Bells palsy · CNS leukemia · Whole brain irradiation

Introduction

Acute lymphoblastic leukemia (ALL) accounts for 15–20 % of all adult acute leukemia. Studies suggest that less than 10 % of adults with ALL have central nervous system (CNS) involvement, defined as evidence of lymphoblasts in the cerebrospinal fluid (CSF), or presence of

significant neurologic dysfunction such as cranial nerve palsy [1–3]. The nerve most commonly affected in ALL is facial nerve (cranial nerve VII). Bilateral involvement, however, is an extremely rare entity. Management and outcomes of these lesions are not well defined. We report a case of B-cell ALL presenting as bilateral facial nerve palsy and review the existing literature regarding optimal management of cranial nerve involvement in ALL.

Case Report

A 41-year-old Hispanic man with a history of type 2 diabetes mellitus (diagnosed 4 years prior) presented to our institution with bilateral facial numbness and tingling for 6 weeks in late 2012. He also reported bilateral ear pain and generalized headaches. He complained of bilateral facial weakness with inability to close eyes completely and chew food for 1 week before presentation. He reported no recent viral infection or immunization, camping or outdoor activity or change in taste. He had a remote history of cigarette smoking (3 pack years), occasional alcohol use and no illicit drug use. His only medication was metformin.

His vital signs were within normal limits and his general exam was notable for bilateral temporal wasting and alopecia. He had no palpable lymphadenopathy. Neurologic exam revealed a bilateral facial droop and an inability to raise his eyebrows or whistle, although bilateral facial sensation remained intact. His sclerae remained visible when he closed his eyes. The rest of his examination was unremarkable. A clinical diagnosis of bilateral cranial nerve 7 palsy was made.

Initial laboratory analysis showed a white blood cell count of $224,000 \times 10^9/L$ with a differential of 72 % lymphocytes, 27 % immature mononuclear cells, and 1 %

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eosinophils. His hemoglobin was 3.6 g/dL and platelet count was $54,000 \times 10^9/L$. Hemoglobin A1c was 6.4 % (no serum fructosamine available) and fasting glucose was 117 mg/dL. Brain MRI was unremarkable. CSF examination revealed lymphoid blasts with 17 nucleated cells/mcL (Fig. 1). Viral studies including HSV-1 and EBV PCR on the CSF were negative. Bone marrow biopsy showed 87 % blasts in a hypercellular bone marrow with decreased trilineage haematopoiesis (Fig. 1). Flow cytometry demonstrated cells positive for TdT, CD10, CD19 and CALLA. FISH analysis demonstrated normal male karyotype with normal cytogenetics without any clonal abnormalities and negative Philadelphia chromosome and MLL gene rearrangements. PCR for bcr-abl performed on the marrow was negative. A diagnosis of B cell-lymphoblastic leukemia with CNS involvement was made.

He received hydroxyurea and prophylactic allopurinol, and HyperCVAD regimen was initiated with appropriate eye care. He received biweekly intrathecal therapy with alternating methotrexate and cytarabine. Eight treatments of whole brain radiation therapy (2400 cGy total) were delivered in conjunction with chemotherapy. After two cycles each of HyperCVAD A and B, his CSF showed no blasts and less than 1 nucleated cells/mcL. However his neurologic symptoms showed no improvement. Bone marrow biopsy 4 months after presentation showed persistent B-cell lymphoblastic leukemia (7 % blasts) with normocellular (50 %) bone marrow with trilineage haematopoiesis and erythroid predominance.

He had unremitting ALL with multiple admissions for symptomatic anemia, neutropenic colitis and influenza. Despite all therapy, the patient's neurologic symptoms remained permanent up to 8 months after initial presentation when he died after refusing further chemotherapy.

Discussion

Cranial nerve palsy can be idiopathic, metabolic, infectious, inflammatory, vascular, or neoplastic in origin [4]. Metastasis from solid tumors (breast, lung, renal cell or prostate cancer) can involve the calvarial base resulting in cranial nerve palsies. Leukemic CNS involvement can also cause cranial nerve palsy. Of patients who develop CNS leukemia, rarely is the cranial nerve palsy bilateral and even more rarely is the initial presenting symptom of ALL.

Direct leukemic infiltration and viral infections have been implicated in the pathogenesis of cranial nerve palsies in ALL. Post mortem examination of 3 leukemic patients with CN VII palsy demonstrated direct leukemic infiltration of CN VII in one case [5] but not in the other two [6, 7]. Leukemic infiltration of the tympanic cavity [8] and the temporal bone [9] has also been implicated as causes of cranial nerve dysfunction in leukemic patients. Epstein–Barr virus [10] and Human T-lymphotropic virus-2 [11] infection have been associated between leukemia and cranial nerve deficits. No large studies have been conducted to definitely support these hypotheses. While syndromes involving facial

Fig. 1 Lymphoblasts containing scant cytoplasm, round to indented nuclei, homogenous chromatin, and occasional small nucleoli are seen involving the **a** peripheral blood, **b** bone marrow, and

c cerebrospinal fluid. The bone marrow core biopsy is approximately 90 % cellular composed predominantly of lymphoblasts **d** Smears and cytospin are shown at $\times 1000$ magnification, core biopsy at $\times 500$

Table 1 Literature review of treatment of acute B-cell lymphoblastic leukemia with nerve palsy

Author	Cancer	Cranial nerve involved	Therapy	Outcome
Averbach-Heller [20]	ALL	IV	IT methotrexate and cytarabine with cranial radiotherapy	Complete response
de Fatima Soares [21]	ALL	II	IT chemotherapy	Death within 10 months of presentation
Ha [15]	AML: 9 patients ALL: 18 patients CML: 2 patients	II: 1 patient III: 11 patients IV: 4 patients V: 5 patients VI: 9 patients VII: 23 patients VIII: 4 patients IX: 4 patients X: 6 patients XII: 3 patients	Cranial radiation: 28 patients IT chemotherapy: 23 patients Systemic chemotherapy: 22 patients	14 patients had complete response 8 patients had partial response
Hsu [22]	AML	III	Leukapheresis, Cytarabine	Not available
Ingram [16]	ALL: 9 patients NHL: 13 patients	II: 1 patient III: 4 patients IV: 4 patients VI: 5 patients VII: 22 patients	IT methotrexate: 6 patients Cranial radiotherapy: 15 patients	11 patients had complete response 11 patients relapsed
Kulkarni [23]	ALL		Vincristine, prednisolone, daunomycin, tioguanina, IT methotrexate, and cranial irradiation	Lost to follow up
Tageja [24]	ALL	VII	IT methotrexate	Complete response
Ozcarar [18]	ALL	VII	Vincristine, cyclophosphamide, daunorubicin, L-asparaginase, IT methotrexate and IT cytarabine	Death due to neutropenic sepsis
Sasaki [25]	ALL	V	Cyclophosphamide, doxorubicin, vincristine, and prednisolone	Complete response
Young [26]	T-cell ALL	VII (alternating sides)	Cyclophosphamide, doxorubicin, vincristine, high dose Ara-C, PEG-asparaginase, and prednisone	Complete response
Ferrari [27]	Hairy cell leukemia	VII (bilateral)	2-CdA	Complete response
Zappia [28]	Acute non-lymphocytic leukemia	VII (unilateral)	Used, but regimen not specified.	Complete response
Sood [29]	AML with granulocytic sarcoma	VII(unilateral)	Cytarabine, daunorubicin	Not available
Bilavsky [30]	AML	VII(unilateral)	BFM-98 protocol	Not available
Karadag [31]	T-cell ALL	V(unilateral)	Methotrexate	Near complete resolution
Marwaha [32]	ALL	VII(unilateral): 4 patients	IT methotrexate, cranial irradiation	One did not opt for treatment. Two had continued palsy. One not available

IT intrathecal

nerve palsies, such as Melkersson–Rosenthal syndrome, have been linked cases of Hodgkin's lymphoma, no such cases have been reported with B-cell ALL [12]. Viral CSF studies were negative, and our patient had relatively well controlled diabetes mellitus, making CNS ALL the most likely cause of his facial symptoms.

One of the most common chemotherapeutic regimens used in the United States for ALL is Hyper-CVAD. Intrathecal chemotherapy is part of this regimen. In patients

with known or suspected CNS involvement, the chemotherapy regimens remain the same, and the addition of radiotherapy is controversial. There is no established protocol on whether radiation therapy should be conventional or hyperfractionated, cranial or craniospacial, but textbooks recommend a total dose of 3000 cGy with 1000–1500 of it applied to the nerve sheath and cranial base [13]. Currently, cranial radiation is used in only those considered at highest risk of subsequent CNS relapse, such

as those with documented CNS leukemia at diagnosis. Prophylactic cranial irradiation has practically been omitted from clinical practice, and replaced by intrathecal chemotherapy.

In a retrospective study by Gray et al., the effectiveness of whole brain irradiation with a median dose of 2400 cGy (range 1000–3000) at 200–300 cGy per fraction was studied in patients with leukemia or lymphoma and cranial nerve palsy [14]. Patients who received whole brain irradiation in addition to chemotherapy had a symptomatic improvement in 40 of 42 nerves affected, for an actuarial response rate of 95 % at 3 months. The complete response rate was 44 % and was better for patients with lymphoma than for those with leukemia (72 vs 19 %, *p* value 0.04).

Ha et al. evaluated the cases of 28 leukemic patients with CNS palsy without prior radiotherapy or intracranial leukemic infiltration by imaging or ophthalmologic examination, for response to intracranial radiation therapy with either concomitant intrathecal chemotherapy, systemic chemotherapy, or both [15]. The study concluded that radiation therapy with whole brain radiation therapy was effective in reversing cranial nerve deficits from leukemia even when leukemia infiltration was clinically but not radiographically present.

A retrospective study of 45 children with ALL or non-Hodgkin's lymphoma with cranial nerve palsies reported an improvement in disease-free survival at 2 years in children receiving radiation therapy compared to those who did not (53 vs 29 %) [16].

Only isolated case reports have evaluated whether bilateral facial nerve palsies respond to chemotherapy and radiation therapy. Buykavci et al. report a 13 year old male with T-cell ALL and bilateral facial nerve palsy who experienced complete resolution of the palsy with Total Therapy Study XIII/BH chemotherapy protocol without radiotherapy [17]. Ozcahar et al. reported a 20 year old ALL patient who presented with bilateral cranial nerve VII palsy and whose neurologic symptoms improved with chemotherapy along with radiotherapy [18]. Smith et al. describe a 13 year old female patient with ALL who had acute left sided facial palsy accompanied by complete right sided facial paralysis during her fourth CNS relapse [19]. With palliative whole brain radiation, her symptoms transiently resolved but recurred 2 months later. Table 1 provides an overview of treatment modalities used and outcomes in cases of acute leukemia with cranial nerve palsy. Most modern literature supports the early use of intrathecal chemotherapy (local effect, fast clearance, less systemic toxicity). Radiation therapy is often employed, especially if mass effect or CN dysfunction is present. Systemic chemotherapy is not sufficient for treatment of CNS ALL as it may not penetrate the blood brain barrier.

It is unfortunate that despite no blasts being found on repeat lumbar puncture, our patient's symptoms did not improve. He had no sign of residual disease in the CSF. Residual micro infiltration of the CN roots too small to be seen on imaging, and not contaminating the surrounding CSF may be responsible. The inflammation at the nerve roots caused by chemo/radiation therapy may also be responsible for the continuing CN dysfunction.

Given that our patient had recurrent systemic ALL based on the repeat bone marrow biopsy, it is unlikely he cleared the disease from the CNS. We believe that persistent CNS ALL was responsible for the continuing CN dysfunction.

Our case highlights a rare presentation of ALL as bilateral cranial nerve palsy and underscores the morbidity and mortality associated with cranial nerve involvement. Although a variety of modalities have been used to treat cranial nerve involvement in leukemia, cranial irradiation and intrathecal chemotherapy is the likely best treatment strategy. Clinicians should remain aware of cranial nerve palsy as a potential harbinger of leukemia.

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