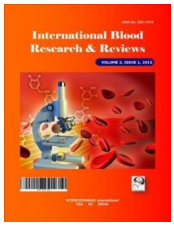

International Blood Research & Reviews
4(2): 1-8, 2015, Article no.IBRR.17731
ISSN: 2321–7219

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A Case of Isolated CNS Relapse in a CML Patient on Chronic Phase

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Authors' contributions

This work was carried out in collaboration between all authors. Authors FZM and LABM drafted and wrote the manuscript. Author MRIDC reviewed and proofread the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IBRR/2015/17731
Editor(s):
(1) Karl-Anton Kreuzer, University Hospital of Cologne, Germany.
(2) Shinichiro Takahashi, Kitasato University School of Allied Health Sciences, Japan.
(3) Tadeusz Robak, Medical University of Lodz, Copernicus Memorial Hospital, Poland.
Reviewers:
(1) Atef Mahmoud Mahmoud Attia, National Research Centre, Egypt.
(2) Golam Hafiz, Bangabandhu Sheikh Mujib Medical University, Bangladesh.
Complete Peer review History: http://sciencedomain.org/review-history/11202

Case Study

Received 24th March 2015
Accepted 14th July 2015
Published 1st September 2015

ABSTRACT

We report a patient who achieved hematologic response with Imatinib mesylate and is in chronic phase, but after several years developed neurologic symptoms and was eventually documented to have an isolated CNS relapse. The patient was treated with intrathecal chemotherapy to clear the spinal fluid of the leukemia cells. Imatinib mesylate (STI-571) is a potent and selective inhibitor of BCR-ABL tyrosine kinase and has emerged as a treatment of choice in chronic myeloid leukaemia. However because of poor penetration of the drug to the blood-brain barrier of the central nervous system (CNS), then the CNS acts as a sanctuary site for malignant cells.

Keywords: CNS leukemia; chronic myelogenous leukemia; extramedullary leukemia.

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1. INTRODUCTION

Extramedullary leukemia is a well-recognized occurrence and that the central nervous system (CNS) is one of those documented to be affected. In Acute lymphocytic leukemia 6% of patients who were diagnosed with the disease have evidence of CNS involvement; the same number is also noted for those with Chronic myelogenous leukemia with note of involvement of the meninges [1]. Imatinib mesylate (IM) a tyrosine kinase inhibitor used for the treatment of CML allowed patients to achieve hematologic and molecular response. An investigation made by Heike Pfeiffer et al. however showed that 12% of the 103 patient population had relapse with CNS involvement and a portion of which have isolated CNS recurrence without hematologic relapse.

In our case report we are presented with a patient who achieved hematologic response with Imatinib mesylate, however later on developed neurologic symptoms and was eventually documented to have a CNS relapse of CML.

2. CASE

A 42 yr old male was diagnosed with chronic myelogenous leukemia (CML) since 2001 with a cytogenetic finding of hypodiploidy karyotype t (9;22) (q34;q11) Philadelphia chromosome positive. He was started on Imatinib 400 mg/day on 2005, with note of hematologic response during his follow-up. On 2012 his Imatinib dose was adjusted to 600 mg/day and then after a few visits he was lost to follow-up and upon clinical evaluation on 2013 he reported that he was not complaint with Imatinib for almost 10 months.

On August 2013, 7 months prior to admission he was already complaining of frontal headache throbbing in character, unrelieved by intake of pain medications. He then sought consult where a Cranial CT scan image was taken, he was then managed as a case of sub-arachnoid hemorrhage and was treated with medical decompression after which he was discharged stable after a month. He was able to do his usual activity of daily living, and that his Imatinib was reduced to 400 mg/day.

On January 2014, he noted recurrence of the same character of headache severe now accompanied with weakness of extremities, he consulted his physicians and cranial imaging was done once more which showed no change from his previous CT scan imaging, symptoms were persistent, but now with note of blurring of vision. He was admitted for work-up where cervicothoracic MRI was done which showed a suspicious cerebellar enhancement along the cerebellar folla. CNS infection or CNS involvement with leukemia are being considered at this time, hence a lumbar puncture was then performed. Analysis of the CSF collected showed lymphocytosis of 99% in a WBC count of 3660 cells/ul with a protein count of 103 mg/dl, gram stain shows no microorganism, other tests done including special stains and immunologic testing for an infectious cause were performed. The decision then is to treat with Anti-Koch's, based on CSF picture of lymphocytosis. The test however eventually showed negative findings and treatment with anti-Koch's was continued. His symptoms eventually progressed; intermittent headache, progression of blurring of vision and decrease in hearing. A lumbar tap and CSF analysis was done once more still showing only lymphocytosis with WBC count of 1890 cells/ul, 100% of which is lymphocytes no blast cells were reported. Fungal tests were done, results were negative. Ophthalmologic examination was done which revealed a possible nerve pathology of both eyes with note of vitreous infiltrate.

Visual loss was progressive until loss of light perception in a span of 1 month despite initial management. Since all treatment and diagnostic options were explored and still symptom was progressive a reevaluation was then contemplated, a 3rd attempt of lumbar puncture was then decidedly done, this time to start treatment with intrathecal chemotherapy for CNS leukemia, opening pressure at this time was noted to be high at 340 mmH20 and closing pressure of 180. Specimens were still sent for analysis and CSF flow cytometry, intrathecal chemotherapy with hydrocortisone and methotrexate was given. The results of the CSF at this time shows 22% blast cells in a WBC count of 3,103 cells/cu mm and flow cytometry positive for leukemic cells confirming CNS leukemia. He then received 3 doses of Intrathecal Methotrexate (12 mg) given 2x a week (every 5 days) followed by 2 doses of methotrexate, hydrocortisone and cytarabine. CSF analysis was done during every lumbar tap for intrathecal chemotherapy, which showed a decreasing pattern of WBC followed by a decrease in blast cells. The patients visual loss however was noted to be persistent still with no signs of improvement. His headache no longer recurred and hearing loss did not progressed. He continued intrathecal chemotherapy and he was

shifted to Nilotinib. During this time his complete blood count was normal. A bone marrow aspiration and biopsy was also done to evaluate the status of his chronic myelogenous leukemia and result was consistent with a chronic phase, CML.

3. DISCUSSION

In the Philippines the annual incidence of CML is at 0.7-0.9 affecting males more than females with a median age of 45-55 [2]. Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder of the hematopoeitic stem cell (HSC), associated with an acquired genetic abnormality, the Philadelphia chromosome. Philadelphia chromosome is present in >90% of patients, which is a shortened chromosome 22 resulting from a reciprocal translocation between the long arms of chromosomes 9 and 22 t(9; 22)(q34;q11) this chromosomes causes the formation of BCR-ABL fusion gene which in turn forms the oncogene, $p210^{BCR/ABL}$ [3]. This oncogene then causes an increase in tyrosine kinase activity and the end result is growth factor independence, leukemic cell growth in hematopoietic cell lines and decrease in apoptosis [3]. With the approval and introduction of tyrosine kinase inhibitors such as Imatinib as treatment for Ph+ leukemia (AML and CML) most were able to achieve hematologic and even molecular response. Despite the remarkable therapeutic effect of Imatinib in inducing remission, some patients still develop refractory disease and some even progress to blastic phase [4]. The progression to blastic phase is influenced by the BCR-ABL gene by which if remained untreated causes genetic instability with impaired DNA repair then DNA damage and eventually leading to blast crisis. [5] Oral tyrosine kinase inhibitors inhibit BCR-ABL-tyrosine kinase. However, the first and second generation tyrosine kinase inhibitors do not penetrate the blood–brain-barrier so that isolated CNS blast crises have been described in several cases [5]. Blastic phase of CML is not limited to peripheral involvement. In a review made by Sohl of 900 patients with CML being treated with Imatinib, they identified 30 patients with extramedullary involvement 15 of which is CNS [6]. Since 1980's reports regarding incidence of CML with extramedullary involvement were documented, most commonly affecting the lymph nodes and a rather small group involving the CNS [7]. CML in accelerated and blastic phase with central nervous system involvement is well known but sporadically reported in literature. Case studies and small series report cerebrospinal fluid with lymphoid or monocytoid blasts as well as parenchymal and dural lesions on patients in blastic phase [8], and more rare are CML in blastic phase presenting as an isolated CNS involvement of leukemia [9-22]. To our knowledge there is no case reported yet in the Philippines regarding CML in blastic phase presenting only in the CSF.

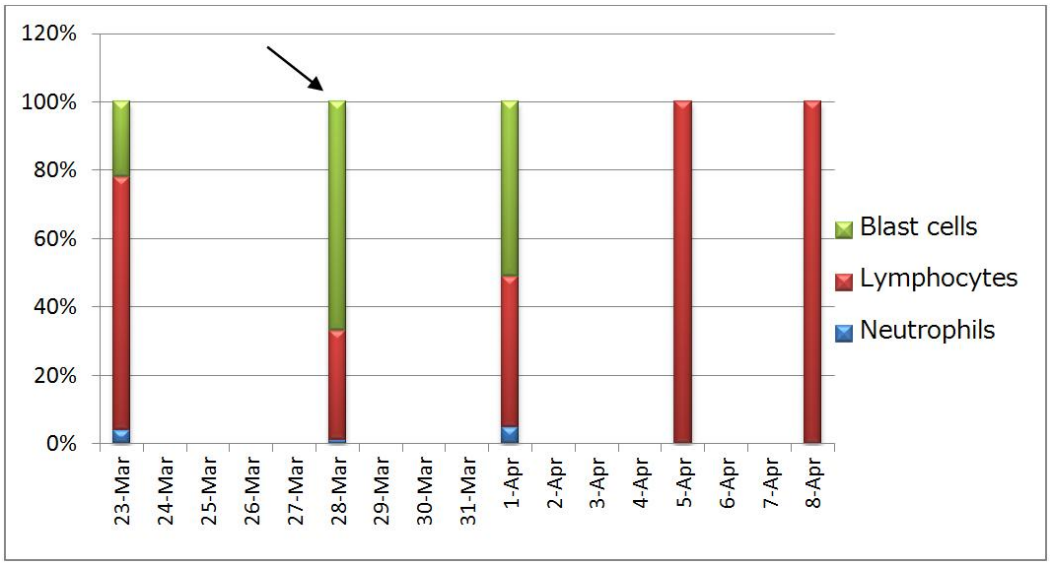

Fig. 1. Spinal cord fluid taken during intrathecal chemotherapy showing a deceasing trend of blast cells upon start of intrathecal chemotherapy, the pointed arrow shows the date of the start of intrathecal chemotherapy

Table 1. Spinal cord fluid analysis showing an overall decrease in total WBC count and a decrease in blast and neutrophil counts, opening and closing pressures was also noted to be decreasing

	Total WBC	Neutrophils	Lymphocytes	Blast cells	Opening pressure	Closing pressure
23-Mar	3,103/mm3	4%	74%	22%	340	180
28-Mar	267/mm3	1%	32%	67%	230	170
1-Apr	843/mm3	5%	44%	51%	270	220
5-Apr	3/mm3	0%	100%	0%	240	190
8-Apr	11/mm3	0%	100%	0%	140	120
28-Apr	19/mm3	0%	100%	0%	120	120
14-May	7/mm3	0%	100%	0%	120	100

The central nervous system is a well-known sanctuary site of leukemic blasts cells. Theoretically, circulating leukemic cells enter the brain or meninges by 5 different routes: 1) passage through the thin walls of the capillaries of the brain and enter the brain tissues directly, 2) migration of leukemic cells through the capillaries and specialized ependymal cells which form the choroid plexus, 3) migration through the walls of vessels which lie in the arachnoid and subarachnoid area, 4) migration through the capillaries of the non-neural areas, and lastly 5) direct migration and growth through perivascular and perineural tissues of vessels and nerves which cross the subdural space. Common to all these routes is the fact that hematogenous spread is the most important vehicle [23].

Leukemia and lymphoma do metastasize to the nervous system but rarely involve brain parenchyma and more characteristically involve the leptomeninges. Leukemic parenchymal tumor also known as chloroma is made up of myeloid leukemic blasts commonly seen in acute myelogenous leukemia and would give mass effect depending on the location of the tumor. While in leptomeningeal metastasis because there is multifocal involvement of the cerebrum, cranial nerves and spinal compartment it may present with symptoms and signs involving one or all of these locations. Headache and mental status changes are the most common cerebral symptoms. Facial weakness, facial numbness, diplopia, visual problems are manifestations of cranial nerve involvement [24]. In our patient, a chronic benign headache was the first manifestation which was attributed to other brain pathology, the clincher to the diagnosis of a possible leptomeningeal metastasis was the development of loss of vision from cranial nerve compression or involvement.

In diagnosis of CNS leptomeningeal leukemia, aside from the patient's clinical presentation of neurologic involvement, a CSF analysis is usually employed to document and strengthen diagnosis. A positive CSF cytology however is just seen in only 50% of patients with documented leptomeningeal metastasis [25]. A repeated spinal tap may sometimes be warranted as it increases the chances of yielding identification of tumor cells and having a positive cytometry test [25]. Neuroimaging may also be used to find diagnostic characteristics of CNS leukemia. Establishing the diagnosis may sometimes be challenging as that said tests may all show negative or equivocal findings, the physician may however deduce the diagnosis by process of elimination and that if all alternative diagnosis has been explored and excluded some clinicians find it acceptable to treat in the absence of diagnostic confirmation [25].

With the introduction of Imatinib more Filipinos are able to achieve hematologic response and even some achieving molecular response [2]. Progression to blastic phase is still documented however, some with CNS involvement or CNS alone despite maintenance of Imatinib. There is no standard of treatment established yet for CML involving the CNS however. Conventional therapy for CNS leukemia, includes intrathecal chemotherapy, high-dose systemic chemotherapy (cytarabine, methotrexate), and radiotherapy. Caution is usually employed in its use however as many patients experience significant toxicity, short-lived responses, and ultimately death resulting from refractory leukemia [26]. Currently tyrosine kinase inhibitor used for CML is Imatinib and though it is effective in controlling CML several studies have shown that the penetration of the drug and its metabolites into the CNS is poor [27].

Table 2. Cases of isolated CNS relapse in CML patients

Case	Year	Author/s	Age	Sex	Presentation	Treatment	Outcome
1	2015	Castillo, Mesina, Morillo (present case)	42yo	Male	Headache, visual loss and hearing loss	IT MTX, Cytarabine and Hydrocortisone Nilotinib	No return of blasts in CSF for a month
2	2015	Gomez J, Dueñas V	33 yo	Male	Headache, Nausea Confusion	Dasatanib 70 mg PO BID Triple Intrathecal chemotherapy	Alive, CCyRwithout signs of systemic and (CNS) relapse
3	2013	Park MJ, Park PW	54 yo	Male	Headache	Dasatinib, intrathecal methotrexate, & cranial irradiation therapy	Alive, Major CyR
4	2013	Nishimoto	22 yo	Male	Headache, Fever Impaired vision	Imatinib+IT+RT+allo-SCT	Alive
5	2012	Fuchs Raenhoffer, Schumm	64 yo	Female	Cognitive and Seizures and polyneuropathy	Triple IT therapy, Cytarabine, MTX, dexamethasone Dasatinib, Allo-PBSCT	Dead
6	2011	Radhika, Minakshi, Rajesh	15 yo	Female	Headache, vomiting and backache	Increased Imatinib to 600 mg/day, with intrathecal and cranial radiotherapy	Not specified
7	2011	Radhika, Minakshi, Rajesh	37 yo	Male	Chills, headache, vomiting and altered sensorium	Increased Imatinib to 600 mg/day, with intrathecal and cranial radiotherapy	Not specified
8	2010	Thomas	33 yo	Male	Back pain and multiple cranial nerve abnormality	IT + RT Dasatanib, Ara-C,Allo-PBSCT	Alive
9	2009	Jeon, Shin et al.	71yo	Male	Dysarthria and R sided weakness with leptomeningeal mass	Imatinib 400 mg/day	Expired
10	2009	Isobe et al.	61 yo	Male	Vomiting and visual disturbances	IT+Auto-PBSCT Imatinib	Alive
11	2009	Lee et al.	39 yo	Male	Headache and diplopia	IT Imatinib	Alive
12	2008	Barlow et al.	68 yo	Male	Headache and cerebellar dysfunction	IT+RT Imatinib	Alive
13	2007	Altintas	39 yo	Male	Headache, vomiting	IT+RT	Alive

		Et al				Imatinib	
14	2007	Aichberger	52 yo	Male	Headache and ataxia	IT+RT Imatinib	Alive
15	2006	Kim et al.	42 yo	Male	Headache and vertigo	IT+craniotomy Imatinib	Dead
16	2005	Johnson et al.	50 yo	Male	Headache, nausea and vomiting	IT+Allo-PBSCT Imatinib	Dead
17	2004	Bujassoum et al.	42 yo	Female	Headache	IT + Allo-PBSCT+RT Imatinib	Alive
18	2004	Bornhauser et al.	56 yo	Female	Ataxia and blurring of vision	IT + Allo-PBSCT+RT Imatinib	Dead
19	2004	Rajappa et al.	39 yo	Male	Headache and vomiting	IT+RT Imatinib	Alive
20	2004	Rytting, Wierda	48yo	Male	Headache, Night sweats and lymphadenopathy	IT therapy with alternating Cytarabine and MTX Craniospinal RT Imatinib	Remission HSCT
21	1978	Meyer and Cuttner	7yo	Male	Frontal headache, vertigo and diplopia	IT Cytosine arabinoside followed by splenectomy and chemoimmunotherapyMylern and methanol extracted residue of BCG	No blastic transformation 42 mos later

Furthermore Robert Ilaria of University of Texas Southwestern Medical Center, USA explains that it does not cross the brain barrier and hence is not effective for CML affecting the CNS. Table 2 shows above different approaches made by different institutions or groups. All of which used Intrathecal therapy with Cytarabine and Methotrexate in combination with Imatinib or Dasatinib. The group of Fuch's however used Dasatinib instead of Imatinib as that it has better penetration to the blood brain barrier and is associated with better survival [27].

4. CONCLUSION

In conclusion an isolated CNS relapse of CML is a rare case, patients on Imatinib with hematologic remission may still progress to blastic phase sometimes presenting as an isolated CNS relapse. CNS leptomeningeal leukemia is challenging to diagnose with a high percentage of the tests to come out negative, however if all other possible disease entities are excluded treatment should already be considered even with the absence of a concrete diagnostic test. Treatment includes Intrathecal therapy with Methotrexate and Cytarabine with Dexamethasone, in combination with a tyrosine kinase inhibitor, among of which Dasatinib as having evidence of blood brain barrier penetration and reduction of mortality. Constant communication with the patient is important especially when diagnosis and treatment is challenging since intrathecal chemotherapy would be frequent, a good rapport with the patient is key and helping them understand their condition better.

CONSENT

All authors declare that 'written informed consent was obtained from the nearest keen for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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