

Case Report

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A Case with Neurofibromatosis and Chronic Myeloid Leukemia in Blastic Crisis Treated with Imatinib

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Abstract

A 61-year-old female presented with complaints of fever, general weakness and hepatosplenomegaly. She had a history of nonfamilial peripheral neurofibromatosis diagnosed as von Recklinghausen's disease since 30 years previous.

Physical examination was remarkable for skin colored cutaneous circumscribed nodules which appeared soft to the touch in both arms, the upper part of her abdomen, back, and posterior thigh. The liver was palpable 10 cm below the inferior border of the costal margin and she had evidence of significant splenomegaly. Laboratory results were as follows: hemoglobin 7.9 g/dl; ESR 142 mm/hour; leukocytes 22400x10⁹/L; neutrophils 35%; eosinophils 3%; basophils 4%; myelocytes 40%; myeloblasts 14%; promyelocytes 2%; and band form 2%. The bone marrow picture was chronic myeloid leukemia in blastic form. Chest CT scan showed the presence of numerous cutaneous nodules (neurofibromatosis). A biopsy of the tissue fragment from the nodules confirmed the presence of diffuse neurofibromatosis. Bone marrow cytology that included cytogenetic and immunophenotyping confirmed the presence of chronic myeloid leukemia with a positive Philadelphia chromosome and diploidy female clone in a blastic form (acute myeloid leukemia). Addition of 600 mg oral imatinib mesylate daily for one month and reduced to 400 mg daily yields complete hematological remission and complete cytogenetic responses.

This case illustrated an association between chronic myeloid leukemia, acute myeloid leukemia and neurofibromatosis in an adult.

Keywords: Neurofibromatosis, Chronic myeloid leukemia, Blast crisis, Philadelphia chromosome, Diploidy, Imatinib

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Introduction

Neurofibromatosis type 1 (NF1) is a multisystem disease that affects 1 in 3500 people worldwide.¹

The clinical course is generally

progressive but highly variable. It is one of the most frequent autosomal-dominant hereditary disorders. Although with a variable expression, there is an almost 100% genetic

component. However, at least 50% of all patients present with new mutations. Therefore, NFI exhibits one of the highest mutation rates in humans. Diagnostic features of this fully penetrant, autosomal dominant disease include café-au-lait spots, skin fold freckles, Lisch nodules, in addition to cutaneous, subcutaneous, and plexiform neurofibromas, optic gliomas (OGs), and bony lesions.^{2,3}

Chronic myeloid leukemia (CML) is a clonal stem cell disorder characterized by increased proliferation of myeloid cells and the presence of the Philadelphia chromosome. It is a common hematological malignancy. The natural history of CML is one of progression from a chronic phase via an accelerated phase to blast crisis. Patients in the blast crisis phase are often refractory to treatment. Chronic myeloid leukemia is diagnosed by the presence of the Philadelphia chromosome. This chromosome leads to a reciprocal translocation between chromosomes 9 and 22, juxtaposing the *BCR* and *ABL* genes onto chromosome 22, which results in the production of a fusion protein with abnormal tyrosine kinase activity.⁴ This leads to a proliferative change in the affected cells.⁵

Treatment of CML with imatinib is highly efficacious, with rates of complete hematologic response (CHR) that approach 100% in patients who are in the chronic phase of this disease.⁶ The use of imatinib mesylate (IM), an original ABL

tyrosine kinase (TK) inhibitor, to treat patients with Philadelphia-positive CML who are in the chronic phase appears to substantially prolong life when compared to treatment with interferon- α or interferon- α plus cytarabine.⁷

Case Report

We report the case of a 61 years old female who presented with general weakness and fever since one month prior. She had multiple café-au-lait spots for 30 years (Figure 1). On physical examination she was febrile and pale. Her abdomen was markedly distended with a firm liver that was palpable 10 cm below the right costal margin and a huge spleen that extended to the umbilical level. Her initial white blood cell count was 22400/mm³ with 35% neutrophils, 3% eosinophils, 4% basophils, 40% myelocytes, 2% stabs, 2% promyelocytes and 14% myeloblasts. The hemoglobin was 7.9 g/dl and she had a platelet count of 96000/mm³.

Bone marrow aspiration was remarkable for hypercellularity and the M:E ratio was 3.6:1. There was an increased myeloid series with a shift to the left and the presence of 46% myeloblasts (Figure 2). The patient's karyotype was 46, XX with t(9;22)(q34;q11.2) (5) and diploid female clone of 46,XX (2). Immunophenotyping results of cluster of differentiation (CD) were: CD3 (7%), CD13 (30%), CD33 (35%), and CD5 (5%). Skin biopsy confirmed the presence of



Figure 1. Neurofibroma on the patient's arm.

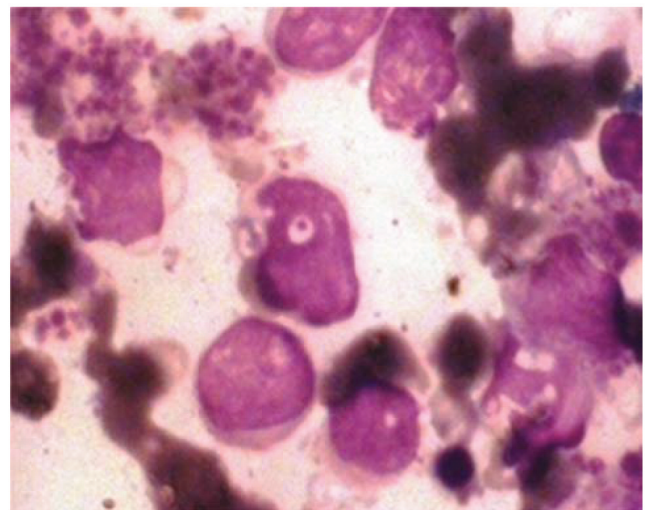


Figure 2. Bone marrow aspiration cytology shows myeloblasts.

diffuse NF1.

The patient was treated with imatinib (600 mg) for four weeks which was reduced to 400 mg daily for two years. Complete remission was achieved after six months of treatment. At the patient's final evaluation after two years, her white blood cell count was 4500/mm³ with 40% neutrophils, 1% eosinophils, 51% lymphocytes and 8% monocytes. The hemoglobin level was 12.0 g/dl and platelet count 186,000/mm³. Bone marrow aspiration was negative and indicated that the patient was in complete remission. She had a karyotype 46, XX with no Philadelphia chromosome noted.

Discussion

The association between hematologic malignancies and germ-line mutations of NF1 have been established.^{10,11} Children with NF1 have a 500-fold increased risk of developing CML, a rare form of leukemia; higher incidences of non-Hodgkin's lymphoma and acute lymphoblastic leukemia have also been reported.^{12,13} As far as adult patients are concerned, although the risk of malignancies in patients diagnosed with NF1 is well known and increases with age, the majority of cancers reported are nonhematologic neoplasms.¹⁴ Nevertheless, the association between both leukemia and lymphoma has been described.¹⁴ Of these, there have been a few cases associated with AML although the association could be supported by numerous studies on somatic mutations of the NF1 gene and AML.¹⁵ In subjects with NF1 mutations, the loss of the remaining NF1 allele is a frequent event in AML, as it is a gene subject to copy number alteration.¹⁶ The frequency of NF1 null AML is estimated to be 7%.¹⁵

In our case, the myeloid lineage and presence of myelocytic precursors resembled the morphology of CML in blastic transformation, which supported the hypothesis of a connection between the patient's leukemia and NF1.¹³

For patients with blast crisis CML who are Philadelphia-positive, the response rate to imatinib is high and toxicity is considerably lower than with

standard chemotherapy. However, the durability of response tends to be quite short. For these reasons, we consider imatinib as part of a treatment strategy that incorporates conventional chemotherapy. A hematologic responses was observed with a major cytogenetic response with no Philadelphia positive cells was observed at 3,6, and 12 months and at the two-year follow up.

Conclusion

Neurofibromatosis 1 is a common inherited syndrome with a high number of potentially associated pathologies and malignancies. A clear correlation between NF1 and leukemia depends on proving the presence of possibly related genetic defects in both tumor cells (leukemia and fibroma). Imatinib mesylate is the current standard first-line therapy for all phases of CML. Treatment with Imatinib mesylate (Glivec) is not available for poor patients in Yemen. We recommend the Ministry of public Health to provide this treatment for free to all patients with CML instead of hydroxyurea.

Conflict of Interest

No conflict of interest is declared.

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