



Case Report

Acute lymphoblastic leukemia with Neurofibromatosis 1 : A case report

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ABSTRACT

Neurofibromatosis type 1 (NF1) or Von Recklinghausen disease is a neurocutaneous genetic disorder with an autosomal dominant transmission. Acute Lymphoblastic Leukemia (ALL) has been rarely seen to be associated with this disease. This case report is of a 15 year male who was diagnosed to have ALL with NF1. There was a history of NF1 with multiple neurofibroma in the mother. Currently on BFM-95 protocol based treatment, the patient is responding well to the therapy.

KEYWORDS: Neurofibromatosis, acute lymphoblastic leukemia.

INTRODUCTION

Neurofibromatosis type 1 (NF1), otherwise known as Von Recklinghausen disease, is a neurocutaneous genetic disorder with an autosomal dominant transmission.[1] The prevalence of NF1 has been estimated as being approximately 1 in 3500, the penetrance is associated with a high phenotypic variability. Neurofibromatosis (NF) has markedly variable expressivity. The most common clinical features are *café au lait* macules, skinfold freckling, Lisch nodules (hamartomas of the iris) and neurofibromas, along with any organ system being affected since it is a multisystem disorder.[2]

The association between NF1 and various pathologies has been established, few of these being orthopaedic abnormalities, neurological and psychiatric disorders, congenital cardiac defects and vasculopathy, ophthalmological diseases and an increased cancer risk.[3] It is estimated that such predisposition as a 2.7-fold increased overall risk of cancer malignancies in patients with NF1, and a cumulative risk of 20% by the age of 50 years.[4] The most represented tumors derive from tissues of neuroectodermal origin such as central nervous system, peripheral nerve sheath tumors and pheochromocytoma. Malignancies such as juvenile monocytic leukemia, gastrointestinal stromal tumors, rhabdomyosarcoma have also been strongly associated to NF1, while the onset of breast cancer, melanoma, acute lymphoblastic leukemia,

non-Hodgkin's lymphoma, carcinoid and Wilm's tumors is considered a possible association and is currently under evaluation.[2]

Acute lymphocytic leukemia (ALL) is the most common paediatric malignancy accounting for nearly 75% of all freshly diagnosed leukemias in childhood.[5] Attention is drawn to the fact that although NF-1 cases have a high risk of developing non lymphocytic leukemia, in rare cases NF patients may develop ALL. This case report is a rare occurrence of concomitant neurofibromatosis and ALL.

CASE REPORT

A 15-year old male was admitted with complaints of fever for 1 month and easy fatigability. The patient's mother had neurofibromatosis 1 with multiple neurofibroma over the body. The patient was examined and was found to have multiple café au lait spots (Figure 1,2), bilateral cervical lymphadenopathy and mild hepatomegaly. Eye examination showed bilateral Lisch nodules (Figure 3). The presence of multiple café au lait macules covering the whole body, Lisch nodule and positive family history of mother having NF1 with multiple neurofibromas over the whole body (Figure 4) established the diagnosis of NF1 in the patient.

Routine investigations were performed, with CBC showing Hb -6.6gm/dL, WBC – 800, with ANC- 0, and platelet – 40,000/dL with no blasts seen in peripheral blood. HIV,

HBsAg and HCV markers were negative. Ultrasonography was suggestive of periportal lymphadenopathy and mild splenomegaly. The Chest X-ray was within normal limits. No abnormalities were detected on ECG and echocardiography. Bone marrow examination was done which was showing predominantly (80%) small blast with scant cytoplasm, coarse chromatin and indistinct nucleolus. Normal marrow elements were not seen ; suggestive of acute leukemia of lymphocytic/lymphoblastic morphology.

Immunophenotyping was performed which was positive for Tdt, CD20, CD79a. PAX5 was focally positive and scattered

CD3 positivity. CD34 and MPO were negative. All these were diagnostic of precursor B cell ALL. There was no CNS involvement and CSF examination was normal. The patient has been started on BFM-95 protocol based treatment and is tolerating therapy well.[6] There was blast clearance on day 8, suggesting good prednisolone response and bone marrow done for reassessment showed remission after induction phase. The patient has completed the reinduction phase of treatment and now on maintenance therapy as per the BFM95 protocol.

Fig 1. Cafe au lait macules



Fig 2. Cafe au lait macules



Figure :3 Lisch nodules

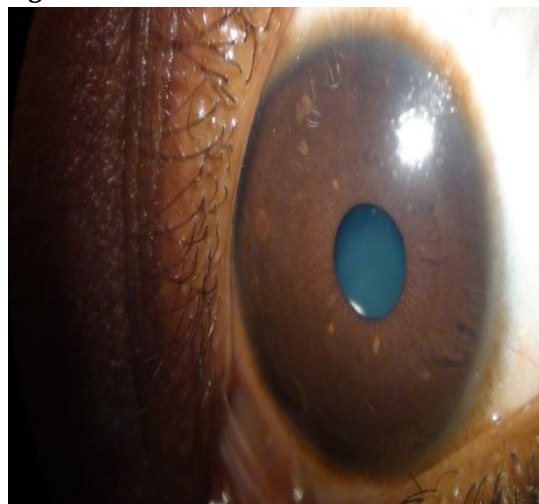


Figure: 4 Mother having NF1 with multiple neurofibromas



DISCUSSION

Leukemia in a child with NF-1 was first reported more than 30 years ago. It develops as a result of mutations in the NF1 gene which is located on 17q11.2. The product of this gene interacts with the ras p21 protein and may regulate ras activity. Mutations of the ras gene have been reported in some myelogenous leukemias (juvenile myelogenous leukemia) and Myelo Dysplastic Syndrome (MDS), but they are relatively less common in ALL. Although children with NF-1 are at increased risk of leukemia, ALL has been rarely seen in this condition, compared to malignant myeloid diseases, such as MDS and myeloproliferative neoplasms.

A population based study revealed a 5-10 fold risk of ALL in association with NF-1 and a much higher risk of chronic myelomonocytic leukemia (200 fold).[7] In another study by Bader and Miller who reviewed 29 patients with childhood leukemia associated with NF-1, the ratio of ALL:AML was 1:2.2, which is markedly different from the ratio of 4:1 found in normal children. [8] There are limited published reports of ALL in NF-1.[9-11]

CONCLUSION Although children with NF1 are at increased risk of developing various malignancies the association of ALL with this is still under evaluation. If treated with standard protocol these patient achieve good response and do well. Further studies are warranted for better understanding of the disease association and the outcome with different treatment protocol.

REFERENCES

1. Littler M, Morton NE. Segregation analysis of peripheral neurofibromatosis (NF1). *J Med Genet* 1990;27:307-10.
2. Boyd KP, Korf BR, Theos A. Neurofibro - matosis type 1. *J Am Acad Dermatol* 2009; 61:1-14.
3. Yohay K. Neurofibromatosis type 1 and associated malignancies. *Curr Neurol Neurosci Rep* 2009;9:247-53.
4. Walker L, Thompson D, Easton D, et al. A prospective study of neurofibromatosis type 1 cancer incidence in the UK. *Br J Cancer* 2006;95:233-8.

5. Pui CH. Acute lymphoblastic leukemia. *Pediatr Clin North Am* 1997;44:831-46.
6. Anja Möricke , Alfred Reiter , Martin Zimmermann , Helmut Gadner, Martin Stanull, Michael Dördelmann et al Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. *Blood* 2008 111:4477-4489
7. Stiller CA, Chessells JM, Fitchett M. Neurofibromatosis and childhood leukaemia/lymphoma: A population-based UKCCSG study. *Br J Cancer* 1994;70:969-72.
8. Bader JL, Miller RW. Neurofibromatosis and childhood leukemia. *J Pediatr* 1978;92:925-9.
9. Horigome H, Sumazaki R, Iwasaki N, Imoto N, Kinugasa H, Saito M, *et al.* Fatal eosinophilic heart disease in a child with neurofibromatosis-1 complicated by acute lymphoblastic leukemia. *Heart Vessels* 2005;20:120-2.
10. Cajariba MM, Reyes-Múgica M. Gaucher or pseudo-Gaucher? The challenge of several diseases colliding in a pediatric patient. *Hum Pathol* 2009;40:594-8.
11. Balgobind BV, Van Vlierberghe P, van den Ouweland AM, Beverloo HB, Terlouw-Kromosoeto JN, van Wering ER, *et al.* Leukemia-associated NF1 inactivation in patients with pediatric T-ALL and AML lacking evidence for neurofibromatosis. *Blood* 2008;111:4322-8.

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