

## A case report of acute myeloid leukemia and neurofibromatosis 1

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### Abstract

We report a case of a 65-year old patient affected by neurofibromatosis 1, documented by the presence of germ-line mutation on the *NF1* gene, who developed various hyperproliferative malignant and benign diseases. He was brought to our attention for the diagnosis of acute myeloid leukemia revealed by major fatigue and dyspnea. The disease characteristics at diagnosis were hyperleukocytosis and complex karyotype with the inversion of the chromosome 16, classifying as a high-risk leukemia. The association between leukemia and neurofibromatosis 1 is controversial and needs to be further investigated. Nevertheless, such patients present a wide number of comorbidities that make therapeutic strategies most difficult.

### Introduction

#### Neurofibrosis type 1

Neurofibromatosis type 1 (NF1), otherwise known as Von Recklinghausen disease, is a neurocutaneous genetic disorder with an autosomal dominant transmission. In 50% of cases, the mutation of the *NF1* gene arises *de novo*.<sup>1</sup> The prevalence of NF1 has been estimated approximately as one in 3500, the penetrance is 100% associated with a high phenotypic variability. The most common clinical features are *café au lait* macules, skinfold freckling, Lisch nodules (hamartomas of the iris) and neurofibromas, but, being a multisystem disorder, any organ system can be affected.<sup>2</sup> The association between NF1 and various pathologies has been established, such as orthopedic abnormalities, neurological and psychiatric disorders, congenital cardiac defects and vasculopathy, ophthalmological diseases and an increased cancer risk.<sup>3</sup> A prospective study has evaluated 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.<sup>4</sup> The most represented tumors derive from tissues of neuroec-

todermal 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, currently under evaluation.<sup>2</sup>

#### Acute myeloid leukemia

AML is a rare aggressive neoplasm of the hematopoietic myeloid stem cell. The incidence of AML development increases with age: less than 4% in patients under 60 years of age and becomes over 19% in patients over 75 years of age. The common clinical presentation is related to the invasion of the bone marrow by blast cells, which blocks the normal hematopoietic process, leading to anemia (shortage of erythrocytes), leukopenia and thrombocytopenia. Resultant symptoms and signs include fatigue, shortness of breath, infections and bleeding.

### Case Report

A 68-year old man was admitted to our hematology department with the diagnosis of AML revealed by routine laboratory tests performed in presence of a major fatigue and a dyspnea at minimum effort. The results showed a hemoglobin level of 7.7 g/dL, a total leukocyte count of  $14 \times 10^9/L$  with 50% blast cells, and a platelet count of  $114 \times 10^9/L$ . The bone marrow biopsy diagnosed acute myeloid leukemia. The morphology and immunophenotyping established the expression of markers connected with precursor stage and monocytic differentiation (FAB M2/M4).

The anamnesis of the patient was most complex, beginning with the diagnosis of neurofibromatosis type 1 at the age of 30 years for the presence of multiple neurofibromas and *tache au lait* macules covering the whole body. The mutation had most likely arisen *de novo* as there is no knowledge of close relatives presenting any of the classical cutaneous characteristics. The physical examination confirmed the presence of multiple neurofibromas, *tache au lait* macules and skinfold freckling. No liver or spleen enlargement was found. The clinical anamnesis reported various hyperproliferative disorders involving different organs. The patient has a history of hypertension since young age, which has led to the first heart attack at the age of 41 years. Following episodes at the age of 58 years, associated with a possible genetic predisposition for heart defects due to NF1, a dilated cardiomyopa-

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thy was revealed for which he received a heart transplant at the age of 59 years. He has been in treatment with cyclosporine since then. A multiple series of benign and malign tumors followed. The patient has undergone: i) a right hemithyroidectomy for an adenomatous thyroid hyperplasia; ii) a right hemicolectomy for an intestinal polyp classified as WHO low-grade dysplasia; iii) the excision of a melanoma Clark level II localized on the back; and iv) an inferior left lung lobectomy associated with lymphadenectomy for a bronchioloalveolar non-mucinous carcinoma. The patient also presented hypertrophy of the prostate (although this is most common in men his age) and a slight kidney failure. The last hyperproliferative disorder diagnosed was the acute myeloid leukemia for which he was admitted to the hematology department. On entering our unit, the patient presented  $9.0 \times 10^9/L$  of hemoglobin,  $55 \times 10^9/L$  platelets and  $21.6 \times 10^9/L$  leucocytes (1% neutrophils and 75% blast cells). The cytogenetic analysis showed a complex karyotype, with the inversion of the chromosome 16, and the molecular biology evaluation revealed the rearrangement of *CBFB-MYH11*. *NMP1* and *FLT3* genes were analyzed and these resulted wild-type. Considering the age and important comorbidities presented, the decision was taken to begin induction treatment with intermediate-dose cytarabine (Ara-C). The complete morphological remission was obtained after the first cycle and maintained during the second and third, without major complications during cytopenia. The patient is currently beginning the fourth cycle of therapy and is in good clinical condition.

## Discussion

*NF1* is a tumor suppressor gene localized on 17q11.2. It encodes neurofibromin, a negative regulator of proto-oncogene Ras. The loss of neurofibromin promotes Ras activity leading to constitutive downstream signaling and increased uncontrolled cell growth.<sup>5</sup> Hyperproliferation is a mechanism that involves every organ system leading to the predisposition for both cancerous and non-cancerous disorders. It is at the base of the so called Ras-opathies, a group of inherited disorders that share a germ-line mutation of the RAS-MAPK pathway, to which *NF1* belongs.<sup>6</sup>

The association between hematologic malignancies and germ-line mutations of *NF1* has been established in the pediatric setting. Children with neurofibromatosis 1 have a 500-fold increased risk of developing a rare form of leukemia, known as juvenile myelomonocytic leukemia (JMML); a higher incidence of non-Hodgkin's lymphoma and acute lymphoblastic leukemia has also been reported.<sup>3,7,8</sup>

As far as adult patients are concerned, even though the risk of malignancies in patients affected by *NF1* is well known and increases with age, most cancer cases reported are not hematologic neoplasms.<sup>4</sup> Nevertheless the association between both leukemia and lymphoma has been described.<sup>4,9-12</sup> Of these, few cases concerned acute myeloid leukemia, although the association could be supported by a wide number of studies on somatic mutations of the *NF1* gene and AML.<sup>13-16</sup> 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.<sup>17</sup> The frequency of *NF1* null AML is estimated to be 7%.<sup>13</sup> Given the incidence of neurofibromatosis type 1 in the population, and that of AML, more studies are needed to establish a direct connection between the two. In our case, the myeloid lineage and the presence of myelomonocytic precursors resembled the morphology of JMML, supporting the hypothesis of a connection between the patient's leukemia and *NF1*.

## Conclusions

What does seem to be certain is that with a patient presenting *NF1*, much attention has to be given to the anamnesis and the overall global clinical evaluation. *NF1* is a common inherited syndrome with a high number of potentially associated pathologies and malignancies.<sup>3</sup> Our patient reported important vasculopathy, hypertension and heart defects, widely described in literature as a consequence of *NF1*.<sup>18-20</sup> Moreover, he had undergone important surgery on more than one occasion for antecedent neoplasms. These patients are, therefore, extremely fragile and any therapy proposed needs to be evaluated and managed according to the elevated number of comorbidities present.

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