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Familial neurofibromatosis type I and adult acute lymphocytic leukemia

Sir,

Individuals with neurofibromatosis type I (NF1; von Recklinghausen's disease) are predisposed to certain cancers. Children are at increased risk of developing benign and malignant solid tumors (mostly neural tumors) as well as hematologic malignancies including juvenile myelomonocytic leukemia (a rare hematologic malignancy that affects patients less than 4 years of age and that is sometimes associated with monosomy 7), the monosomy 7 myelodysplastic syndrome and acute myelogenous leukemia.[1] The risk of young children with NFI developing a malignant myeloid disorder is 200 to 500 greater than the normal risk[2] and several lines of evidence support the notion that the loss or mutation of the NF1 gene (a tumor suppressor gene) deregulates the Ras pathway which is responsible for the leukemogenesis in these children.[3] The relative risks for non-Hodgkin's lymphoma and acute lymphocytic leukemia (ALL) were increased in one series[2] but the risk of developing ALL was not increased in two other reports.[4,5]

In contrast to the situation in childhood, the association between NF1 and malignant blood disorders has not been demonstrated in adulthood.[3,6,7] A Medline® search of reports from the last 10 years uncovered only 2 adult patients with NF1 who developed an acute myelogenous leukemia[6,8] and none an ALL

It is, therefore, of considerable interest that we have seen 2 cases of adult-ALL, diagnosed over the last 12 months, in patients with familial NF1. This represents a 1.1% incidence in 176 ALL in patients over the age of 14 years seen in our Service during the last 25 years.

The diagnosis of NF1 is mainly clinical (*café-au-lait* spots, freckling, cutaneous neurofibromas, lentigo, Lisch's nodules). Our two patients had these signs and several relatives with the disease (Table 1) . Case #1 was a 19 year-old male with a familial history of NF1 (mother and the only sister affected) and case #2 a 31 year-old woman with NF1 extending through 4 generations (grandfather, mother, 2 uncles, 1 aunt and her only 14-year-old son affected). Both patients had the common ALL cell phenotype, a normal karyotype and very aggressive clinical evolution.

Table 1. Clinical characteristics of the patients.

	Case #1	*Case #2*
Age at diagnosis of ALL/sex	19/M	31/F
Familial history of neurofibromatosis (affected relatives)	Mother Sister Uncles (2) Aunt Son	Grandfather Mother
Clinical features of neurofibromatosis:		
>6 café-au-lait spots	+	+
Cutaneous neurofibromas	+	+
Freckles	+	+
Other abnormalities	-	-
ALL phenotype	Common	Common
Karyotype	Normal	Normal

Because NF1 in one of the most common autosomal dominant disorders (with an incidence of 1:3000 neonates), one must be aware that the association observed could easily occur by chance. Although case reports are not appropiate for causation assessment, they have the potential to generate new knowledge by stimulating reporting of additional single cases or the development of more traditional epidemiologic surveys that may lead to a precise estimate of risk. For additional information about the molecular pathoegensis of acute lymphoblastic leukemia, the reader is referred to recent papers in this journal.[9,10]

Thus, besides the well known association between NF1 and myeloid disorders in children, our two case reports reveal a possible causal relation between familial NF1 and adult onset ALL.

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Key words

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Central nervous system involvement in acute promyelocytic leukemia. A description of two cases and review of the literature

Sir,

Extramedullary involvement is infrequent in acute promyelocytic leukemia (APL), but it has been suggested that its incidence might be increasing. Two patients with APL and central nervous system (CNS) involvement are described and the possible relationship between this complication and new treatment approaches of APL are discussed.

Case #1. A 45-year-old woman was diagnosed with APL. Cytogenetic studies revealed a complex karyotype in bone marrow (46,XX,r(9) t(17;15;10) (q11; q22;q24) and a bcr-1 pattern of the PML-RARα fusion protein. A molecular complete remission (CR) was achieved within the first month from starting ATRA and standard chemotherapy. Five days after administration of a consolidation course she presented with a third cranial nerve palsy and examination of the cerebrospinal fluid revealed the presence of promyelocytes in which the PML-RARα rearrangement was detected. She was given ATRA plus intrathecal chemotherapy without achieving a response and died shortly thereafter from progressive disease.

Case #2. A 45-year-old man was diagnosed with APL and a bcr-1 pattern of the PML-RARα fusion protein was demonstrated in peripheral blood. CR was achieved after treatment with ATRA and standard chemotherapy. Twenty months later he presented with a bone marrow relapse. After attaining a second CR he underwent an allogeneic bone marrow transplantation (BMT). Twenty months after the BMT he developed a spinal cord syndrome due to a paravertebral mass. Biopsy of the tumor revealed promyelocytes with a PML-RARα rearrangement (bcr-1). Despite treatment with ATRA and local radiotherapy, the patient died from disease progression.

Extramedullary involvement, including CNS infiltration, has been rarely reported in APL. It usually occurs

Table 1. Reported cases of extramedullary disease in APL.

Author	*Year*	*A/S*	*ATRA**	*Extramedullary site*	*Interval*	*Cyto*	*Outcome*
Bermengo	1975	82/M	No	Cutaneous	0m	NA	Death (PD)
Belasco	1978	9m/M	No	Soft tissue	0m	NA	CR
Nihei	1984	55/M	No	Mediastinum and muscle	4m	NA	Death (PD)
Kubonishi	1984	23/M	No	Mediastinum	0m	NA	Death (PD)
Kanakura	1987	44/F	No	Intracerebral mass, CSF	0m	NA	CR (23m)
Baer	1989	59/F	No	Cutaneous	36m	NA	BM relapse
Zuiable	1989	31/M	No	SNC (extradural mass)	0m	No	BM relapse
Rush	1990	13m/M	No	Mandibular	22m	No	CR (16m)
Ajarim	1990	21/M	No	Mediastinum (also BM)	0m	No	BM relapse
Niazi	1991	26/M	No	Cutaneous and CNS	NA	NA	Death (PD)
Brown	1992	37/F	No	Optic nerve (also BM)	22m	Yes	CR (NA)
Longacre	1993	19/M	NA	Cutaneous	NA	NA	NA
Thomas	1994	68/F	Yes	Subcutaneous	10m	Yes	CR (8m)
Weiss	1994	31/M	Yes	External auditory canal	11m	Yes	CR (NA)
Weiss	1994	33/M	Yes	Cutaneous &lymph node	11m	Yes	CR (NA)
Giralt	1994	23/M	Yes	Cutaneous & CSF	13m	Yes	CR (NA)
Giralt	1994	35/M	Yes	Cutaneous	1,5m	Yes	Death (PD)
Giralt	1994	47/F	Yes	Cutaneous	5m	NA	Death (PD)
Tosi	1995	27/M	No	Epidural	0m	Yes	CR (14m)
Hazneradoglu	1995	19/M	No	Gingiva	15m	NA	Death (PD)
Békássy	1995	24/F	NA	Cutaneous	NA	NA	Response
Békássy	1995	3/F	NA	Spinal	NA	NA	Death (PD)
Békássy	1995	26/M	NA	Testicle&spinal	NA	NA	Death (toxic)
Lederman	1995	46/F	No	Subcutaneous&CNS	6m	Yes	Response
Selleri	1996	31/F	No	Cutaneous	18m	Yes	CR (25m)
Wiernik	1996	5/F	Yes	Gingiva	21m	Yes	Death (PD)
Wiernik	1996	25/F	No	Cutaneous (also BM)	6m	Yes	Death (PD)
Chen	1996	74/M	No	Spleen	0m	Yes	Death (PD)
Martinelli	1997	42/M	No	Bone (L4)	0m	Yes	BM relapse
Evans	1997	23/M	Yes	CNS	15m	Yes	Death (GVHD)
Evans	1997	22/M	Yes	Bone (mastoid)	6m	Yes	CR (NA)
Evans	1997	49/F	Yes	CNS(CSF+)	NA	Yes	Death (PD)
Molero	1997	40/M	Yes	CNS(CSF+)	13m	Yes	Death (PD)
Ueda	1997	66/M	Yes	Cutaneous (also BM)	7m	Yes	NA
Del Río	1997	28/F	No	Cutaneous (also BM)	7m	NA	PD
Kishimoto	1997	11/F	Yes	Cutaneous	2-3m	Yes	PD
Castagnola	1997	23/M	No	CNS	11m	Yes	Death (PD)
Maloisel	1997	42/M	Yes	Colon	NA	Yes	Death(PD)
Forrest	1997	34/M	Yes	Testicle	120m	Yes	Death (PD)
Liso	1998	17/M	No	Lymph node	25m	Yes	Death (PD)
Liso	1998	48/M	No	Cutaneous	14m	Yes	Death (PD)
Liso	1998	22/F	No	Cutaneous	14m	Yes	Death (GVHD)
Liso	1998	25/F	No	Cutaneous	12m	Yes	Death (PD)
Liso	1998	30/M	Yes	CNS (CSF+)	9m	Yes	CR (12m)
Liso	1998	44/F	Yes	Cutaneous	10m	Yes	CR (20m)
Liso	1998	45/M	Yes	Cutaneous	0m	Yes	CR (31m)
Present case		37/F	Yes	CNS (CSF+)	1,5m	Yes	Death (PD)
Present case		45/M	Yes	CNS (extradural mass)	31m	Yes	Death (PD)

A/S: age and sex; ATRA: prior therapy with ATRA; Interval: months from diagnosis to extramedullary disease; Cyto: t(15;17)/PML-RARα fusion protein. BM: bone marrow; CSF: cerebrospinal fluid; PD: progressive disease; NA: not available.