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Research paper

Pulmonary Langerhans cell histiocytosis, acute myeloid leukemia, and myelofibrosis in a large family and review of the literature

Matthew P. Blakley[a,b,1], Janice P. Dutcher[a,*], Peter H. Wiernik[a,2]

[a] Cancer Research Foundation of New York, USA
[b] College of Human Ecology, Cornell University, USA

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ABSTRACT

Background: There is mounting evidence that Langerhans cell histiocytosis (LCH) and acute myeloid leukemia (AML) are hematopoietic neoplasms that arise from the same myeloid precursor cell. In addition, studies suggest a relationship between LCH and primary idiopathic myelofibrosis (MF). Furthermore familial LCH, AML, and MF have each been reported.

Methods: We examined more than 750 pedigrees of familial hematologic malignancies for evidence of familial LCH, AML, and/or MF and identified one family with all three neoplasms, which is presented here.

Findings: In four generations of this large family there are five cases of AML in three generations, two cases of LCH in two generations and three cases of MF in two generations. Anticipation of −18 and −6 years was present in the patients with MF, and −8 years in the patients with LCH. Anticipation was also identified between one AML patient pair in generations III and IV (−18 years) and three patients with AML in generations II, III, and IV (−5 years and −10 years).

Interpretation: This is the first report of familial LCH, AML, and MF in one family. The pedigree suggests a common basis for these entities, which is further suggested by the presence of anticipation in the pedigree.

1. Introduction

Eosinophilic granuloma (now termed Langerhans cell histiocytosis) has been recognized as a distinct entity since described by Lichtenstein and Jaffe in 1940 [1]. Subsequently it was shown to be a histiocytic reticulosis related to Letterer-Siwe disease and Hand-Schüller-Christian disease [2]. Clinical aspects of primary pulmonary Langerhans cell histiocytosis (LCH) were well described by Friedman, et al. [3]. Here we report a large family with multiple cases of LCH of the lung, primary myelofibrosis and acute myeloid leukemia (AML). It is possible that there is a common genetic aberration in this family that caused or facilitated the development of these disorders. The recent discovery that LCH may be of hematopoietic origin makes the family reported here especially interesting [4,5].

2. Materials and methods − new family

We present here a large family (Table 1, Fig. 1) with two cases of LCH of the lung, three cases of primary myelofibrosis, five cases of AML, and nine cases of other hematologic and non-hematologic malignancies, including one each of myelodysplastic syndrome and chronic myelocytic leukemia (CML). Although LCH was not biopsy proven in patient 6, he had classic radiographic findings of pulmonary LCH. In such cases biopsy is not necessary to establish the diagnosis [6]. The subjects in this family were enrolled in an IRB-approved protocol and provided written informed consent for the Cancer Research Foundation to publish their information anonymously. However, they did not provide consent for tissue acquisition, despite attempts at retrieval as the family history evolved.

In the pedigree (Fig. 1), patient 3 (AML) was the mother of patient 8 (CML); patient 6 (LCH) was the father of patients 13 (myelofibrosis) and 14 (LCH); patient 9 was the brother of patients 10 (AML) and 11 (MDS and renal cell carcinoma) and the son of patient 4 (multiple myeloma); patient 12 (myelofibrosis) was the mother of patients 16 (AML) and 17 (myelofibrosis); patient 14 (LCH) was the brother of patient 13 (myelofibrosis) and the son of patient 6 (LCH); patient 16 (AML) was the sister of patient 17 (myelofibrosis). Because of the multigenerational occurrence of these diseases, we evaluated their transgenerational appearance for anticipation. Anticipation is defined in genetic diseases, to be the expression of a given phenotype at a younger

* Corresponding author at: 750 Kappock Street, # 511, Riverdale, NY 10463 USA.
E-mail addresses: matthewblakley19@gmail.com (M.P. Blakley), jpd4401@aol.com (J.P. Dutcher), pwiernik@aol.com (P.H. Wiernik).
[1] 730 University Avenue, Ithaca, NY 14850 USA.
[2] 43 Longview Lane, Chappaqua, NY 10514 USA.

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Table 1
Family with Langerhans cell histiocytosis, acute myeloid leukemia, and myelofibrosis in the pedigree.

Patient Number	Generation	Age at Dx/ Gender	Diagnosis
0	I	61/F	Ruptured spleen and leukocytosis
1	II	Adult/F	Breast Cancer
2	II	Adult/M	Larynx Cancer
3	II	54/F	AML
4	II	51/F	Myeloma
5	II	29/F	AML
6	II	57/M	LCH
7	III	74/M	CLL
8	III	Adult/F	CML
9	III	44/M	AML
10	III	67/F	AML
11	III	56/F	MDS/RCC
12	III	62/F	MF
13	III	50/M	MF
14	III	49/M	LCH
15	IV	27/F	Large Cell Lymphoma
16	IV	49/F	AML
17	IV	44/M	MF

Dx – diagnosis; AML – acute myeloid leukemia; LCH – Langerhans cell histiocytosis; CLL – chronic lymphocytic leukemia; CML – chronic myeloid leukemia; MDS – myelodysplasia; RCC – renal cell cancer; MF – myelofibrosis.
1. All Generation II subjects are siblings and all are children of Patient 0.
2. All Generation III subjects are siblings or first cousins.

age or with greater severity in successive generations, reflecting a genetic role in the development of these diseases.

Males and females were diagnosed with malignancy with equal frequency in this family and all were adults when diagnosed. The 2 LCH patients (patients 6 and 14) were males who were heavy smokers. There is weak evidence for anticipation in the pedigree among patients with AML (generation I–III, −5 years), LCH (generation I–II, −8 years) and myelofibrosis (generation I–II, −18 years) which supports the hypothesis that these entities have a genetic etiology in this family.

2.1. Details of patients with LCH, myelofibrosis or AML in the family (Table 1, Fig. 1)

Patient 3. A 54 year old woman was diagnosed with acute monocytic leukemia by bone marrow morphology in 1955. It is not clear how she was treated. She died one year later with active disease.

Patient 5. A 29 year old woman was diagnosed with acute monocytic leukemia in 1939 by peripheral blood morphology. She died a month after diagnosis with a white blood cell count (WBC) of 150,000/μL. An autopsy showed splenomegaly.

Patient 6. A 56 year old male obstetrician was admitted to the National Jewish Hospital in 1969 for a change in a chest X-ray. He had been a moderate smoker for 25 years and his father died at the age of 91 with emphysema. He had a prior admission in 1944 at age 31 for recurring episodes of severe chest pain and X-rays revealing a mass in the superior segment of the right upper lobe. A tuberculin skin test was positive but additional diagnostic evaluation was negative for active tuberculosis and no treatment was given. Subsequent annual chest X-rays showed no change in the lung lesion until October, 1969 and he requested further evaluation. The right upper lobe mass was now largely resolved but new interstitial changes were found. Evaluation for active tuberculosis and other infections was again negative but pulmonary function test results were consistent with early emphysema and an interstitial process. A chest CT scan revealed bilateral diffuse pulmonary interstitial infiltrates with multiple small cysts throughout both lungs, consistent with LCH. The patient died two years later with progressive pulmonary decompensation at age 58 years. An autopsy was not performed.

Patient 9. A 44 year old man diagnosed in May, 1974 with AML. His WBC was 32,000/μL with 89% myeloblasts. He was treated with cyclophosphamide, vincristine, cytarabine and prednisone and had a brief response. He relapsed in September, 1974 with a WBC of 12,000/μL and 90% blasts. He died one month later.

Patient 10. A 67 year old woman was diagnosed with myelodysplastic syndrome in March, 1998 with normal cytogenetics. By February, 2000 she had evolved into AML with M2 morphology and 36% peripheral blood myeloblasts. Her cytogenetics were still normal. She was not treated for leukemia and died four months later.

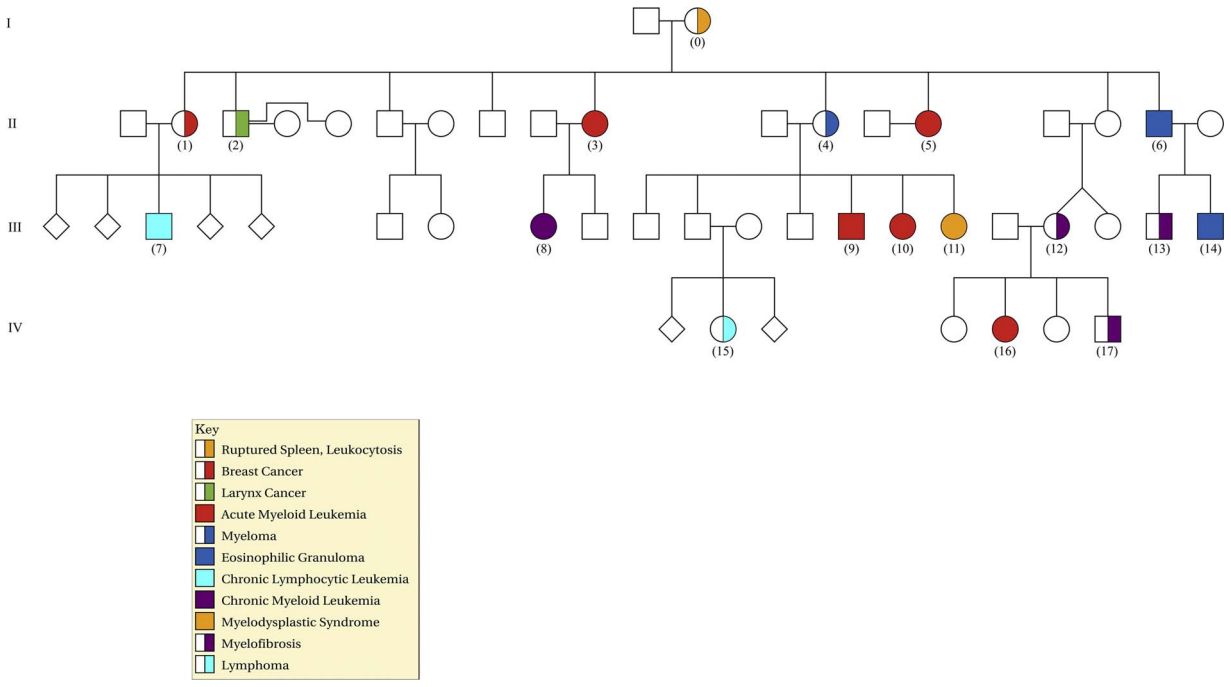

Fig. 1. Legend: Pedigree of the family with acute myeloid leukemia, idiopathic myelofibrosis and Langerhans cell histiocytosis. Numbers in the pedigree refer to individuals listed in Table 1.