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Familial Eosinophilia: Clinical and Laboratory Results on a U.S. Kindred

Albert Y. Lin,[1,4]* Thomas B. Nutman,[3] David Kaslow,[3] John J. Mulvihill,[5] Laura Fontaine,[6] Beverly J. White,[7] Turid Knutsen,[2] Karl S. Theil,[8] P.K. Raghuprasad,[9] Alisa M. Goldstein,[1] and Margaret A. Tucker[1]

[1]*Genetic Epidemiology Branch, National Cancer Institute, Bethesda, Maryland*
[2]*Medicine Branch, National Cancer Institute, Bethesda, Maryland*
[3]*Laboratory of Parasitic Disease, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, Maryland*
[4]*Division of Hematology/Oncology, Department of Medicine, Santa Clara Valley Medical Center, San Jose, California*
[5]*Department of Human Genetics, University of Pittsburgh, Pittsburgh, Pennsylvania*
[6]*Westat Inc., Rockville, Maryland*
[7]*Department of Cytogenetics, Corning Nichols Institute, San Juan Capistrano, California*
[8]*Division of Cytogenetics, Department of Pathology, The Ohio State University Medical Center, Columbus, Ohio*
[9]*Allergy and Asthma Center, Odessa, Texas*

We describe a five-generation kindred with familial eosinophilia (FE; MIM131400), characterized by the occurrence of sustained eosinophilia of unidentifiable cause in multiple relatives. The inheritance pattern is consistent with an autosomal dominant pattern. Among 52 related subjects studied, 19 were affected and 33 were unaffected. Ten unaffected spouses were also evaluated. Four subjects with sustained eosinophilia were diagnosed with cardiac abnormalities and two of them also had neurologic symptoms. In comparison with the unaffected or spouses, evaluation of complete blood counts showed that the affected relatives had, as expected, significantly higher white cell ($P < 0.005$) and absolute eosinophil counts ($P < 0.001$) and lower red cell counts ($P < 0.05$). Evaluation of serum cytokine levels (IL-5, IL-3, and granulocyte-macrophage colony-stimulating factor (GMCSF) and serology for parasitic helminth infection demonstrated no differences between the affected and unaffected individuals; no individuals studied had serologic evidence for parasitic infection. There were also no differences in anti-nuclear antibody, serum cobalamin (vitamin B_{12}) level, immunoglobulin level, leukocyte alkaline phosphatase, rheumatoid factor, HLA analysis, and stool findings for ova and parasites. Among eight affected persons who had peripheral blood or bone marrow karyotype analysis, two carried the same chromosome abnormality, a pericentric inversion of chromosome 10, inv (10) (p11.2q21.2). A gene mapping study is currently underway to study the underlying genetic mechanism(s) of this syndrome. Am. J. Med. Genet. 76:229–237, 1998.

KEY WORDS: familial eosinophilia (FE); hypereosinophilic syndrome (HES)

INTRODUCTION

Since Paul Ehrlich first described the eosinophil [Ehrich, 1879], investigators have been intrigued by the structure and function of this cell. Although patients with overproduction of eosinophils were identified prior to 1900 [Brown, 1898], the term "hypereosinophilic syndrome" (HES) was formally coined in 1968 [Hardy and Anderson, 1968]. HES is characterized by persistent and unexplained peripheral and bone marrow eosinophilia. The diagnostic criteria for HES are sustained peripheral eosinophilia of greater than 1,500/μL for at least 6 months, signs and symptoms of organ involvement, and no demonstrable secondary cause of eosinophilia such as neoplasms, connective tissue diseases, or parasitic infections [Chusid et al., 1975]. Familial eosinophilia (FE; McKusick [1994] number 131400) was noted as early as 1909 [Gaugain, 1909]. Naiman et al. [1964] reported a three-generation family with seven affected cases and reviewed 17 published families. From this experience,

*Correspondence to: Dr. Albert Y. Lin, National Cancer Institute, EPN 439, Bethesda, MD 20892. E-mail: lina@epndce.nci.nih.gov

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the investigators defined FE as the presence of: (1) significant eosinophilia (>400 × 10^3/L), (2) familial incidence, i.e., with more than one generation being affected, and (3) absence of other recognized causal factors [Naiman et al., 1964]. FE is thought to be part of the spectrum of HES. We present the clinical and laboratory findings from a large five-generation kindred with FE that has 19 affected members; an additional 33 unaffected blood relatives and 10 spouses were also evaluated.

MATERIALS AND METHODS

Case Report

The propositus, III-17 (Fig. 1), was born in 1930. In 1955, he was diagnosed with eosinophilia following a blood test which had been prompted by the diagnosis of eosinophilia in one of his sons (IV-34) who had had routine blood work. The propositus was asymptomatic and remained so until 1971, when he had atypical chest pain and underwent a cardiac catheterization. At the time, his white blood cell count was 12,400 × 10^6/L with an absolute eosinophil count of 3,224 × 10^6/L. The catheterization showed a normal mitral valve, normal left ventricular function, and normal coronary arteries. The symptoms subsided until 1980, when he developed dyspnea on exertion and generalized fatigue. His evaluation demonstrated thickening of the mitral valve with severe stenosis and moderate pulmonary hypertension. A white cell count was 10,400 × 10^6/L with an absolute eosinophil count of 4,680 × 10^6/L. In 1981, a repeat cardiac catheterization documented normal coronary arteries, a thickened mitral valve, and severe mitral stenosis. Left ventricular function was mildly to moderately impaired and right heart catheterization showed moderate pulmonary hypertension.

The patient underwent mitral valve replacement. Postoperatively the patient had an episode of amaurosis fugax consistent with embolization. He was treated with coumadin and the visual defect resolved within 1 week. Over the next 5 years, he had progressive worsening of symptoms related to congestive heart failure. He was hospitalized several times with possible myocardial infarction; however, he was noted to have intermittent atrial fibrillation, which was controlled effectively by quinidine. In March 1987, he underwent a third catheterization which showed severe left ventricular systolic dysfunction with a 15–20% ejection fraction. Endomyocardial biopsy revealed fibrosis with eosinophilic infiltration. He was treated with prednisone (80 mg/day) and referred (by P.K.R.) to the National Institutes of Health in April, 1987. At the initial evaluation, the patient had a loud S3 with a grade III/VI systolic ejection murmur at the left lower sternal border radiating to the apex. Neurologic examination showed diminished motor and general sensory function in the distribution of both ulnar nerves and the right anterior tibial nerve, consistent with mononeuritis multiplex. His white cell count was 8,100 × 10^6/L with an absolute eosinophil count of 2,268 × 10^6/L. A serum vitamin B_{12} level was minimally elevated (929 pg/mL). Electrocardiogram showed first-degree atrioventricular block, left axis deviation, and left bundle branch block. Echocardiogram demonstrated moderate tricuspid regurgitation and small mitral regurgitation with an ejection fraction of 31%. Bone marrow aspiration showed slightly hypocellular marrow with 8% eosinophils. The patient was discharged with prednisone, 60 mg/day, and hydroxyurea, 500 mg/day. He died suddenly in August 1988. Autopsy demonstrated eosinophilic infiltration in the heart, lungs, gastrointestinal tract, and meninges, thickened endocardium and myocardium, a marked increase in elastic and fibrous tissue in the endocardium extending into the myocardium (Fig. 2), and scattered eosinophils infiltrating the intestitial tissue.

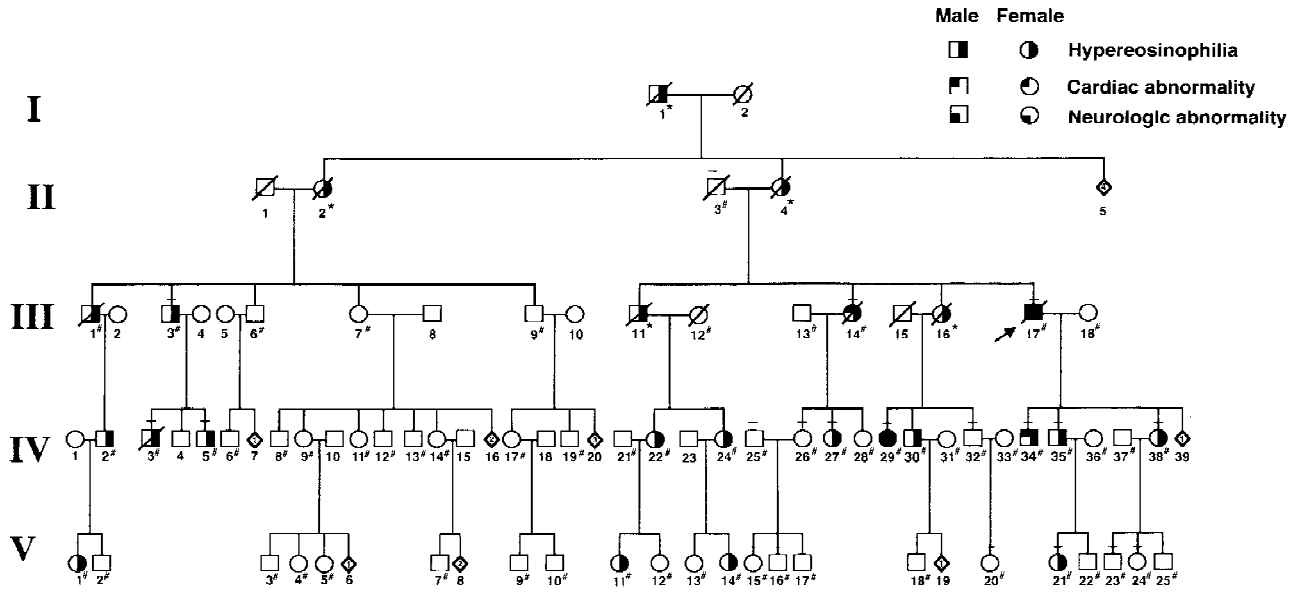

Fig. 1. Family pedigree. (#), complete blood counts, including absolute eosinophil counts, were available. *, diagnosis not confirmed.

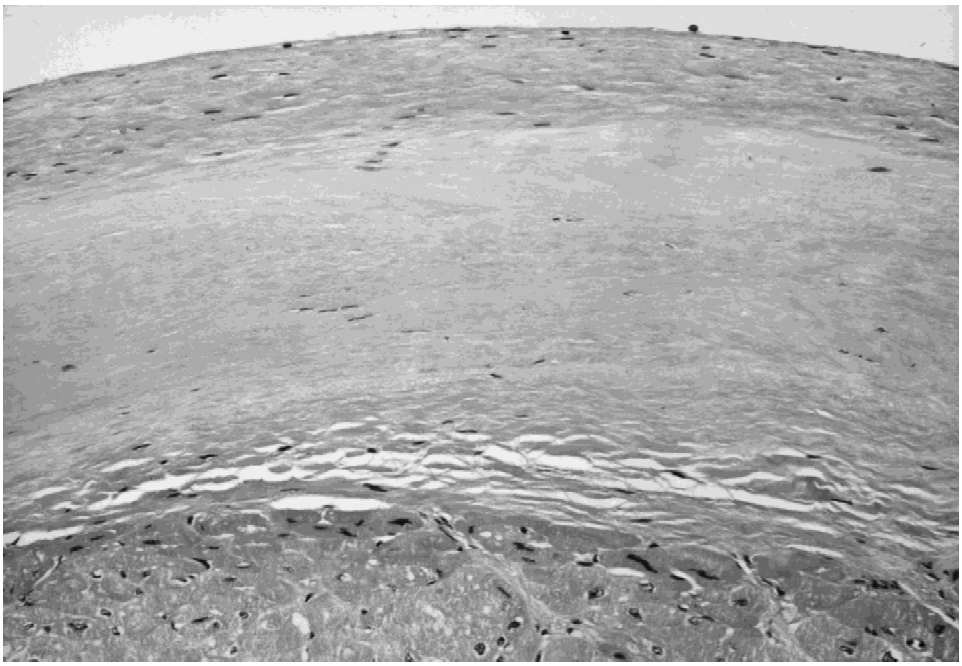

Fig. 2. A section from the heart of the propositus obtained at autopsy shows endocardial fibroelastosis (hematoxylin-eosin, magnification 600×). The thickened endocardium, stained positive for elastic and trichrome stainings (not shown), contains marked increase in elastic and fibrous tissues extending into myocardium.

Patients

At the time of referral of III-17, a family history of hypereosinophilia was elicited and the family agreed to participate in an etiologic study of HES. For purposes of this study, a diagnosis of HES was made if a person had at least two documented absolute eosinophil counts >1,500 × 10^6/L more than 6 months apart. Fifty-two bloodline relatives and 10 spouses from this kindred were evaluated either by field trip with laboratory evaluation only (n = 41) or by clinical examination at NIH (n = 21). Clinical examination included physical examination, complete blood counts with differential, examination of stools for parasitic ova or larvae, echocardiogram evaluation, and peripheral blood cytogenetic study for constitutional karyotype. Informed consent was obtained prior to participation in the clinical and/or laboratory evaluations under an IRB-approved clinical study protocol.

Cytogenetic Analysis

Chromosomes were studied according to standard procedures by direct preparations or short-term cultures of bone marrow aspirates, or by PHA-stimulated short-term cultures of peripheral blood leukocytes. Metaphase cells were stained by the trypsin-Giemsa banding technique.

TABLE I. Demographic and Hematologic Findings in Affected and Unaffected Bloodline Relatives and Spouses

Finding	Affected	Unaffected	Spouse
Number of subjects	19	33	10
Sex (male/female)	9/10	19/14	5/5
Age (years) at initial evaluation (mean age)	12–70 (37.2)	0.3–65 (27.6)	33–91 (52.5)
Complete blood count at initial evaluation (mean)			
White blood cells (10^6/L)	6,100–14,300[a] (10,297)	4,000–12,800 (6,734)	5,000–9,800 (7,570)
Red blood cells (10^{12}/L)	3.8–5.0[b] (4.3)	4.1–5.6 (4.8)	3.8–5.8 (4.8)
Hemoglobin (g/L)	11.5–16.5 (13.7)	12–17.3 (14.6)	11.5–17.0 (14.7)
Platelets (10^9/L)	211–381 (290)	171–560 (304)	192–449 (274)
Absolute eosinophil counts (10^6/L)	1,952–4,998[c] (3,200)	47–1,024[d] (318)	35–395 (158)

[a] $P < 0.005$ as compared with the unaffected or the spouse group.
[b] $P < 0.05$ as compared with the unaffected or the spouse group.
[c] $P < 0.001$ as compared with the unaffected or the spouse group.
[d] $P < 0.05$ as compared with the spouse group.

TABLE II. Patient Profile at Initial Evaluation (n = 11)

Pedigree No.	Age (yr)/Sex	Cardiac examination				Neurological findings	Atopic history
		Murmur	Echocardiogram	ECG	Endomyocardial biopsy		
III-3	63/M	I-II/VI early diastolic murmur and a I/VI soft systolic murmur at LLSB[k]	Thickening of left ventricle, posterior leaflet of mitral valve, aortic valve, and left atrium; mitral and aortic regurgitation	NSR[n] and LVH[l]	ND[m]	Normal	None
III-14	62/F	II/VI systolic ejection murmur at LLSB	Midly thickened aortic valve leaflets and posterior mitral leaflet, dilated left ventricle, and mitral regurgitation	NSR and LVH	Myocardial cell hypertrophy without endomyocardial fibrosis or cellular infiltrates (6/18/87)	Normal	None
III-17	57/M	Systolic ejection murmur	Thickened mitral valve, severe mitral stenosis, and no mitral regurgitation	LAD,[h] LBBB,[j] first-degree AV[d] block, and multiple APC[c]	Endocardial fibroelastosis scattered with infiltrated eosinophils (Fig. 2)	Diminished motor and sensory function in the distributions of the ulnar nerve bilaterally and the right anterior tibial nerve	Morphine sulfate (rashes)
IV-3	39/M	None	Normal	NSR with LVH	ND	Normal	None
IV-5	24/M	None	Normal	NSR	ND	Normal	None
IV-27	25/F	None	Normal	NSR	ND	Normal	Pollen
IV-29	41/F	III/VI decrescendo murmur in the mitral area and a II/VI diastolic crescendo murmur at the aortic area	Mild mitral regurgitation	NSR	ND	Complete absence of pinprick in both small toes	Mold
IV-34	37/M	II/VI systolic murmur at right sternal border	Thickened aortic valve and dilated left ventricle	NSR	Mild fibrosis but no eosinophil infiltration (5/4/88)	Normal	None
IV-35	36/M	None	Normal	NSR	ND	Normal	None
IV-38	28/F	None	Normal	ND	ND	Normal	Animals
V-21	12/F	None	Normal	NSR	ND	Normal	None

Evaluation of Cytokines and Antifilarial Antibodies

Serum levels of IL-5, IL-3, granulocyte macrophage colony-stimulating factor (GM-CSF) were evaluated using cytokine-specific enzyme-linked immunosorbent assay (ELISA) as described previously [Limaye et al., 1993]. Serum antifilarial IgG (known to be cross-reactive in patients with nonfilarial nematodes, trematodes, and cestodes) and serum IgG4 (noncross-reactive) were evaluated using an ELISA previously described [Lal and Ottessen, 1988].

Statistical Analysis

Complete blood count and mean values for cell counts in affected relatives, unaffected relatives, and spouses were compared by the Mann-Whitney test. Titers of IL-5 and antifilaria antibody were also compared among the three groups by the Mann-Whitney test. To estimate the fluctuations in eosinophil counts over time, we examined the eosinophil counts among 12 affected and 10 unaffected individuals who had eosinophil counts available 5 or more years between the initial and the most recent counts. A paired *t*-test was used to evaluate the changes of eosinophil counts over

TABLE II. (Continued)

Laboratory															
									HLA						
AEC[a] ($\times 10^6$/L)	ANA[b]	B_{12}[e] (pg/mL)	Cyto-genetics (source)	IgA[g]	IgG (mg/dL)	IgM	LAP[i] (U/L)	RF[q]	A	B	C	DR	DQW	DRW	O and P[o]
2,862	Neg	473	46,XY (BM)[f]	95	815	50	107	Neg	1/2	8/55	W3	3/4	2/3	52/53	Neg
3,051	Pos in a speckled pattern at 1:160	1,167	46,XX, inv(10) (BM)	202	1,310	170	149	1:320	1/3	8/27	—	2/3	1/2	52	Neg
3,128	Neg	929	46,XY (BM)	145	802	68	ND	Neg	1/26	7/14	W7	1/2	1	—	Neg
3,276	ND	ND	46,XY (PB)[p]	WNL[r]	WNL	WNL	ND	ND	1/11	7/8	—	2/3	1/2	52	Neg
2,944	Neg	488	46,XY (PB)	202	994	63	ND	1:488	2/11	7/55	W3	2/4	1/3	53	Neg
2,548	Neg	442	ND	139	1,140	99	106	Neg	1/-	7/8	—	2/3	1/2	52	Neg
2,542	Neg	106	46,XX, inv(10) (PB)	219	1160	155	ND	Neg	1/-	7/8	—	2/3	1/2	52	Neg
3,456	Neg	312	46,XY (BM)	229	1258	197	1:64	Neg	1/2	7/62	W3	2/3	1/2	52	Neg
2,691	Neg	374	46,XY (PB)	186	879	100	1:177	Neg	1/-	7/8	—	2/3	1/2	52	Neg
2,880	ND	ND	ND	ND	ND	ND	ND	ND	1/-	7/8	W7	2/3	1/2	52	Neg
2,825	Neg	642	ND	ND	ND	ND	1:97	Neg	ND	ND	ND	ND	ND	ND	Neg

[a]AEC, absolute eosinophil count (reference range 50–400 × 10^6/L).
[b]ANA, anti-nuclear antibody.
[c]APC, atrial premature complex.
[d]AV, atrial-ventricular.
[e]B_{12}, serum vitamin B_{12} level (reference range: 200–900 pg/mL).
[f]BM, bone marrow.
[g]Ig, immunoglobulin (reference range, IgA: 65–415 mg/dL; IgG: 650–1,600 mg/dL; IgM: 50–320 mg/dL).
[h]LAD, left axis deviation.
[i]LAP, leukocyte alkaline phosphatase (reference range: 36–91 U/L).
[j]LBBB, left bundle branch block.
[k]LLSB, left lower sternal border.
[l]LVH, left ventricular hypertrophy.
[m]ND, not done.
[n]NSR, normal sinus rhythm.
[o]O and P, examination of stool for ova and parasites.
[p]PB, peripheral blood.
[q]RF, rheumatoid factor.
[r]WNL, within normal limits.

time. Correlation coefficient was used to examine the fitness of the trend. All statistical tests were two-sided.

RESULTS

Patient Evaluation

Table I shows the demographic and hematologic characteristics among 62 evaluated subjects. Ten of the 19 affected subjects were female. The age at initial evaluation of the affected individuals (n = 19) ranged from 12 to 70 years (mean age, 37.2 years). As expected, the affected subjects had significantly greater total white cell counts ($P < 0.005$) and absolute eosinophil counts ($P < 0.001$) compared with either the unaffected or the spouse group at initial evaluation. The affected individuals also had significantly lower total red cell counts, compared with the unaffected individuals or spouses (both $P < 0.05$). Of note, the unaffected relatives had significantly higher absolute eosinophil counts, compared with the spouses.

Eleven of 19 affected individuals were available for clinical evaluation and were evaluated at the National Institutes of Health (Table II). Five patients had cardiac murmurs and echocardiographic abnormalities. Four patients had abnormal electrocardiograms. All three patients with heart tissue for pathology examination had eosinophilic infiltration or fibrosis in the endomyocardium by cardiac biopsy or at autopsy. Abnormal neurological findings were reported in two patients. Only one patient had abnormal antinuclear antibodies; this patient also had Sjögren syndrome. Serum cobalamin (vitamin B_{12}) level was elevated in one patient, with another one being borderline high. Immunoglobulin levels were within normal limits among all nine affected individuals examined. Leukocyte alkaline phosphatase was found to be elevated in five of six tested patients. Abnormal rheumatoid factor was documented in the one patient who also had an abnormal anti-nuclear antibody titer. There were no ova or parasites found in stools.

Cytogenetic Analysis

Among eight affected individuals who had peripheral blood (IV-3, 5, 29, and 35) or bone marrow (III-3, 14, 17, and IV-34) karyotype analysis (Table II), two (III-14 and IV-29) carried the same chromosomal abnormality, a pericentric inversion of chromosome 10, inv (10) (p11.2q21.2) (Fig. 3).

Cytokines and Antifilaria Antibody Titer

Cytokines (IL-5, IL-3, and GM-CSF) and antifilarial antibody titers, used as a screen for exposure to tissue-invasive helminths, were evaluated among 14 affected individuals, 22 unaffected relatives, and six spouses. Most individuals had undetectable IL-5 levels (<15.6 pg/dL), although three affecteds (III-3, IV-34, and V-14), three unaffecteds (IV-9, 28, and V-13), and two spouses (III-12 and IV-33) had measurable IL-5 levels. There were no statistically significant differences between the groups. No individual had detectable levels of IL-3, GM-CSF, or seropositivity in the antifilarial antibody assay.

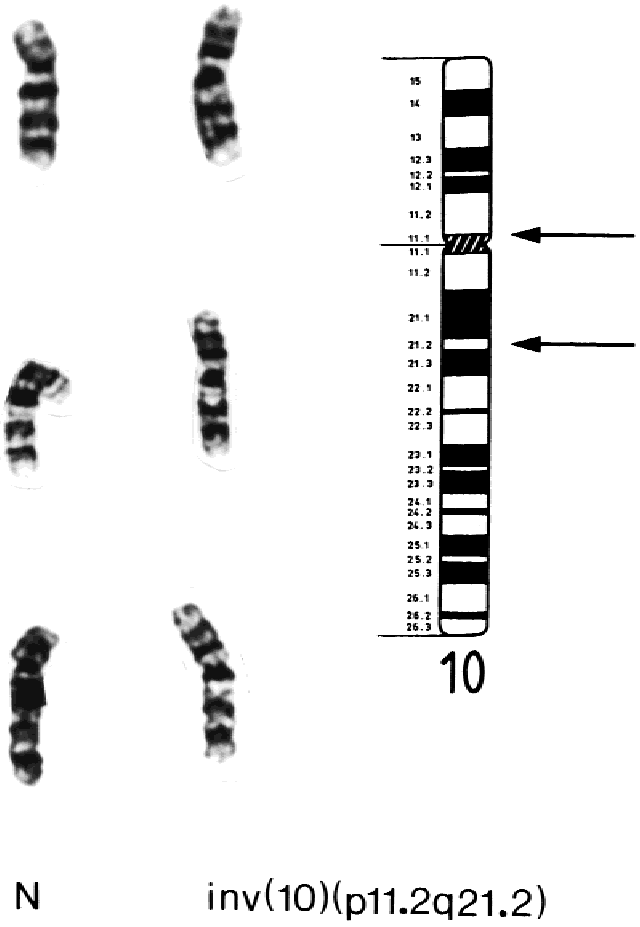

Fig. 3. Peripheral blood karyotype and idiogram from III-17 showing three different chromosome 10 pairs: normal 10s on left and inverted 10s on right. Idiogram of normal 10 (far right) shows chromosomal breakpoints (arrows).

Time Course Evaluation

Among the affected subjects (n = 12), the initial absolute eosinophil counts ranged from 2,548 to 3,541 × 10^6/L and the most recent counts ranged from 880 to 5,670 × 10^6/L. The difference between the two time periods was not statistically significant (Fig. 4). Among the unaffected subjects (n = 10), the initial counts ranged from 90 to 1,024 × 10^6/L, and the most recent counts ranged from 81 to 1,075 × 10^6/L (Fig. 4). This difference between the two time periods was also not statistically significant. However, the correlation between these two time periods among the unaffected relatives was statistically significant ($P < 0.05$).

DISCUSSION

We report the clinical and laboratory data on 52 bloodline relatives and 10 spouses from a kindred with FE. The affected individuals not only have significantly higher eosinophil counts but also have significantly lower red cell counts compared to the unaffected individuals. There was no difference in cytokine levels between the affected and unaffected individuals. Similar to idiopathic HES, cardiac manifestations are the most

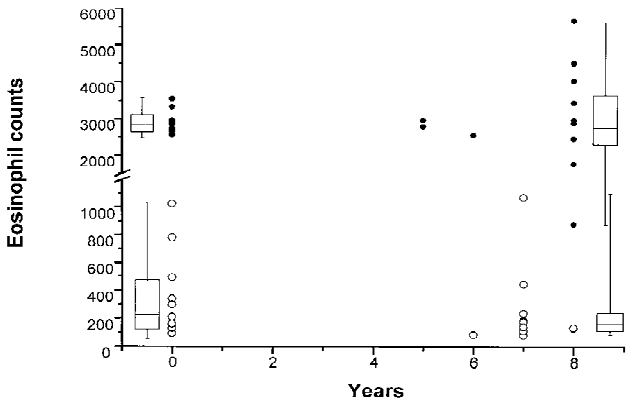

Fig. 4. Stability in absolute eosinophil counts over time. Absolute eosinophil counts (1 μL) are shown for the affected individuals (closed circles) and unaffected individuals (open circles) assessed at the initial evaluation (time 0) and after 5 to 8 years. Boxes contain 50% of values falling between 25th and 75th percentiles. The mean values are indicated by bars in the boxes. The extended lines indicate the range of values above or below the 75th or 25th percentile, respectively.

devastating complication and the most common cause of death among the affected individuals.

Reactive eosinophilia may be found in various conditions, including allergies, parasitic infections, neoplasms, vasculitis, and some autoimmune diseases [Wardlaw and Kay, 1995]. In HES the cause of eosinophilia is unknown. FE appears to be the subset of HES postulated to have an underlying genetic mechanism responsible for the disease. The distinction between eosinophilia with identifiable causes and FE or HES is important for treatment implications. The two disorders may be especially difficult to distinguish in areas endemic for parasitic infection where multiple relatives may present with eosinophilia [Moro-Furlani and Krieger, 1992]. The affected subjects from our FE kindred had no evidence of parasitic infections based on stool or serological assessment. In addition, most had no common history of allergies, had no evidence of antinuclear antibody or rheumatoid factor, and had normal immunoglobulin levels, all suggesting the absence of autoimmune disease. This kindred, similar to those previously reported [Naiman et al., 1964], shows a transmission pattern consistent with autosomal dominant inheritance. This pattern is further supported in the pedigree by direct male-to-male transmission, a male-to-female ratio among the affected of approximately 1:1 [Naiman et al., 1964], the appearance of the trait in every generation, and about 50% of the offspring of an affected parent being affected.

It is unclear whether the onset of HES/FE is related to age. In 57 patients with HES, Chusid et al. [1975] noted that the age at onset of symptoms attributable to HES ranged from 5 to 80 years. The diagnosis could be made incidentally or secondary to associated symptoms such as congestive heart failure. In a three-generation family, the youngest affected person was 2 months old [Naiman et al., 1964]. The youngest patient in our kindred with documented eosinophila was 6 years old (IV-34). The presence of several published cases under 1 year of age suggests that the disease may be present from early infancy or even at birth [Naiman et al., 1964]. However, neonatal eosinophilia persisted at least 4 months in an infant born to a mother with HES, suggesting the presence of a transplacental eosinophilic growth factor [Carey and Burke, 1982]. This finding underscores the importance of careful interpretation of eosinophil counts in infants born to mothers with HES.

Abnormal hematological findings are, of course, the most common clinical manifestation among individuals with HES/FE. Although there is a normal diurnal variation in the level of circulating eosinophils, with the highest level in the morning and the lowest in the afternoon [Wardlaw and Kay, 1995], a normal nonallergic subject has an absolute peripheral eosinophil count of less than 400×10^6/L. The eosinophil counts in patients with HES can fluctuate during the course of the disease [Wolz et al., 1993]. Among 12 affected individuals who were followed at least for 5 years after initial diagnosis, all but one (IV-22) continued to have elevated eosinophil counts during the follow-up period. Conversely, all 10 unaffected relatives who were followed for more than 5 years continue to have normal eosinophil counts (less than $1{,}500 \times 10^6$/L; Fig. 4). This information may be reassuring for unaffected relatives, who seem to need no long-term follow-up, once they have two normal eosinophil counts 6 month apart. Anemia, which occurred in three (17%) patients in this family, was found in up to 50% of patients with HES in one series ($n = 50$) [Fauci et al., 1982]. Attempts to identify other hematological or laboratory parameters that correlate with the severity of HES have been unsuccessful [Flaum et al., 1981]. As observed in our patients, both serum vitamin B_{12} and leukocyte alkaline phosphatase levels may be normal or elevated in patients with HES [Zittoun et al., 1984].

Cardiac disease is a principal cause of morbidity and mortality in patients with HES [Weller and Bubley, 1994; Fauci et al., 1982]. The primary damage to the heart is thought to occur in the endocardium [Fauci et al., 1982]. Eosinophilic infiltrates may or may not be observed, depending on the stage of damage. Histologically, endomyocardial necrosis, thrombosis, and fibrosis have been described, with congestive heart failure as the end result of cardiac damage [Fauci et al., 1982]. A previous study suggested that patients with HES who carry a HLA-Bw44 allele might have a predilection for cardiac disease [Harley et al., 1983]; none of the affected subjects with cardiac disease in the present kindred had a HLA-Bw44 allele (Table II).

Abnormal neurologic manifestations associated with HES are also frequent, including diffuse central nervous system abnormalities, focal central nervous system deficits, and peripheral neuropathies [Fauci et al., 1982; Weller and Bubley, 1994]. The mechanism for peripheral neuropathy is largely undefined, although it may be related to direct infiltration or production of eosinophil-derived neurotoxin [Rosenberg et al., 1989]. Two affected subjects (III-17 and IV-29) had evidence of mononeuritis multiplex.

Karyotype analysis is normal in most HES patients [Weller and Bubley, 1994]; however, abnormal chromosomal findings have been reported. Most of the abnor-

malities were associated with myeloproliferative disorders: 49,XYY,t(3;5)(p21;q11),+8,+mar [Bitran et al., 1977]; trisomy 8 [Golomb and Ultman, 1977]; 4q+,−5 [Ellman et al., 1979]; 49,XY,del(3),+10,+15,+19 [Huang et al., 1979]; monosomy 7 [Humphrey et al., 1981]; 45, X-X,del(15)(q22) [Goffman et al., 1983]; 46,XY,t(5;11)(p15;q13) [Yoo et al., 1984] deletion of 16q; trisomies of 8 and 14, deletions of 6q,11p,11,22q, monosomies of 9, 14, 15, 16, 18, 22, loss of X and Y, translocations (11q;22q),(14q;15q) [Goh et al., 1985]; 46,XY,t(7;12) [Da Silva et al., 1988]; 45,X,-Y [Needleman et al., 1990]; 47,XX,+8 [Michel et al., 1991]; 46,XX,der(7) [Wolz et al., 1993]. It is intriguing to note that two patients in our study, III-14 and IV-29, had the same chromosome abnormality: a pericentric inversion of chromosome 10 involving the segment between p11.2 and q21.2 (Fig. 3). Four previous reports have noted chromosomal changes on chromosome 10 associated with eosinophilia: 47,XX,+10 [Goldman et al., 1975]; 49,XY, del(3),+10,+15,+19 [Huang et al., 1979]; (10p+;11q−) [Broustet et al., 1986]; 46,XY,t(10;11)(p14;q21) [Fischkoff et al., 1988]. Although the significance of the cytogenetic findings is unclear, they could provide clues to the genetic mechanism(s) of the disease.

Despite extensive investigation and speculation, the pathogenesis of HES remains largely unknown [Fauci et al., 1982; Liesveld and Abboud, 1991; Weller and Bubley, 1994]. Cytokines such as interleukin-5 (IL-5), interleukin-3 (IL-3), and GM-CSF are involved in the development and differentiation of eosinophils [Weller, 1991]. Overproduction or dysregulation of cytokines may be a possible underlying mechanism of eosinophilia [Weller and Bubley, 1994]. Indeed, several in vitro and ex vivo studies have shown indirect evidence that sera from HES patients contain higher levels of IL-5 than unaffected individuals [Owen et al., 1989; Enokihara et al., 1990]. However, among 14 patients evaluated here, no elevated IL-5 levels were observed.

HES encompasses a heterogeneous groups of disorders [Weller and Bubley, 1994]. There is a wide spectrum of clinical manifestations among these conditions, ranging from localized benign entities (such as Löffler syndrome or eosinophilic granuloma) to clonal proliferations (such as eosinophilic leukemia or Letterer-Siwe disease) [Hardy and Anderson, 1968]. The latter entities not only have a worse prognosis but also have been classified as malignant neoplasms. A better understanding of FE, a genetically defined subset of HES, may give clues to the etiology of HES and lead to improved management of HES/FE.

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