The idiopathic hypereosinophilic syndrome

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SUMMARY A 14 year old girl with idiopathic hypereosinophilic syndrome is described. In addition to weight loss, anaemia, amenorrhoea, general lethargy, anorexia, mouth ulcers, blisters of hands and feet, and petechial skin rash, she had features of involvement of the cardiovascular system as the major complication. She responded well to treatment.

After a comprehensive search of the published reports 18 cases of this syndrome were identified in children under 16 years. Fifteen of these children had involvement of the cardiovascular system as the major source of their morbidity and mortality. Summary of the clinical details and laboratory, biopsy, and necropsy findings of the involvement of the various organ systems of the 18 children is presented.

Hypereosinophilia of over $1.5 \times 10^9/l$ accompanies various diseases. In some cases no cause can be found and the hypereosinophilia may be accompanied by multiple organ involvement, especially of the cardiovascular system, with high morbidity and mortality. The idiopathic hypereosinophilic syndrome is primarily a disease of middle age, but an occasional case has been encountered in children.

Case report

A 14 year old white girl presented six weeks after an illness that lasted 10 days, in which she had developed mouth ulcers and blisters of the hands and feet. These had settled spontaneously, but the lethargy, nausea, and anorexia had persisted, and she had complained of aching limbs. She had described symptoms of increasing dyspnoea on minimal exertion and orthopnoea and developed a fine petechial rash two days before presentation. Her menses, which had started a year earlier, had stopped during the illness.

She had had asthma for two years, which was controlled with regular inhalations of beclomethasone and occasional inhalations of salbutamol. She was allergic to feathers. There was no recent infectious or relevant travel history.

On examination she was unwell, with a temperature of 38°C , pulse rate 128 beats/minute, regular, respiratory rate of 28/minute, blood pressure 130/100, weight 46 kg (25th centile), and height 163 cm (60th centile). There was a sparse petechial rash on the upper trunk and upper arms, with splinter haemorrhages under her fingernails, and the pulps

of her fingertips were tender on palpation. She was in congestive heart failure, with clinical evidence of a pericardial effusion. A grade 2/4 pansystolic murmur radiated from the apex to the axilla. There was no lymphadenopathy or splenomegaly, but the liver was enlarged, 2 cm below the costal margin at the mid-clavicular line, and tender.

Investigations. Her haemoglobin concentration was 9.3 g/dl, mean corpuscular volume 78.7 fl, mean corpuscular haemoglobin 26.7 pg, platelets $315 \times 10^9/l$, white blood cells $13.4 \times 10^9/l$ (neutrophils 45%, lymphocytes 15%, monocytes 1%, and eosinophils 39% ($5.2 \times 10^9/l$), showing partial degranulation), and erythrocyte sedimentation rate 66 mm in the first hour. The prothrombin and kaolin cephalin clotting times were normal. Bone marrow biopsy and trephine examination showed a hypercellular marrow with pronounced eosinophilia but no evidence of malignancy. Chest x ray film showed considerable cardiac enlargement, with a globular shaped heart, pulmonary oedema with vascular redistribution, and a small right sided pleural effusion. M mode and 2D echocardiography showed a large pericardial effusion and areas of increased echodensity in the region of the apex of the left ventricle and the posterior leaflet of the mitral valve, suggesting endocardial thickening. An electrocardiogram (ECG) showed sinus tachycardia.

The serum electrolytes, glucose, and liver function tests yielded normal results except for a low albumin concentration (32 g/l) and slightly raised lactate dehydrogenase activity (351 IU/l (normal 100–300 IU/l)). Serum concentrations of vitamin B₁₂

were 501.3 ng/l (normal 180–710 ng/l), of folate were 2.2 µg/l (normal >2.5 µg/l), and of ferritin were 70 ng/ml (normal 10–64 ng/ml). Protein electrophoresis (in g/l) showed total protein 62, albumin 25, globulins 37, (alpha₁ 4 (normal 2–4), alpha₂ 10 (5–8.5), beta 7 (7–11), and gamma 16 (18–16)), IgG 19.22 (7–19), IgM 1 (0.50–2.2), and IgA 0.93 (0.9–4.5). Serum total IgE concentration was 154 KU/l (normal <70.3 KU/l), functional CH50 3.25 min (1.82–3.62), C3 209 mg/dl (70–160), C4 29 mg/dl (10–30) properdin factor B 58.1 mg/dl (20–50), and C reactive protein 0.61 mg/dl (<0.6). Rheumatoid factor was 240 IU/ml (<15). Antibodies for nuclear, mitochondrial, smooth muscle, parietal, canalicular, glomerular, and reticulin were negative. Anti-double stranded deoxyribonucleic acid (DNA) binding capacity was 0.9 mg/l (normal <5 mg/l).

Serial blood cultures and faeces examination, throat swab, Paul-Bunnell test, and tests for viral titres, hepatitis B surface antigen, and hepatitis A IgM yielded negative results. Antistreptolysin O was <100 Todd Units and antistreptococcal deoxyribonuclease B 1/75 (upper limit 1/200). Antibodies to cysticerci, filaria, fasciola, hydatid disease, toxocara, toxoplasma, *Aspergillus fumigatus*, *Microspora faeni*, and *Thermoactinomyces vulgaris* were negative. Tests on urine samples showed protein 3+, white blood cells <1/HPF, few granular casts and large number of epithelial cells and mucus, no growth, and a 24 hour protein excretion of 0.3 g. Her karyotype was normal.

On the basis of the clinical syndrome, eosinophilia without a recognisable cause, and the echocardiogram findings, a diagnosis of idiopathic hypereosinophilic syndrome was made. She was begun on treatment with prednisolone 2 mg/kg/day, frusemide, and folic acid, and was anticoagulated with warfarin.

The signs of congestive heart failure improved appreciably within two days and the petechial rash disappeared within three days. The eosinophil count returned to normal within two days. The erythrocyte sedimentation rate, lactate dehydrogenase activity, rheumatoid factor, and serum IgE and folate concentrations returned to normal. The endocardial echoes and pericardial effusion decreased within a few days of beginning treatment and had completely disappeared within three months. Signs of mild mitral regurgitation confirmed by Doppler ultrasound persisted.

After her dramatic clinical improvement the steroids were gradually withdrawn and were stopped after six weeks. She then developed mild bronchospasm on excitement, which responded to inhaled salbutamol with concomitant improvement in the peak flow rate and forced expiratory volume in one second/forced vital capacity percentage, and was

restarted on inhaled beclomethasone. Within two weeks of stopping oral steroids her eosinophil count increased to $1.5 \times 10^9/l$, and her total white blood cell count was $8.0 \times 10^9/l$. She was restarted on prednisolone at a dose of 10 mg on alternate days, after which the eosinophil count returned to normal. She remains anticoagulated with warfarin.

Discussion

Eosinophilia. Eosinophilia is the term applied to an increase in the total blood eosinophil concentrations. In normal individuals living in the United Kingdom the blood eosinophil count is less than $0.55 \times 10^9/l$. The practice of referring to eosinophil concentrations as 'percentages' may be misleading and absolute figures ($\times 10^9/l$) should be used. Usually, the presence of eosinophilia has no detrimental effect on the body and there is evidence that it may have a role in the body defence mechanisms. It accompanies many disease states, mainly allergic and parasitic (Table 1), or it can be an incidental finding, but occasionally patients with eosinophilia are found to have one of the more serious and rarer causes, such as Hodgkin's disease.¹ Treatment of the primary disease will usually resolve the eosinophilia.

Hypereosinophilia. Hypereosinophilia is the term applied empirically when the blood eosinophil count

Table 1 Some recognised causes of eosinophilia. All disorders mentioned might cause hypereosinophilia. Those that might be associated with a very high eosinophil count are underlined

- 1 Allergic disorders: asthma, hay fever, allergic rhinitis, urticaria, eczema, pulmonary aspergillosis
- 2 Drug reactions
- 3 Parasitic infestations: visceral larva migrans (toxocariasis), trichinosis, ascariasis, hookworm disease, strongyloidiasis, filariasis (tropical eosinophilia), schistosomiasis, hydatid disease, malaria
- 4 Skin disorders: eczema, dermatitis herpetiformis, exfoliative dermatitis, psoriasis, pemphigus
- 5 Infections: brucellosis, scarlet fever, acute infectious lymphocytosis, infections due to mycobacteria, chlamydia, cytomegalovirus, and *Pneumocystis carinii*
- 6 Haematological: Fanconi's anaemia, thrombocytopenia with absent radii, post-splenectomy
- 7 Neoplastic disorders: Hodgkin's disease, lymphosarcoma, leukaemia, carcinoma of lung and gut
- 8 Connective tissue/vasculitis/granulomatous disorders, especially those involving the lungs: polyarteritis nodosa, Churg-Strauss syndrome, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, cryptogenic pulmonary eosinophilia
- 9 Immune deficiency disorders: congenital immune deficiency syndromes, hyper-IgE with infections
- 10 Miscellaneous: liver cirrhosis, radiation treatment, Crohn's disease, ulcerative colitis, peritoneal dialysis, congenital heart disease, familial eosinophilia (? autosomal dominant), idiopathic hypereosinophilic syndrome (including eosinophilic leukaemia)

is $1.5 \times 10^9/l$ or higher. Some disorders usually give rise to counts above $1.5 \times 10^9/l$,¹—for example, drug reactions, intrinsic asthma (a surprising fact compared with patients with extrinsic asthma, in whom the eosinophil count is usually below $1 \times 10^9/l$), parasitic diseases, vasculitis and granulomatous diseases, and neoplasms. Certain other diseases are associated with striking eosinophilia: leucocyte counts of $30 \times 10^9/l$ – $100 \times 10^9/l$ or higher may be seen where 50–90% of the blood leucocytes may be eosinophils. Diseases that are more commonly associated with such high counts are underlined² in Table 1, but in general any of the disease processes mentioned in the Table—that is, any cause of eosinophilia—may be associated with hypereosinophilia of whatever degree.

Hypereosinophilia can be primary. This may be an isolated finding. On the other hand, it might be associated with organ system dysfunction of varying extent and severity, the cardiovascular and nervous system and skin being most commonly involved—the idiopathic hypereosinophilic syndrome.

The idiopathic hypereosinophilic syndrome. In 1968 Hardy and Anderson drew attention to the fact that persistent hypereosinophilia of any type could be associated with a range of similar complications and they grouped these together as the hypereosinophilic syndrome.³ Chusid *et al* confirmed this in 1975 but restricted the diagnosis of hypereosinophilic syndrome to patients in whom no underlying cause for the hypereosinophilia could be shown,⁴ so that the term idiopathic hypereosinophilic syndrome is applied when the following criteria are fulfilled:

- (1) Eosinophilia $\geq 1.5 \times 10^9/l$;
- (2) Persists for at least six months or fatal in a shorter time;
- (3) Results in organ system dysfunction;
- (4) Absence of a recognised cause for the eosinophilia.

The term encompasses various diagnostic terms applied previously to a range of cases with almost similar natural history, physical findings, laboratory data, and autopsy findings, including eosinophilic leukaemia, disseminated eosinophilic collagen disease, and Loeffler's fibroplastic endocarditis with eosinophilia. The condition called eosinophilic gastroenteritis is probably part of the wide range of this syndrome.⁵

The idiopathic hypereosinophilic syndrome has a wide range of severity with at least three different forms. Some patients only have hypereosinophilia with lung involvement and angio-oedema. Others present with (or develop) severe cardiac and central nervous system complications. A third group have eosinophil cytogenic abnormalities and other fea-

tures of a leukaemic disease, characterised as eosinophilic leukaemia. Occasionally, the second form terminates as a blast cell leukaemia.⁶ Hypereosinophilia as an isolated finding is not considered to be a subgroup of this syndrome and probably has no special clinical relevance, although the patient will require regular reviews to exclude an occult underlying disease process.

Aetiology

Several theories have been put forward to explain the idiopathic hypereosinophilic syndrome. Some authors have claimed that it is an autoimmune disease.⁷ It is also possibly of a neoplastic nature.⁸ Parrillo *et al* showed a variety of immunological abnormalities in the patients they studied.⁹ In most of the cases described by Spry *et al* the findings suggested that a parasitic or allergic disease had preceded the onset of hypereosinophilia, and some had high serum IgE concentrations.¹⁰ These findings raised the possibility that an initial eosinopoietic stimulus may lead to a late and exaggerated response, which persists. Carey *et al* reported a case of transient hypereosinophilia in an infant of a mother with this syndrome and suggested that the infant's hypereosinophilia could be a response to an eosinophilia producing factor by the mother, with transplacental transfer.¹¹

A definitive cause for this syndrome, however, has not been identified, but perhaps understanding the factors that influence the production and distribution of the eosinophil and the mechanisms of tissue damage might give some insight into its aetiology.

Factors that influence blood and tissue eosinophil concentration. Eosinophils normally constitute a small proportion of the circulating leucocytes. A diurnal variation that is the converse of the variation in plasma corticosteroid concentrations occurs, with blood eosinophilia peaking at night. The production of the eosinophil in the bone marrow is under the control of the T lymphocytes. Lymphocytes also produce factors that are chemotactic for eosinophils. Once eosinophils are released from the marrow they circulate in the blood only briefly, with a half life of six to 12 hours. They leave the blood stream and are distributed in tissues where they persist for at least several days, being a tissue dwelling cell. They are most abundant in those tissues with epithelial surfaces exposed to the environment, including the gastrointestinal tract, the skin, and the upper respiratory tract.¹²

Apart from the lymphocytes, several other factors may influence eosinophil concentrations in blood and tissue. On triggering and degranulating the mast

Table 2 Summary of clinical, biopsy, and necropsy findings of 19 children with the idiopathic hypereosinophilic syndrome

Author (years)	Age at onset (years)	Sex	Presenting symptoms	Cardiovascular system	Nervous system	Skin/muscle/joints	Renal	Pulmonary	Gastrointestinal tract	Hepatic
Bentley (1961) ¹⁵	5	M	Fever, macular rash, petechial rash, coma	<i>Postmortem examination:</i> Myocardial petechiae and scarring, mural thrombus in left ventricle	Coma, decorticate posture. <i>Cerebrospinal fluid:</i> No abnormality. <i>Postmortem examination:</i> Mycoblastic infiltrate of meninges and brain	Macular and petechial rash. Subcutaneous nodules over parietal bones. <i>Biopsy:</i> Lymphoid and eosinophil infiltration	<i>Postmortem examination:</i> Petechiae in both kidneys. Blast cells infiltration of kidneys and bladder	Dry cough. <i>Chest x ray:</i> Lung infiltrates. <i>Postmortem examination:</i> Haemorrhagic areas. Pulmonary oedema and myeloblast infiltration	<i>Postmortem examination:</i> Stomach dilatation. Petechiae all over gastrointestinal tract	Hepatomegaly. <i>Postmortem examination:</i> Blast cells infiltration
Chusid (1975) ⁴	5-5	M	Periodic attacks of fever, rash, diarrhoea, and angio-oedema	None	Abnormal electroencephalogram	Rash, angio-oedema. <i>Skin biopsy:</i> Perivascularitis, eosinophil infiltration	Mild to moderate intermittent proteinuria	Transient infiltration	None	<i>Biopsy:</i> 'Eosinophilic trinitis'
De Vaan (1979) ¹⁶	1	F	Refusing to walk or stand	Gallop rhythm and sinus tachycardia. <i>Postmortem examination:</i> Endocardial thickening of left atrium and subendocardial fibrosis with iron pigment deposition in myocardium of both ventricles and left atrium. Coronary thrombosis. Eosinophil infiltration, including blast cells in myocardium	None	Refusing to walk or stand. <i>Skin biopsy:</i> Papillomatosis and scattered mature eosinophil infiltration and hyperkeratosis. <i>Muscle biopsy:</i> Some focal atrophy, no eosinophil infiltration	<i>Postmortem examination:</i> Eosinophil infiltration, including blast cells	Pneumonia. <i>Postmortem examination:</i> Increase in weight of lungs. Vascular thrombi. Areas of red blood cell extravasation, fibrin in alveolar spaces, and formation of hyaline membranes. Macrophages and eosinophils in alveolar spaces	None	Hepatomegaly. <i>Biopsy:</i> Diffuse eosinophil infiltration. <i>Postmortem examination:</i> Enlarged, eosinophil infiltration, including blast cells
Donohue (1950) ¹⁷	7	M	Joint pains and fever	Congestive heart failure, cardiomegaly, mild hypertension, systolic murmur, mitral regurgitation	None	Subcutaneous oedema, arthralgia	None	Bilateral basal crepitations	None	Hepatomegaly
Engback (1942) ¹⁸	7	M	Headaches, fever, neck stiffness, and arthralgia	Congestive heart failure, cardiomegaly. <i>Postmortem examination:</i> Hypertrophy, dilatation and parietal thrombus in both ventricles and myocardial scarring/obliteration of coronaries	Not described	Not described	Not described	<i>Postmortem examination:</i> Lungs indurated, cyanotic, mottled, and inflamed. Thrombi, oedema, and eosinophil infiltration	Not described	None
Engfeldt (1956). ⁷ Case 1	8	M	Fatigue, anorexia, abdominal pain, vomiting, dyspnoea, cough, pains in back and neck	Terminal acute heart failure. <i>Postmortem examination:</i> Biventricular hypertrophy, thrombus in right auricle and ventricles. Endo-, myo-, and pericardial scarring and inflammatory cells infiltrate, mainly eosinophils	<i>Electroencephalogram:</i> Dysrhythmic	Pains in back and neck. <i>Postmortem examination:</i> Eosinophil infiltration of muscle	Moderate albuminuria, hyaline casts, and red blood cells in urine. Uraemia. <i>Postmortem examination:</i> Eosinophil infiltration of kidneys	Dyspnoea, cough. <i>Chest x ray:</i> Peribronchial thickening and pleural effusion. <i>Postmortem examination:</i> Eosinophil infiltrate	Abdominal pain and vomiting	Hepatomegaly. <i>Postmortem examination:</i> Eosinophil infiltration
Case 2	10	M	Headache, fever, rash, hyperkeratosis, and scaling of face, arms, and legs, pronounced alopecia, conjunctivitis, myalgia	Cardiomegaly, apical systolic murmur	None	See presenting symptoms. Subcutaneous oedema and redness over wrists and knees. Arthralgia. <i>Biopsy of skin and muscle:</i> Inflammatory cells, especially eosinophils and plasma cells. Non-specific changes in small blood vessels, thrombosis, and endarteritic changes	Slight proteinuria	Atelectasis of right middle lobe. Pleural effusion	None	Hepatomegaly
Foasso (1984) ¹⁹	6-7	F	Sore throat. Tuberculosis over previous 12 months; on isoniazid, rifampicin, ethambutol	Congestive heart failure, cardiomegaly, hypertension. <i>Echocardiogram:</i> Dilated left ventricle and left auricle. <i>Catheterisation:</i> Left ventricular lumen was reduced	Not described	Ulceration of fingertips. Swelling of right sternocleidomastoid. <i>Skin biopsy:</i> Perivascular inflammatory cell infiltration. <i>Muscle biopsy:</i> Endothelial thickening and alteration of media, no perivascular inflammation	Microscopic haematuria. <i>Biopsy:</i> Focal glomerulonephritis	Pulmonary hypertension and oedema	Not described	Hepatomegaly

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Lymphatic/spleen	Total white blood cell count ($\times 10^9/l$) at presentation	Eosinophil count ($\times 10^9/l$) at presentation	Haemoglobin (g/dl) at presentation	Platelets ($\times 10^9/l$) at presentation	Peripheral blood white blood cell morphology	Bone marrow	Other laboratory findings	Duration	Treatment	Authors' diagnosis
Splenomegaly. Generalised lymphadenopathy. <i>Post-mortem examination:</i> Blast cells in lymph node and spleen	185	157.25	8	60	64% Polymorphonuclear eosinophils, 17% eosinophil metamyelocytes, 3.4% eosinophil myelocytes	Initially: eosinophil hyperplasia. Terminally: an increase in myeloblastic forms (85.3%)	—	7 months	Cortisone, then busulphan, then cortisone, radiation to lungs, and 6-mercaptopurine	Eosinophilic leukaemia
Lymphadenopathy during attacks. <i>Lymph node biopsy:</i> Hyperplastic germinal centres. Increased eosinophils	35.7	21.42	11.3	400	Most primitive cell in the circulation was eosinophil myelocyte. No morphological abnormality of eosinophils	Not described	Raised IgE	Reported alive 5.5 years after presentation	Prednisone on alternate days, increasing to daily during attacks	Idiopathic hypereosinophilic syndrome manifesting as periodic attacks of fever, malaise, angio-oedema, and hypereosinophilia
Generalised lymphadenopathy and splenomegaly. <i>Lymph node biopsy:</i> Follicular hyperplasia and some eosinophils in blood vessels. <i>Postmortem examination:</i> Enlarged spleen and mesenteric lymph node. Eosinophil infiltration, including blast cells in both	49.9	19.96	7	63	Neutrophils: Myelocytes 1%, metamyelocytes 2%, band forms 4%, segmented 28%. Eosinophils: 40% band and segmented forms, no younger forms. Lymphocytes: 23%. Monocytes: 1%. Plasma cells: 1%	Hypercellular. Some disrupted unidentified cells seemed to originate mainly from eosinophil series. Increase in eosinophil series at all maturation stages. Later on, decrease in megakaryocytes	Coombs and IgE normal. IgG and IgM raised. Latex and antinuclear factor – ve. "Rose" test +ve. Serum folate low normal. Serum vitamin B ₁₂ raised.	3 months	Prednisolone, 6-mercaptopurine	Eosinophilic leukaemia or a variant of juvenile chronic myeloid leukaemia
Cervical lymphadenopathy, splenomegaly	22.1	10.387	8.8	200	Eosinophils deficient in granules	Blast forms 53%, myeloblasts 0.5%, eosinophil myelocytes 2.5%, eosinophil metamyelocytes 2.5%, juvenile eosinophils 2.5%, adult eosinophils 7.5%	—	Reported alive 12 years later. ? Any treatment	Adrenocorticotrophic hormone. Eosinophils increased twice on its withdrawal	Eosinophilic leukaemia
<i>Postmortem examination:</i> Splenomegaly. Eosinophil infiltration of lymph node and spleen	101.2	78.936	Not described	Not described	Eosinophils of mature type. Variable size, number, and distribution of granules. 2–3 lobed nuclei	Very cellular with enormous increase in eosinophils, especially lobulated forms	—	11 weeks	—	Eosinophilic leukaemia
Lymphadenopathy and splenomegaly. <i>Postmortem examination:</i> Eosinophil infiltration of spleen and mediastinal lymph node	113	79.1	Normochromic anaemia	Normal	Mature eosinophils initially. Later on, more immature forms	Initially: Proliferation of granulocytes and numerous myelocytes, mainly eosinophils. Later: 40% Mature eosinophils, 60% undifferentiated cells and very few erythroblasts, neutrophils, myelocytes, or metamyelocytes	Increased gammaglobulin, decreased albumin. Wassermann reaction and lupus erythematosus cell –ve. Heterophilic antibodies –ve.	8 months	Adrenocorticotrophic hormone	Disseminated eosinophilic collagen disease
Generalised lymphadenopathy	21.7	10.85	10.8, normocytic anaemia	Normal	Mature eosinophils	Hypercellular. 30% Of myeloid series were eosinophils	Decreased serum albumin, pronounced hypergammaglobulinaemia. Wassermann reaction, heterophil antibody, Coombs, and lupus erythematosus cell –ve.	Reported well 22 months later	Adrenocorticotrophic hormone, twice weekly. Lowering of dose was followed by relapse	Disseminated eosinophilic collagen disease
Not described	12	4.8	Normal	Normal	—	Several blast cells, which disappeared later on	Autoimmune, antinuclear factor and circulating immune complexes –ve. IgE normal	3 years 6 months	Diuretics, digitalis, and steroids	Idiopathic hypereosinophilic syndrome

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Table 2 Summary of clinical, biopsy, and necropsy findings of 19 children with the idiopathic hypereosinophilic syndrome (continued)

Author (years)	Age at onset (years)	Sex	Presenting symptoms	Cardiovascular system	Nervous system	Skin/muscle/joints	Renal	Pulmonary	Gastrointestinal tract	Hepatic
Goldstein (1952) ²⁰	7	M	Fever. Pain in abdomen and right axilla	None	None	None	None	None. Chest x ray: No abnormality	None	None
Herrerg-Goepfert (1985) ²¹	9	M	Myalgia, arthralgia, fever, delirium, facial and leg oedema, progressive dyspnoea	Congestive heart failure, cardiomegaly, systolic murmur (mitral regurgitation). <i>Postmortem examination:</i> Ventricular dilatation and hypertrophy. Thrombi in auricle and right ventricle. Extensive subendocardial fibrosis. Thrombosis and inflammatory cell infiltration by lymphocytes, plasma cells, and eosinophils in blood vessels of myocardium	None. <i>Postmortem examination:</i> Cysticercus in left putamen, thought to be an incidental finding	Myalgia, arthralgia. <i>Muscle biopsy:</i> Non-specific	Not described	Chest x ray: Infiltrative pulmonary changes. <i>Postmortem examination:</i> Thrombi, infarcts, and inflammatory cells infiltration by lymphocytes, plasma cells, and eosinophils in blood vessels of lungs	Not described	Hepatomegaly. <i>Postmortem examination:</i> Eosinophil infiltration
Knorr (1958) ²²	7.5	F	Fever, sore throat, pains in feet, anorexia, irritability	Acute heart failure. Cardiomegaly, systolic murmur (mitral regurgitation). <i>Postmortem examination:</i> Left atrium greatly dilated. Ventricles enlarged, subendo- and myocardial fibrosis, especially of left. Endocardial fibrosis, immediately under the posterior leaflet of mitral valve, extending into chordae tendineae. Destruction of posterior leaflet of mitral valve. Arterial embolus in right leg	Extensive involuntary choreiform hyperkinesia, pronounced hypotonia, absent abdominal reflexes	Pains in feet. Generalised coarse brown/macular rash. Erythema annulare. Joints normal	<i>Urine:</i> Numerous epithelial cells, no other abnormality	Attacks of bronchopneumonia, dyspnoea and wheezing, associated with cardiac decompensation. <i>Postmortem examination:</i> Lung oedema. Pneumonic changes with eosinophil infiltration	None	Hepatomegaly
Libanoff (1976) ²³	9	M	Dizzy spells, fatigue, shortness of breath	Congestive heart failure, cardiomegaly, systolic murmur (mitral regurgitation). <i>Postmortem examination:</i> Extensive endocardial and myocardial fibrosis in both ventricles, most severe at the apical position of right ventricle. Anterior leaflet of mitral valve was destroyed. Pericardial effusion. No eosinophil infiltrate	None	None	None	Dyspnoea. Chest x ray: Increased vascular markings. <i>Postmortem examination:</i> Pleural effusion	<i>Postmortem examination:</i> Ascites	Hepatomegaly. <i>Postmortem examination:</i> Liver congestion
Olson (1982) ²⁴	9	M	Fatigue, anorexia, weight loss, fever, cough	Congestive heart failure, cardiomegaly, systolic murmur (mitral regurgitation). <i>Postmortem examination:</i> Biventricular endomyocardial fibrosis (mural thrombi in left ventricle)	Not described	<i>Skeletal muscle biopsy:</i> Normal	Not described	Cough. Chest x ray: Bilateral alveolar pneumonitis. <i>Biopsy:</i> Hypersensitivity pneumonitis	Not described	Clinically not described. <i>Postmortem examination:</i> Chronic passive congestion and centrilobular necrosis
Rasche (1973) ²⁵	5	F	Abdominal pain, diarrhoea, vomiting, fever	Congestive heart failure, cardiomegaly. <i>Postmortem examination:</i> Biventricular dilatation, thrombi in both ventricles and right atrium, containing abundant eosinophils. Coronary thrombosis and myocardial necrosis	Irritability, confusion, restlessness, coma. <i>Postmortem examination:</i> Thrombi in cerebral arterioles and venules, necrosis in thalamus and cerebellum	None	Normal serum creatinine and urica. <i>Postmortem examination:</i> Focal proliferative glomerulitis	Dyspnoea. Chest x ray: Linear opacities in both bases. <i>Postmortem examination:</i> Red and congested. Vascular thrombosis and lung infarct	Abdominal pain, diarrhoea, and vomiting	Hepatomegaly. Prolonged prothrombin time. <i>Postmortem examination:</i> Thrombi in sinusoids and eosinophil infiltration

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<i>Lymphatic/spleen</i>	<i>Total white blood cell count ($\times 10^9/l$) at presentation</i>	<i>Eosinophil count ($\times 10^9/l$) at presentation</i>	<i>Haemoglobin (g/dl) at presentation</i>	<i>Platelets ($\times 10^9/l$) at presentation</i>	<i>Peripheral blood white blood cell morphology</i>	<i>Bone marrow</i>	<i>Other laboratory findings</i>	<i>Duration</i>	<i>Treatment</i>	<i>Authors' diagnosis</i>
Splenomegaly. Generalised lymphadenopathy. Tender lymph node in right axilla. <i>Lymph node biopsy</i> : Eosinophil and polymorph infiltration. Fibrosis. In general, picture is of lymphadenitis, no other specific changes, no parasites and no calcification	38.3	19.9	'Moderate anaemia'	Not described	Neutrophil: band forms 3%, segmented forms 31%. Eosinophil segmented forms 52%. Lymphocytes 13%. Monocytes 1%. Normal granules in eosinophils	Pronounced increase in eosinophils. Otherwise normal	Wassermann reaction - ve. Mantoux test 1/1000 + ve. Globulin and albumin normal	When last seen 7 months later was well and attending school, but generalised lymphadenopathy. leucocytosis ($19.6 \times 10^9/l$), and eosinophilia ($2.35 \times 10^9/l$) had persisted. On repeated examination of blood, stools, and urine during the above period, no parasites were seen	None. The fever, splenomegaly, and anaemia disappeared spontaneously	Eosinophilia infectiosa
Generalised lymphadenopathy. <i>Lymph node biopsy</i> : Non-specific. <i>Post-mortem examination</i> : Spleen and lymph node enlarged. Eosinophil infiltration	Not specified	Not specified	Not described	Not described	At some stage white blood cell count was $85 \times 10^9/l$, with 75% eosinophils of normal morphology	Increased eosinophils of normal morphology. <i>Post-mortem examination</i> : Increased eosinophils (98%)	Total serum protein 82 g/100 ml, inversion of albumin/globulin ratio. Latex test, lupus erythematosus cells and antinuclear factor - ve	6 months	Not described	Idiopathic hypereosinophilic syndrome
Generalised lymphadenopathy. Splenomegaly	27	18.3	Hypochromic anaemia	Not described	Neutrophils: segmented 13%, band forms 3%, metamyelocytes 1%. Eosinophils: segmented 54%, band forms 13%, myelocytes 1%. Monocytes 2%. Lymphocytes 13%	Hyperssegmentation of the neutrophils. Pronounced eosinophilia. Eosinophils 13.5%, eosinophil precursors 20%. Mature eosinophils show degranulation. No evidence of leukaemia	Direct Coombs test - ve. Albumin reduced. Alpha ₁ and alpha ₂ and gammaglobulins raised	10.5 months	Initially thought to be rheumatic fever; penicillin, Glutisal (salicylamide + ethenazamide), and Nirvanol (a hydan-toin) with some improvement. Later: cortisone (5 days)	Fibroplastic parietal endocarditis with blood eosinophilia
Splenomegaly. <i>Post-mortem examination</i> : Spleen congestion	188.5	169.65	10.2	120	—	Increase in eosinophils at myelocyte, metamyelocyte, and segmented cells level. Slight increase in plasma cells	Albumin and globulin normal	3 years	Not described	Eosinophilic leukaemia
Clinically not described. <i>Post-mortem examination</i> : Lymph node and spleen showed extramedullary haematopoiesis	55	48.4	Not described	Not described	Mature eosinophils	Initially: eosinophil hyperplasia without an increase in immature forms. <i>Second biopsy</i> : Hypercellularity and increased myeloblasts (7%)	Rheumatoid factor - ve	10 months	Diethyl carbamazepine with no improvement. Prednisone	Hypereosinophilic syndrome, preleukaemia state
Splenomegaly. <i>Post-mortem examination</i> : Splenic infarcts. Eosinophil infiltration of lymph node and spleen	152	130.72	8.1	195	8% Segmented neutrophils, 1% neutrophil band forms, 5% lymphocytes, 83% eosinophils, 2% eosinophil band forms, 1% eosinophil myelocytes	Myelocyte: Erythrocyte ratio=20:1. Predominant cells were eosinophil myelocytes, metamyelocytes, and mature eosinophils. <i>Post-mortem examination</i> : Hyperplasia of eosinophil series with orderly maturation	Lupus erythematosus cell - ve. Total serum protein, protein electrophoresis, and immunoglobulin normal	25 days	Digitalis, antibiotic, steroids	Acute rapidly fatal case of Loeffler's endocarditis

Continued

Table 2 Summary of clinical, biopsy, and necropsy findings of 19 children with the idiopathic hypereosinophilic syndrome (continued)

Author (years)	Age at onset (years)	Sex	Presenting symptoms	Cardiovascular system	Nervous system	Skin/muscle/joints	Renal	Pulmonary	Gastrointestinal tract	Hepatic
Spry (1983) ¹⁰	14	M	Diarrhoea, fever, sweating, abdominal pain	None	None	None	None	None	Diarrhoea, abdominal pain. <i>Biopsy</i> : Inflammatory cell infiltration, containing many eosinophils in caecum, large bowel, and rectum	None
Tallgren (1974) ²⁶	3	M	Persistent febrile upper respiratory tract infection, dry cough, dyspnoea, arthralgia, and slight knees swelling	<i>Postmortem examination</i> : Cardiomegaly, pericardial effusion, epicardial petechiae. Haematoma in right atrial wall, white milky myocardial infiltrate. Leukaemic infiltrate and atypical eosinophils in myocardium	<i>Postmortem examination</i> : Brain swelling. Leukaemic infiltrate and atypical eosinophils in leptomeninges	Macular and petechial rash. Arthralgia, slight swelling of knees	<i>Postmortem examination</i> : Enlarged kidneys. Leukaemic infiltrate and atypical eosinophils	Dyspnoea, cough. <i>Chest x ray</i> : Miliary infiltrates. <i>Postmortem examination</i> : Lungs enlarged. Leukaemic infiltrate and atypical eosinophils	Bleeding	Hepatomegaly. <i>Postmortem examination</i> : Liver enlargement. Leukaemia infiltrate and atypical eosinophils
Thomsen (1939) ²⁷	11	M	Sore throat, cervical lymphadenopathy, fever	Congestive heart failure, cardiomegaly, pericarditis. <i>Postmortem examination</i> : Pericardial thickening and petechiae. Heart dilated, right half hypertrophic. Right auricle enlarged, with a parietal thrombus. Myocardial and endocardial fibrosis	None	Generalised oedema, especially of face. Migratory polyarthritis and joint deformities	<i>Postmortem examination</i> : Enlarged kidneys	<i>Postmortem examination</i> : Oedema and blast cells infiltrate	None	Hepatomegaly. <i>Postmortem examination</i> : Blast cells infiltration
Yam (1972) ²⁸	12	M	Cough, rhinorrhoea, fever, chest pain, tingling, and numbness of hands	Congestive heart failure, cardiomegaly. <i>Postmortem examination</i> : Heart dilated. Mural thrombosis and fibroplastic parietal endocarditis	Tingling and numbness of hands. Hyperreflexia, clonus, and bilateral Babinski syndrome	Petechiae. Erythematous rash. Muscle weakness	None	Cough, chest pain. <i>Chest x ray</i> : Diffuse granular infiltrate and enlarged hilar lymph node. <i>Postmortem examination</i> : Multiple infarctions and diffuse pneumonia	Diarrhoea, vomiting, nausea, abdominal pain. Perforated antral ulcer	Hepatomegaly. <i>Postmortem examination</i> : Massive liver enlargement. Heavy infiltrate of immature eosinophils and blast forms
Present case	14	F	Weight loss, anaemia, breathlessness, anorexia, lethargy, nausea, diarrhoea and vomiting, amenorrhoea, petechial rash, mouth ulcers, blisters of hands and feet, with joint and limb pain	Congestive heart failure, cardiomegaly, hypertension, systolic murmur (mitral regurgitation), pericardial effusion	None	Petechial rash, joint and limb pains	Haematuria	Cough, breathlessness. <i>Chest x ray</i> : Interstitial lung oedema, vascular redistribution, small right sided pleural effusion	Diarrhoea and vomiting	Hepatomegaly

Lymphatics/spleen	Total white blood cell count ($\times 10^9/l$) at presentation	Eosinophil count ($\times 10^9/l$) at presentation	Haemoglobin (g/dl) at presentation	Platelets ($\times 10^9/l$) at presentation	Peripheral blood white blood cell morphology	Bone marrow	Other laboratory findings	Duration	Treatment	Authors' diagnosis
None	27	14-63	Not described	Not described	Vacuolated and degranulated eosinophils	Not described	Iron deficiency anaemia. High serum IgG	Reported as doing well after 4 years while on Salazopyrine. Diarrhoea returns within one day of stopping it	Incomplete response to prednisolone. Very good response to Salazopyrine	Hyper eosinophilic syndrome with isolated gastrointestinal tract involvement
Lymphadenopathy and splenomegaly. <i>Postmortem examination:</i> Lymph node and spleen; leukaemic infiltrate and atypical eosinophils	79	57-275	Normal	Normal	72.5% Segmented eosinophils, 2% eosinophil myelocytes and metamyelocytes	Initially: Increase in myeloid cells predominantly eosinophils at various stages of maturation. 'Paraleucoblasts' were seen. Later: Myelocytes with few 'paraleucoblasts' dominated	Mycoplasma orale type 1 isolated from bone marrow. Cold agglutinins raised. Cryoprecipitate +ve. IgM G and A raised. Antinuclear factor -ve. Rheumatoid factor -ve, later became +ve. Lupus erythematosus cell -ve.	11 months	6-Mercaptopurine, prednisolone, methotrexate, vincristine	Eosinophilic leukaemia; mycoplasma could be cause, result or fortuitous
Generalised lymphadenopathy. Splenomegaly. <i>Postmortem examination:</i> Blast cells infiltration of lymph node and spleen	42	31-08	10-3	140	Eosinophils showed slightly basophilic cytoplasm, containing variable, mostly few coarse granules. Later myeloblasts appeared in increasing numbers	Initially: Increase in stem cells and cells of eosinophil series. Later: Myeloblasts made 45% and 'erythropoiesis completely paralysed'	Reduced serum albumin. Wassermann reaction and Widal's test -ve	12 months	Splenic radiation and bone radiation	Eosinophilic leukaemia
Hilar lymphadenopathy and splenomegaly. <i>Postmortem examination:</i> Massive splenomegaly and lymphadenopathy. Heavy infiltrate of immature eosinophils and blast forms	71	51-12	12-8	Not described	Mainly mature eosinophils of different size, vacuolated cytoplasm, large unevenly distributed granules, decreased number of granules and mixed basophilic granules. Nuclear hypo- and mainly hypersegmentation	Hypercellular. Myeloid hyperplasia and eosinophilia	Coombs test -ve. Lupus erythematosus cell -ve.	4 months	Prednisolone, busulphan	Eosinophilic leukaemia
None	13-4	5-2	9-3	315	Eosinophils, showing partial degeneration	Hypercellular. Pronounced eosinophilia	IgE, rheumatoid factor, alpha2 globulin and IgG raised. Albumin low. Antinuclear factor -ve. Serum folate low. Serum vitamin B12 high normal	After 15 months doing well	Prednisolone, alternate days. Eosinophils raised when prednisolone was stopped	Idiopathic hypereosinophilic syndrome

cells and basophils, peptides are released that are strongly chemotactic for eosinophils,^{8 12} such as eosinophil chemotactic factor of anaphylaxis. Histamine has also been shown to be chemotactic for eosinophils. As IgE is directly involved in the triggering of mast cells with subsequent degranulation the association of eosinophilia with IgE mediated immediate hypersensitivity reaction can be explained by such chemotactic mechanisms. Eosinophil chemotactic factors that are derived from the complement system include the proteolytic fragment of C5, C5a, and the trimolecular complex C567. Other recognised factors are leucotriene B4 and substances produced by some parasites.¹²

On the other hand, factors that have an eosinopenic effect on blood concentrations include corticosteroids and beta adrenergic agonists, as well as an eosinopenic factor present in inflammatory exudate, which may account for the well documented eosinopenic response that is associated with most bacterial and viral infections, apart from a few exceptions (see Table 1).^{1 12}

Mechanisms of tissue damage in the idiopathic hypereosinophilic syndrome. In addition to their possible beneficial role, there is evidence that the eosinophils may occasionally be harmful to the host. For example, in asthma, it was generally held until recently that the eosinophils were protective, destroying the mast cell products that induce such clinical features of asthma as bronchoconstriction and changes in blood supply to the lungs. Several groups now feel, however, that the eosinophils may be responsible for some of the serious complications of asthma, including bronchial epithelial cell injury and even pulmonary fibrosis. It is the proteins in the distinctive cytoplasmic granules of the eosinophil that are suspected of damaging the lungs.¹

The cytotoxic effect of eosinophil granular basic proteins on parasites has led to an examination of the potential cytotoxicity for mammalian cells.¹² Cultured intestinal, splenic, cutaneous, and peripheral blood mononuclear cells are damaged by major basic proteins. There is evidence that these enzymes play a major role in the pathogenesis of the idiopathic hypereosinophilic syndrome.⁸ Of these proteins, the eosinophilic major basic protein, as well as the eosinophilic cationic protein, were found to be raised in the serum samples of patients with this syndrome.^{8 10} Furthermore, degranulated eosinophils in peripheral blood smears are common in idiopathic hypereosinophilic syndrome and their presence seems to be a valuable indication of endocardial disease.¹³ In vitro experiments with rat myocardial cells support the idea that components of the granules are released from the circulating

eosinophil and directly damage the myocardium.¹⁴ Eosinophilic cationic protein may also be partially responsible for the thromboembolic phenomena characteristic of this syndrome. Eosinophil granules contain potent neurotoxin, which causes demyelination and damage Perkinje cells in laboratory animals. It might be that the same, or similar, neurotoxin causes disease in patients with this syndrome.¹²

Other potential mechanisms of tissue damage include tissue infiltration with eosinophils (space occupying) and thromboembolic phenomena related to thrombi associated with endomyocardial disease.

Incidence

Idiopathic hypereosinophilic syndrome mainly affects patients between 20 and 50 years of age. The incidence is not known, but over 150 patients from different age groups have now been described. After a comprehensive search of the published reports 18 cases of this syndrome were identified in children under 16 years.^{4 7 10 15-28}

Summary of the clinical details and laboratory, biopsy, and autopsy findings of the involvement of the various organ systems of the 18 children reported in these reports and the present case is shown in Table 2. Fourteen boys and five girls were affected—that is, the male predominance is less pronounced than in older age groups.

The cardiovascular system in the idiopathic hypereosinophilic syndrome

Involvement of the cardiovascular system is the main source of morbidity and mortality. Sixteen children showed evidence of this. Cardiovascular involvement in these children was generally similar to that in adult patients in its frequency and distribution.

The cardiovascular involvement in this syndrome is nearly always biventricular, but it spares the outflow tracts. Characteristically, patients develop endocarditis with overlying thrombosis and, later, endomyocardial fibrosis. Involvement of the supporting structures of the atrioventricular valves often results in mitral and sometimes tricuspid regurgitation. The endocardial thrombi give rise to peripheral emboli, which further complicate the clinical picture. Patients with this syndrome are also at increased risk of developing thromboembolic disease in blood vessels of medium to large size. Disease in small blood vessels also occurs, with thickening of intimal tissue.⁶

Cases that were previously called Loeffler's eosinophilic endocarditis are probably synonymous with hypereosinophilic syndrome with severe cardiac involvement. It is now accepted that there is a range of eosinophilic heart disease, varying in severity

from Loeffler's eosinophilic endocarditis, the most acute and fatal form, to Ugandan type endomyocardial fibrosis. The heart in the condition described in 1948 in West Africa by Davies, originally called endocardial fibrosis and later endomyocardial fibrosis,²⁹ is indistinguishable from the heart of a patient with Loeffler's fibroplastic parietal endocarditis, or eosinophilic leukaemia. Further, endomyocardial fibrosis is also known to present in non-tropical countries.

There have been reports of patients who present with an initial hypereosinophilic illness, survive, and are found at necropsy to have endomyocardial fibrosis, sometimes with features identical to Ugandan type endomyocardial fibrosis.³⁰ Endomyocardial fibrosis seems to be the burnt out phase of an eosinophilic heart disease.

Hearts from patients with heart failure secondary to other causes of hypereosinophilia also had necropsy appearances similar to those of patients with the idiopathic hypereosinophilic syndrome. Thus the common denominator of the cardiac lesion is probably the eosinophilia itself and not an unrecognised underlying factor.⁸

In a study of 50 patients Harley *et al* defined the non-cardiovascular characteristics that distinguish patients at risk of developing endomyocardial fibrosis from those who remained free of heart disease.³¹ Patients with clinically overt heart disease were more likely ($p < 0.05$) to be male and HLA-Bw44 positive and have splenomegaly, thrombocytopenia, raised serum vitamin B₁₂ concentrations, and hypogranulated or vacuolated eosinophils and abnormal early myeloid precursors in the peripheral blood. Those patients with heart disease were also more likely to have fibrosis and decreased megakaryocytes in the bone marrow. In contrast, those who remained free of heart disease tended to be female and have angio-oedema, hypergammaglobulinaemia, raised serum IgE concentration, and circulating immune complexes. Appreciation of this relative degree of risk for the major complication of the idiopathic hypereosinophilic syndrome should prove useful in the early identification and appropriate treatment of patients in whom endomyocardial fibrosis might develop.

Involvement of other organs/systems

The clinical manifestation and pathological findings of the involvement of the various systems in those children who had cardiovascular involvement might have been secondary to the latter either in the form of congestive heart failure, causing, for example, pulmonary or gastrointestinal symptoms or hepatomegaly, or embolic phenomenon, originating from intracardiac thrombosis. In many cases,

however, the primary involvement of the various systems was also proved by biopsy or necropsy findings (Table 2).

In addition to the involvement of the cardiovascular system, which was the major problem in our present case, there are certain other features that need some emphasis.

- (1) Previous history of asthma. None of the other 18 children had a similar history. Also there are a few well described adult patients who had both bronchial asthma and this syndrome.^{6 10}
- (2) Dramatic response to corticosteroids.
- (3) Raised serum rheumatoid factor. This has rarely been observed in patients with this syndrome.^{9 32} Furthermore, the concentration decreased after treatment.
- (4) The serum IgE concentration returned to normal after treatment. This has also been reported by Bush.³² The changes in serum IgE concentration might be of benefit in monitoring progress, as is the eosinophil count.
- (5) Low total white blood cell count at presentation, which, like initial high serum IgE concentration, has been reported to be associated with a better response to treatment.
- (6) In our case, her illness initially started with mouth ulcers and blisters of hands and feet. This combination has not been reported before. Presentation of the idiopathic hypereosinophilic syndrome with mouth ulcers has been reported in two patients, who were 26 and 51 years old.³³ In these patients, however, there was ulceration of other mucous membranes, including the genitalia.

Treatment

The idiopathic hypereosinophilic syndrome is a rare disorder, but one that is accompanied by high morbidity and mortality. Recent vigorous treatment regimens, however, directed at lowering the eosinophil count with symptomatic treatment of complications of the organ systems, has brought about a tremendous improvement in survival and prognosis. The mainstay of treatment is corticosteroids. Hydroxyurea is used in patients who do not respond or only partially respond to steroids.³⁴ Its use may also be required to allow the steroid dosages to be reduced in patients who require maintenance treatment. Vincristine has also been used recently in a number of patients with aggressive disease. Anti-coagulants are required in most patients.¹⁰ Drugs that inhibit platelet function—for example, dipyridamole, have also been used. Leucopheresis and plasma exchange do not seem to have any clinical

benefit, unless the patient also had increased whole blood viscosity and widespread vessel occlusions.

Patients without dysfunction of organ systems are not treated and are followed closely at three to six monthly intervals.³⁴ If patients show dysfunction of organ systems they are treated initially with corticosteroids. If the disease stabilises or improves the steroid is continued on an alternate day regimen. Ultimately, it is tapered to the lowest possible dose that will control that disease. If the disease progresses despite steroids a cytotoxic agent, specifically hydroxyurea, is added with the aim of maintaining the leucocyte count at less than $10 \times 10^9/l$ with a normal eosinophil count.

Prognosis

Favourable prognostic factors that indicate better response to treatment are high serum IgE concentration, the presence of angioneurotic oedema, and unmistakable eosinopenia within a few hours after the first dose of prednisolone. Unfavourable prognostic signs are pronounced leucocytosis and myeloblasts in peripheral blood and congestive heart failure.^{4 34} It is also important to look for the possibility of high serum vitamin B₁₂ and low serum folate concentrations, abnormal leucocyte alkaline phosphatase activity, chromosomal abnormalities, and basophilia of more than 3%. These leukaemic markers as a group seem to have a predictive value in terms of symptomatology and response to treatment. Those with positive findings had more severe disease.⁴

Eosinophilic leukaemia

Many patients of various age groups with this syndrome, including eight children in our review, were reported as having eosinophilic leukaemia. Although this is one extreme of this syndrome, most patients do not seem to have leukaemia. Rickles and Miller suggested the following criteria for a diagnosis of eosinophilic leukaemia.³⁵

- (1) Pronounced and persistent eosinophilia, associated with immature forms, either in the peripheral blood or bone marrow.
- (2) Greater than 5% blast forms in the bone marrow.
- (3) Tissue infiltration by immature cells of predominantly eosinophilic type.
- (4) An acute natural history measured in months, accompanied by anaemia, thrombocytopenia, increased susceptibility to infection, and/or haemorrhage.

Although the hypereosinophilic syndrome was originally defined in the context of primary eosinophilia, it is now recognised that the same involvement of organ systems may arise when eosinophilia

occurs secondary to a defined condition—for example, drug reactions and parasitic disease^{1 2 4}—so that early identification and prompt treatment of the primary condition, which usually results in the disappearance of the hypereosinophilia, may prevent these complications.

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