

Relation between thyroid state and cardiac rhythm in 75 patients with Graves' disease and atrial fibrillation treated with 600 MBq ¹³¹I

Thyroid state after treatment	Reversion to sinus rhythm	Persisting atrial fibrillation	Total
Euthyroid	14	17	31
Hypothyroid	33	11	44

became hypothyroid (75% v 45%; $p < 0.01$; χ^2 analysis) (table). Of the 33 patients who developed thyroid failure and reverted to sinus rhythm, 30 became hypothyroid within six months of treatment, two at nine months, and the remaining patient at five years. Only six of the 11 patients rendered hypothyroid but remaining in atrial fibrillation developed thyroid failure within six months. There was no difference in the use of digoxin or β adrenoceptor antagonists between those reverting to sinus rhythm and those remaining in atrial fibrillation.

Discussion

Our findings show that patients with Graves' disease and atrial fibrillation who become hypothyroid within six months of receiving a therapeutic dose of ¹³¹I are more likely to revert to sinus rhythm than are those who are rendered euthyroid during this period. The different cardiac responses appear to be related to the degree and to the rate of lowering of thyroid hormone concentrations. Although thyrotrophin releasing hormone tests were not performed routinely after treatment, conceivably in some of the euthyroid patients "normal" concentrations of total T4 and T3 were associated with an absent thyrotrophin response. This combination of results

(often referred to as subclinical hyperthyroidism) has been implicated in the development of atrial fibrillation.³ Evidence suggests that the longer a patient is in atrial fibrillation the less likely he is to revert to sinus rhythm after successful antithyroid treatment.⁴ Nevertheless, it is extremely difficult to date the onset of the arrhythmia, and we did not attempt to correlate these uncertain data with eventual outcome of cardiac rhythm.

Although we intended to induce hypothyroidism with 600 MBq (16.2 mCi) ¹³¹I—a dose previously considered ablative⁵—thyroid failure developed in only 36 (48%) of our patients within the first six months. Hence in order to increase the incidence of early hypothyroidism and thereby maximise the rate of spontaneous reversion to sinus rhythm there is now a case for administering a larger dose—say, 900-1200 MBq (24.3-32.4 mCi)—to patients with Graves' disease complicated by atrial fibrillation.

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Deposition of eosinophil cationic protein in granulomas in allergic granulomatosis and vasculitis: the Churg-Strauss syndrome

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Abstract

Biopsy specimens and tissues obtained at necropsy from two women who died after developing the Churg-Strauss syndrome were analysed to see whether granulomas in these patients contained activated eosinophils or secreted eosinophil cationic proteins, or both. Immunocytochemical studies with monoclonal antibody EG2 showed large

amounts of eosinophil cationic protein and eosinophil protein-X (which are toxic for heart cells and other tissues) in the granulomas. Many activated and degranulating eosinophils were seen to be migrating from the blood into these areas.

Eosinophils may play a central part in the development of lesions in the heart and other tissues in the Churg-Strauss syndrome.

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Introduction

Granulomatous and vasculitic diseases have a wide range of clinical features, which have been classified into several named disorders and syndromes. One of these is allergic granulomatosis and angiitis or the Churg-Strauss syndrome.¹ The classical description and analysis of 14 patients by Churg and Strauss in 1951 showed that most patients were young women with a history of asthma and very high blood eosinophil counts.² Necrotising and granulomatous lesions rich in eosinophils were present in the heart, lungs, muscles, kidneys, nervous system, spleen,

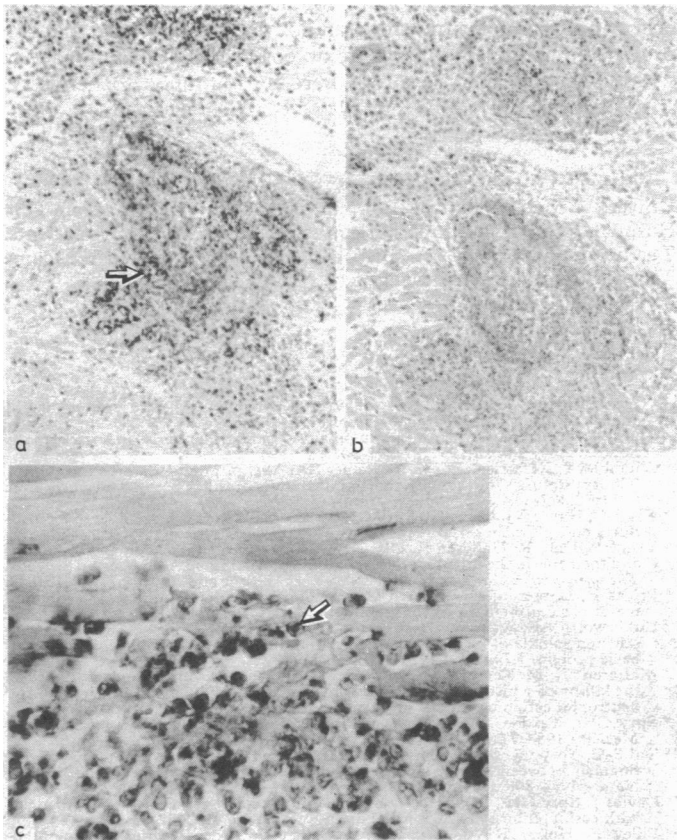


FIG 1—Localisation of activated eosinophils in myocardial granulomas in a patient (case 1) who died with acute allergic granulomatosis and angiitis. Sections of the heart obtained at necropsy were stained with an alkaline phosphatase-linked monoclonal antibody EG2 and counterstained with haematoxylin. The reaction product defines activated and secreting eosinophils. (a) Many activated and degranulating eosinophils present in the granulomas (arrow) and adjacent tissues, $\times 400$. (b) Control slide stained with an unrelated monoclonal antibody, $\times 400$. (c) Activated and degranulating eosinophils (arrow) closely applied to heart cells, many of which are necrotic, $\times 800$.

and other viscera. The largest published series is of 30 patients.³ This syndrome is distinct from polyarteritis nodosa, in which the infiltrate is composed mainly of neutrophils, granulomas are absent, and aneurysms are often present. Also, the lungs are rarely affected in polyarteritis nodosa.¹

A characteristic feature of the Churg-Strauss syndrome is the presence of large numbers of eosinophils in the blood and tissues. Although little was known until recently about the roles of human eosinophils in disease, it has now been shown that eosinophil cationic protein, eosinophil major basic protein, and eosinophil protein-X (which may be identical with the eosinophil derived neurotoxin) have now been shown to be toxic to many cells and tissues, including heart cells,⁴ brain tissues,⁵ and bronchial epithelium.⁶ These proteins are also able to kill schistosomules of *Schistosoma mansoni* and other parasites.^{7, 8} Eosinophils can become activated, when they acquire an increased cytotoxic capacity.⁹

In view of these new approaches to the study of eosinophils in disease, we examined whether the granulomas in patients with the Churg-Strauss syndrome contained activated eosinophils or secreted cationic proteins, or both. This was possible because monoclonal antibodies have been developed that bind (1) to eosinophil cationic protein and eosinophil protein-X in activated but not normal eosinophils, and (2) to secreted eosinophil cationic protein and eosinophil protein-X.¹⁰ The presence of these activated cells and their secreted products in granulomas would support the view that they are important and possibly pathogenetic components in these lesions.

Patients and methods

Case 1—A 17 year old woman with asthma was admitted to hospital with a three week history of upper respiratory tract symptoms, a one week history of nausea, vomiting, and chest pain, and discomfort and bruising of both palms and the dorsum of the right foot. Four days before admission she had developed diarrhoea and a right lateral popliteal nerve palsy. The white cell count was $20 \times 10^9/l$ (eosinophils $7.6 \times 10^9/l$). Soon after admission she developed further chest pain and collapsed with cardiac arrest. Postmortem examination showed a widespread eosinophilic inflammatory infiltrate of the myocardium, liver, and spleen, with granulomas in the myocardium (fig 1). There was focal arteritis affecting coronary, bronchial, small bowel, and renal arteries.

Case 2—A 45 year old woman with a four year history of asthma and rhinitis was admitted with a three week history of nausea, vomiting, rash, and increasing breathlessness and a two day history of pain in her jaw and neck, radiating to her arms with paraesthesias and swelling of her fingers. A full blood count one week before had shown a white cell count of $17.4 \times 10^9/l$ (eosinophils $13.2 \times 10^9/l$). She developed left ventricular failure and became rapidly hypotensive. Nodular vasculitic lesions were present on both hands and elbows and

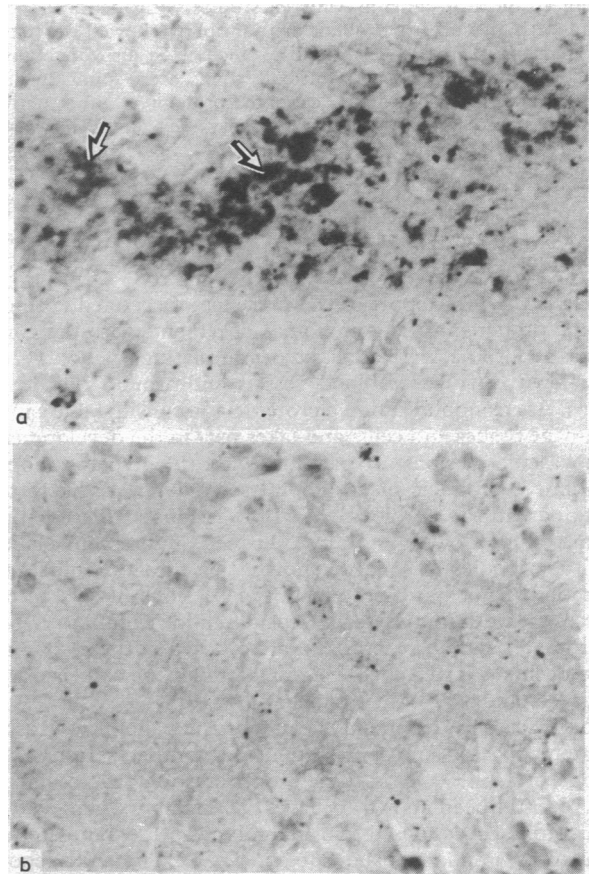


FIG 2—Localisation of eosinophil secretion products in sections of the spleen obtained at necropsy containing many granulomas (case 2). Immunocytochemical staining with an alkaline phosphatase-linked monoclonal antibody EG2 and counterstained with haematoxylin. The extracellular reaction product (arrow) shows the presence of secreted eosinophil cationic protein and eosinophil protein-X. (a) Necrotic lesion containing eosinophil cationic protein and eosinophil protein-X, $\times 800$. (b) Control slide stained with an unrelated monoclonal antibody, $\times 800$.

on her nose. An electrocardiogram showed sinus tachycardia and left bundle branch block. The white cell count was $27.6 \times 10^9/l$ (eosinophils $3.9 \times 10^9/l$). There was no response to intravenous steroids or treatment of her cardiac failure. She suffered a cardiac arrest and died seven hours after admission. Postmortem examination showed extensive necrotising granulomas and eosinophilic infiltration of arteries and

veins in the myocardium, pericardium, spleen (fig 2), lungs, trachea, stomach, and kidneys. There was focal glomerulonephritis. Analysis of serum obtained before death showed a grossly increased eosinophil cationic protein concentration of 3000 $\mu\text{g/ml}$ (normal < 750 $\mu\text{g/ml}$).

Histology and immunocytochemistry—Biopsy specimens and tissues obtained post mortem from the two patients were fixed in formalin and embedded in paraffin, then sectioned at 5 μm . The localisation of activated eosinophils and secreted eosinophil cationic protein and eosinophil protein-X was assessed with mouse monoclonal antibody EG2.¹⁰ A double antibody immunocytochemical technique was used with intestinal alkaline phosphatase conjugated rabbit antimouse IgG and goat antirabbit IgG (Sigma, Poole). A red colour developed after 30 minutes with fast red combined with beta-naphthol AS-MX phosphate and 1 mM levamisole to inhibit endogenous alkaline phosphatase. An unrelated mouse monoclonal antibody of the same isotype (IgG1) was used as a control. The slides were counterstained with haematoxylin and mounted in Apathy's medium.

Results

Immunocytochemical studies with monoclonal antibody EG2 (antieosinophil cationic protein and antieosinophil protein-X) showed that large amounts of these cationic proteins were present within the granulomas and necrotic lesions in tissues from the heart and spleen of both patients. Control studies with identical sections treated with an unrelated monoclonal antibody showed no staining. Activated and secreting eosinophils, which were also distinguished from normal eosinophils with antibody EG2, were found in granulomas containing eosinophil cationic proteins. Some activated eosinophils were also present in the blood vessels and in perivascular sites, from which they were presumably migrating towards the granulomas.

Discussion

This is the first report of the presence of secreted eosinophil cationic proteins in the granulomas of patients with the Churg-Strauss syndrome. Activated and degranulating eosinophils were also shown in adjacent blood vessels and around the necrotic lesions. As eosinophil cationic protein has a considerable capacity to damage tissues and cells⁴ and takes part in the development of cardiovascular lesions in patients with the hyper-eosinophilic syndrome,¹¹ products of eosinophil secretion were likely to be taking part in the development of the lesions in these patients. Recent studies with affinity purified fluorescein labelled rabbit antibodies have also shown the presence of secreted eosinophil major basic protein in focal lesions in several other diseases including asthma,¹² eosinophilic cellulitis (Wells's syndrome),¹³ and chronic urticaria.¹⁴ In each of these conditions it has been suggested that eosinophils might be associated with the development of tissue lesions.

This disease has commonly been found in patients with asthma and atopic disease, and some patients have raised serum concentrations of IgE.^{15, 16} It is therefore interesting that eosinophils have recently been shown to have IgE receptors that take part in cytotoxic reactions.¹⁷ Eosinophils also degranulate after stimulation with complexed C3b and IgG.¹⁸ There is a report of three patients with circulating immune complexes,¹⁵ but tissue lesions have not been found to contain immune complexes.¹⁶ This does not support the suggestion that IgG complexes are responsible for degranulation of eosinophils or formation of granulomas in this disease.¹⁹

The clinical features in our two patients and in others¹⁻³ suggest that there are two principal forms of the Churg-Strauss syndrome: an acute and usually rapidly fatal illness, and a sub-acute relapsing disorder. The development of irreversible heart failure is characteristic of the first group, although chronic myocardial and pericardial damage has been described in the second group.^{15, 20} The severity of the disease may be related to the extent of degranulation of eosinophils in tissues, especially the heart. Steroids appear to be of considerable benefit to these patients and could be life saving if given early enough to those with acute disease. This may be due to the inhibitory effects of

steroids on degranulation of eosinophils,²¹ which was found to be occurring in and around the granulomas. We conclude that the presence of large amounts of toxic eosinophil cationic proteins within the granulomas, shown here by immunocytochemistry, suggests that eosinophils may play a central part in the development of these lesions.

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ONE HUNDRED YEARS AGO

A gratifying proof of the utility of *crèches* for the care of children during the day, when the mothers are compelled to be at work, is afforded by Dr. J. W. Taylor in a recent report on Scarborough. He observes that, since the *crèche* was opened in 1873, it has been largely used during the height of each season; and he believes that those mothers who placed their children in it had every reason to be satisfied with the improved health of their infants. One very clear fact stands out—that the ladies who constantly attended at the nursery observed a decided change in the manners and habits of the children after a short attendance; and also that, although infantile diarrhoea prevailed during the summer months, when the children were brought to the nursery, they rapidly recovered from this affection, but generally had a recurrence of the attack on the following Monday, in consequence of improper feeding when at home on the Sunday. Abundant evidence is forthcoming elsewhere of the great good that has followed the establishment of these institutions; and it is to be hoped that the example set by Scarborough and several other towns will be more extensively followed. (*British Medical Journal* 1884;ii:972.)