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THE PATHOPHYSIOLOGY OF ENDOMYOCARDIAL FIBROSIS

Endomyocardial fibrosis is the principal cause of a restrictive cardyomyopathy in most parts of the world. Comparisons of the pathology of eosinophilic endomyocardial disease and tropical endomyocardial fibrosis show that the two diseases are indistinguishable, and it has been suggested that they have a common pathogenesis. Clinical and experimental studies on the nature of eosinophilic endomyocardial disease have implicated eosinophil granule products in the heart cell damage and the development of fibrosis in the endocardium. A high proportion of patients with hypereosinophilia from any cause will develop heart damage of this kind. There is a correlation between the presence of degranulated eosinophils, both in the blood and tissues, and the development of this complication, and clinical studies have also linked episodes of increased blood eosinophil counts and increasing numbers of degranulated blood eosinophils with the development of heart disease. Experimental work using isolated rat heart cells has shown that eosinophil secretion products are toxic to heart cells in vitro. Eosinophil products affected the plasma membrane and inhibited two of the principal oxidative enzymes of the mitochondrial respiratory chain, pyruvate dehydrogenase and 2-oxoglutarate dehydrogenase.

The results of these clinical and experimental studies led to the conclusion that eosinophils may induce endocardial injury leading to endomyocardial fibrosis. Further work on patients with hypereosinophilia in tropical countries is needed to study the possibility that eosinophils also cause tropical endomyocardial fibrosis.

Endomyocardial fibrosis presents in two clinical forms. One is associated with a marked increase in blood eosinophil counts and has been generally known under the diagnosis of Löffler's endomyocardial disease, but is now known as eosinophilic endomyocardial disease. The second type, which is most common in parts of India, Africa and South America, is known as tropical endomyocardial fibrosis, and is usually found with only a moderate increase in blood eosinophil counts. Although some clinical differences have been reported they have a strikingly similar pathological appearances both macroscopically and microscopically. For this reason it has been suggested that the two diseases have a similar pathogenesis. Recent work, which has implicated blood eosinophils in the development of endomyocardial damage in patients with hypereosinophilia, has opened up the possibility that both diseases have a common pathogenesis, related in some way to toxic products released from eosinophils.

The purpose of this paper is to review these findings and to describe recently developed methods for studying these patients.

EOSINOPHILIC ENDOMYOCARDIAL DISEASE

This disease became well known following the description of two patients by Löffler in Switzerland in 1936[1]. There had been a number of earlier reports of endomyocardial damage and heart disease in association with high blood eosinophil counts, but the syndrome only became generally recognised following Löffler's study, and subsequently over 100 patients have been described with this disorder.

Pathological features - The patients described by Löffler[1] showed two different forms of eosinophilic endomyocardial disease. In one patient the heart disease was associated with a severe illness, whereas the other presented with

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heart failure without a systemic illness. In one patient the eosinophilia increased whereas it the other patient it disappeared shortly before his death. Later work has shown that the eosinophilia which precedes and is continuous with the development of heart disease, is over 1.5 x 10^9/L for many weeks or months and it only rarely disappears, usually reappearing severa weeks or months later[2]. The eosinophil count may occasionally be normal just before death. The pathological features characteristic of eosinophilic endomyocardial disease are as follows:

Typically, at macroscopic level, endocardial thickening is prominent. The normal endocardium in the left ventricle does not exceed 20 ,µm[3], but in this condition it is several mm thick. Usually, the inflow tract as well as the apex of the left ventricle are involved (fig. 1). In cases of right ventricular disease, the apex may be severely obliterated and the region of the tricuspid valve is also affected. Atrioventricular valve thickening is frequently seen. This may be due to involvement by the endomyocarditic process or can be secondary to valvar insufficiency. Thrombus may or may not be superimposed[4]. Septae can be seen to extend into the underlying myocardium, usually limited to the inner third of the myocardium but occasionally reaching the subepicardial region.

Histologically, the thick endocardium is arranged in zones with loose connective tissue superficially merging imperceptibly with superimposed fibrin (when present). The middle layer consists of dense collagen tissue in which varying amounts of elastic fibres may be present. In the deepest layer, loose connective tissue is seen in which blood vessels and a sparse cellular infiltrate is usually found. It is from this layer the septae extend into the underlying myocardium[4].

INVOLVEMENT OF EOSINOPHILS IN THE PATHOGENESIS OF ENDOMYOCARDIAL DISEASE

The possibility that eosinophils could in some way injure the heart was suggested in 1970[5]. It was proposed that in patients with eosinophilic leukaemia, blood eosinophils could be toxic to the heart and induce endomyocardial fibrosis. A similar suggestion was made in relation to patients with the idiopathic hypereosinophilic syndrome. Here it was proposed that eosinophils released a toxic substance analogous to 5-hydroxy tryptamine in patients with carcinoid induced heart lesions [6]. Another suggestion was that forceful contraction of the heart night disrupt eosinophils within the ventricles, producing local endocardial damage[7]. This mechanism would account for the distribution of cardiac lesions in patients with high blood eosinophil count. The concept of eosinophilia in association with endomyocardial disease was tested by investigating 90 previously published cases diagnosed as Löffler's endomyocardial disease[8]. Tissue for morphological examination was also made available. Three stages, according to the length of history, could be recognised at histological level: 1 - the acute/necrotic stage (average duration of symptoms 5.5 weeks). In this stage intense myocarditis, mostly due to eosinophils was present as well as perivascular infiltration; 2 - the thrombotic stage, (average duration of symptoms 10 months). Superimposition of thrombus was the characteristic feature at this stage. Eosinophils were still prominent and emdocardial thickening began to appear. Vessel walls showed evidence of damage, the lumina were often occluded by thrombus; 3 - the fibrotic stage (average duration of symptoms 24.5 months) The endocardium was severely thickened and arranged in layers as already described.

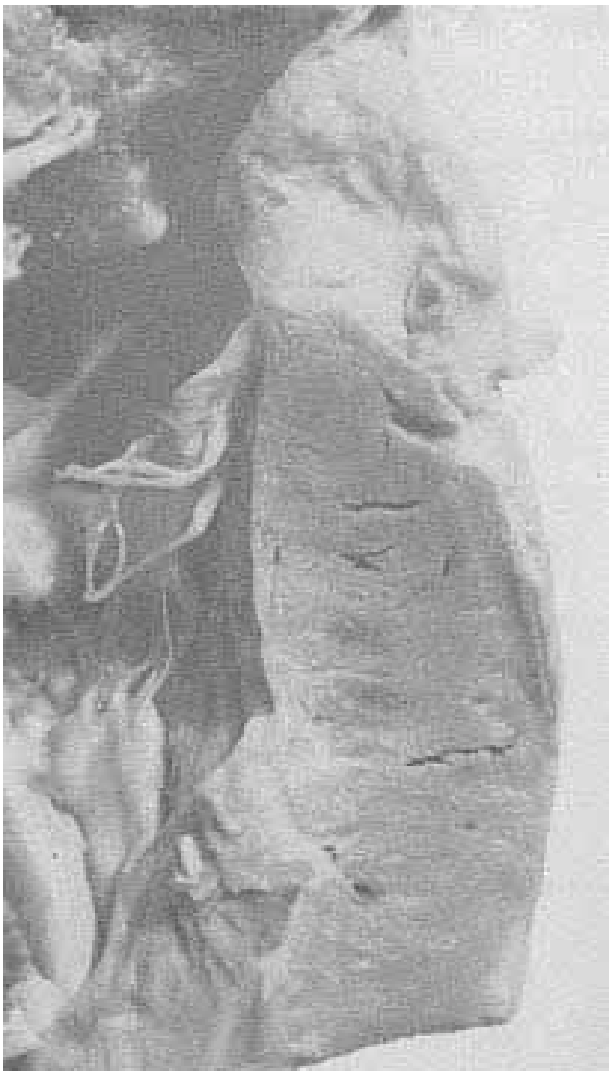

Fig. 1 - Part of the ventricular free wall (inflow tract) has been sectioned to show the severe thickening of the endocardium. Septae extending into the underlying myocardium can be clearly seen. The papillary muscles are also involved. Note the abrupt change from normal to affected endocardium. Thrombus is also superimposed.

The main argument supporting the suggestion that eosinophils were toxic to the heart centered on the occurrence of endomyocardial fibrosis in patients with hypereosinophilia due to a very wide variety of diseases The only common component of these diseases appeared to be eosinophilia. Lists of these diseases in which eosinophilia and heart disease occurs have been reported[8,10].

Tumor induced eosinophilia and endomyocardial disease - Some of the most important clinical data to support the suggestion eosinophils cause endomiocardial disease has come from. the study of tumor induced hypereosinophilia[11]. A detailed discussion of this is provided by Olsen and Spry[9]. These observations led to first: the realization that the eosinophilia preceded the heart damage; and second: the recognition of early acute necrotic lesions in the heart several weeks or months after the very high blood eosinophil count had developed. These patients usually had asymptomatic heart disease which was only found at postmortem. The third, and most recent observation has been that the blood eosinophils in these patients are often degranulated, suggesting that some granule products released into the circulation could be responsible for the heart disease[12]. Fourth: tumors which were comparable in all respects (except that they did not produce an eosinophilia) were never found to produce endomyocardial disease.

Degranulated blood eosinophils - It has been known for many years that in patients with hypereosinophilia of unknown cause, a high proportion of the patients have blood eosinophils which contain less than the normal content of specific eosin staining granules. We first recognised this in 1975 in a patient who had eosinophilic endomyocardial disease in the late fibrotic stage. As bone marrow eosinophils were not degranulated it was clear that these were acquired changes in the cell, probably the result of the release or secretion of granules into the circulation. A large amount of work has been done since then, to find out how degranulation occurs, and its relationship to endomyocardial disease.

It was found that eosinophils in patients' endomyocardial disease often had an increased capacity to bind to IgG and it was thought possible that immunoglobulin was in some way responsible for inducing degranulation and hence endomyocardial fibrosis [13]. An in vitro study with normal eosinophils showed, that degranulation of the kind seem in patients could not be produced by immune complexes or a wide variety of other types of stimuli. Sera from patients with eosinophilic endomyocardial disease did not induce normal eosinophils to degranulate. The stimulus which appeared to mimick the effects on blood eosinophils most closely was concanavalin A. This induced dissolution of the crystalloid in the centre of the specific granules, which is a common finding in patients' own blood eosinophils. However concanavalin A did not induce secretion and there was no loss of granules in vitro[14].

Recent work on the enzyme content of degranulated blood eosinophils from patients with eosinophilic endomyocardial disease showed that they had reduced amounts of peroxidase and eosinophil cationic protein, which are normally present in the specific crystalloid granules, but normal amounts of arylsulphatase which is largely confined to the small granules (Fattah & Spry 1981, unpublished observations) This suggested that the stimuli which induced degranulation in patients act specifically on the crystalloid granules, but their nature remain unknown.

Vacuolate eosinophils - An even more commonly noted abnormality in blood eosinophils in patients with eosinophilic endomyocardial disease was vacuolation. These appear to be swollen granules, which are in the process of dissolving and releasing their granule contents, but they are not specific for this condition, as they are found in a wide variety of drug induced, parasitic and other types of eosinophilials. For this reason vacuolated eosinophils do not provide a useful measure of the extent of eosinophil degranulation and it is preferable to count the number of eosinophils containing less than 50% of the normal granule content in order to produce a measure of the degree of granule content loss into the circulation.

Eosinophilic granule constituents in the circulation - Within the last few years it has become possible to measure the amounts of eosinophil derived basic proteins which are released in the circulation. Four components have been identified: eosinophil cationic protein, eosinophil major basic protein, eosinophil Charcot-Leyden crystal protein and eosinophil. peroxidase. These were all raised in patients with high blood eosinophil counts, including patients with the hypereosinophilic syndrome. Measurements in our patients of the concentrations of serum eosinophil cationic protein (assayed by Dr Inge Olsson in Sweden) showed that in one patient degranulated blood eosinophil counts correlated with the serum levels of eosinophil cationic protein However, in a group of eleven patients with eosinophilic endomyocardial disease, there was no association between the number of degranulated blood eosinophils and serum eosinophil cationic protein[2]. Levels fluctuated with disease activity and were highest in one patient for several weeks before she died with extensive cardiovascular thrombi and necrotic changes in the endomyocardium. Raised levels of eosinophil peroxidase have also been found in the sera of patients who have many degranulated eosinophils: Now that specific assays for these constituents have been developed, it should be possible to determine which ones correlate most closely with the development of endomyocardial disease.

Eosinophil damage to heart cells in vitro - Although intact eosinophils were not found to injure cardiac cells in vitro[16], recent studies have shown that products from degranulated blood eosinophils cause rapid heart cell death[17]. This was found to be the result of an initial stimulation of the plasma membrane sodium pump, probably as a result of an alteration in membrane permeability, and a secondary inhibition of two mitochondrial enzymes (pyruvate dehydrogenase and 2-oxoglutarate dehydrogenase) which play important roles in cardiac cell respiration. Endothelial cells were mot damaged in this way and neutrophils did not injure heart cells or endothelial cells.

ENDOMYOCARDIAL FIBROSIS

This disease entity was first described morphologically by Davies[18]. The pathological findings are identical to those that have already been described under eosinophilic endomyocardial disease. Reports of this condition have not

been confined to Uganda but have also come from India[19,20], Ceylon[2l], Brazil[22-25] and Venezuela[26,27], as well as from Columbia[28]. Referring to the retrospective Study[8] sixteen patients belonged to the fibrotic stage. These cases were compared with pathological material from cases with endomyocardial fibrosis received from the tropical zones, including Brazil, Uganda and Nigéria. No differences could be found. At this late stage vessels showed only non specific changes and the suggestion that the distinction between endomyocardial disease from the temperate zone differed from that in the tropics in that an arteritis is present in the former could not be substantiated. There are, therefore, no differences as far as morphology is concerned between these two conditions. It was suggested that eosinophilic endomyocardial disease and endomyocardial fibrosis belonged to the same disease spectrum, the origin of which could be traced back to the presence of eosinophils in the myocardium. Other reports include those from the temperate zones indistinguishable from the African type and the reports include those from the United States[29,30], Britain[31,32], Denmark[33] and Switzerland[34]. At one time it was suggested that the distribution of the thickened endocardium differed from the disease in the temperate zone but the variability of distribution of emdocardial thickening in the cases reviewed in Uganda have shown five types of sites in which the thick endocardium can be located[35].

EARLY DIAGNOSIS OF EOSINOPHILIC ENDOMYOCARDIAL DISEASE AND TROPICAL ENDOMYOCARDIAL FIBROSIS

Most patients with endomyocardial disease present at a late stage in their illness with lesions which are probably several months or years old. For this reason it has been very difficult to study the processes which lead to their heart disease. Clearly techniques are needed for identifying patients at an early stage and for predicting which patients with high blood eosinophil counts will go on to develop heart disease. It has become clear that clinical assessment of patients with hypereosinophilia is an insensitive method for detecting underlying heart disease until it reaches a late stage. Patients who have many degranulated blood eosinophils appear to be most at risk from developing heart damage and this group should be studied by a range of cardiac investigations to see whether early disease is present. In the past, reliance has been placed on M mode echocardiography, angiocardiography and intracardiac pressure traces looking for evidence of restriction of ventricular filling. Two important new developments have been the introduction of 2-D echocardiography and endocardial biopsy.

Echocardiography[16] - Unfortunately M mode echocardiography does mot provide specific features which allow the recognition of endomyocardial disease at an early stage. The M mode abnormalities, which are found in patients with eosinophilic endomyocardial disease, are usually the result of mitral valve reflux which is a common late event in this disorder. Standard 2-D echocardiography has provided more information, but this only gives a visual assessment of cardiac anatomy and function. The development of color coded, amplitude processed 2-D echocardiography appears to have been a major advance in that it allows the recognition of small areas of increased echo density in the heart. This appears to be the most effective non-invasive method for detecting eosinophilic endomyocardial disease, and can detect early acute disease as well as late fibrotic lesions.

Angiocardiography and Cardiac Biopsy[37] - Cardiac biopsy has become the definitive method for diagnosing eosinophilic endomyocardial disease in the early acute necrotic stage. In the later thrombotic and fibrotic stages angiocardiograms may show blunting of the apex of one or both ventricles and involvement of the atrioventricular valves. Although cardiac biopsy is the best technique for diagnosing early disease, it can fail later in the course of the disease when the biotome may not attach to areas of dense endocardial fibrosis. However these patients are easily diagnosed by echocardiography and angiocardiography.

BLOOD EOSINOPHILS IN PATIENTS WITH TROPICAL ENDOMYOCARDIAL FIBROSIS

The association of a significant eosinophilia and endomyocardial fibrosis has been documented in several studies in the tropics[18,38,39], even though many patients living in areas where tropical endomyocardial disease is common, have a moderately raised blood eosinophil count. Other studies on patients with late stage disease in Uganda[40] and South India have failed to show significant differences between blood eosinophil counts of patients with and without tropical endomyocardial fibrosis. In addition degranulated blood eosinophils were not seen in these patients, and the clinical features of their illnesses differed in several respects from those described in patients with eosinophilic endomyocardial fibrosis. Emboli, which are common in eosinophilic heart disease, were rare in the tropical disease and patients in the tropics did not have a systemic disease involving many organs and tissues, at the time of presentation with heart disease.

These apparent differences in clinical features and blood eosinophils could be accounted for if it were shown that tropical endomyocardial fibrosis was an insidious disease, in which the period of cardiotoxicity preceded clinical presentation. This seems quite possible, but remains to be proved. Careful study of patients with hypereosinophilia in the tropics may allow the recognition of the early stages of tropical endomyocardial fibrosis, and it may be possible to develop a blood test for the disease based on the finding that eosinophil constituents could be responsible for this type of cardiac injury. Considerable effort should be directed at finding a technique which allow early diagnosis. Only then will it be possible to determine whether the two forms of the disease have an identical pathophysiology and pathogenesis. This review has shown that several important steps in this direction have already been taken, and it is likely these questions will be resolved within the next few years.

RESUMO

Sem considerar áreas geográficas, a endomiocardiofibrose (EMY) é a principal causa da cardiomiopatia restritiva. Estudos comparativos da patologia da doença endomiocárdica, eosinofílica e da endomiocardiofibrose tropical mostram que se trata de um mesmo processo de aparente patogênese comum. O desenvolvimento de fibrose no endocárdio parece associado com produtos de células eosinofílica, havendo uma associação esportiva entre cardiopatia e o número de eosinófilos degranulados, no sangue e nos tecidos trabalhos experimentais em células isoladas de coração de ratos mostram a toxicidade para essas células produzidas por elementos de secreção dos eosinófilos. Esses, produtos, além de causarem alterações morfológicas nas membranas, inibem as principais enzimas oxidativas da cadeia respiratória das mitocôndrias. Esses resultados devem estimular novos estudos em doentes com hipereosinofilia em áreas tropicais, a fim de com substanciar a hipótese de que os eosinófilos são também responsáveis pela endomiocardiofibrose tropical.

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