CARDIAC AFFECTION IN COLLAGEN DISEASES

An Essay

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By

Dr. Youssef Alphonse Wahba

M.B.B.CH.

Supervised by

Prof.Dr.M.Mamdouh M.El Ashry

Ass.Prof.Of Cardiology.

Faculty of Medicine

Ain Shams University

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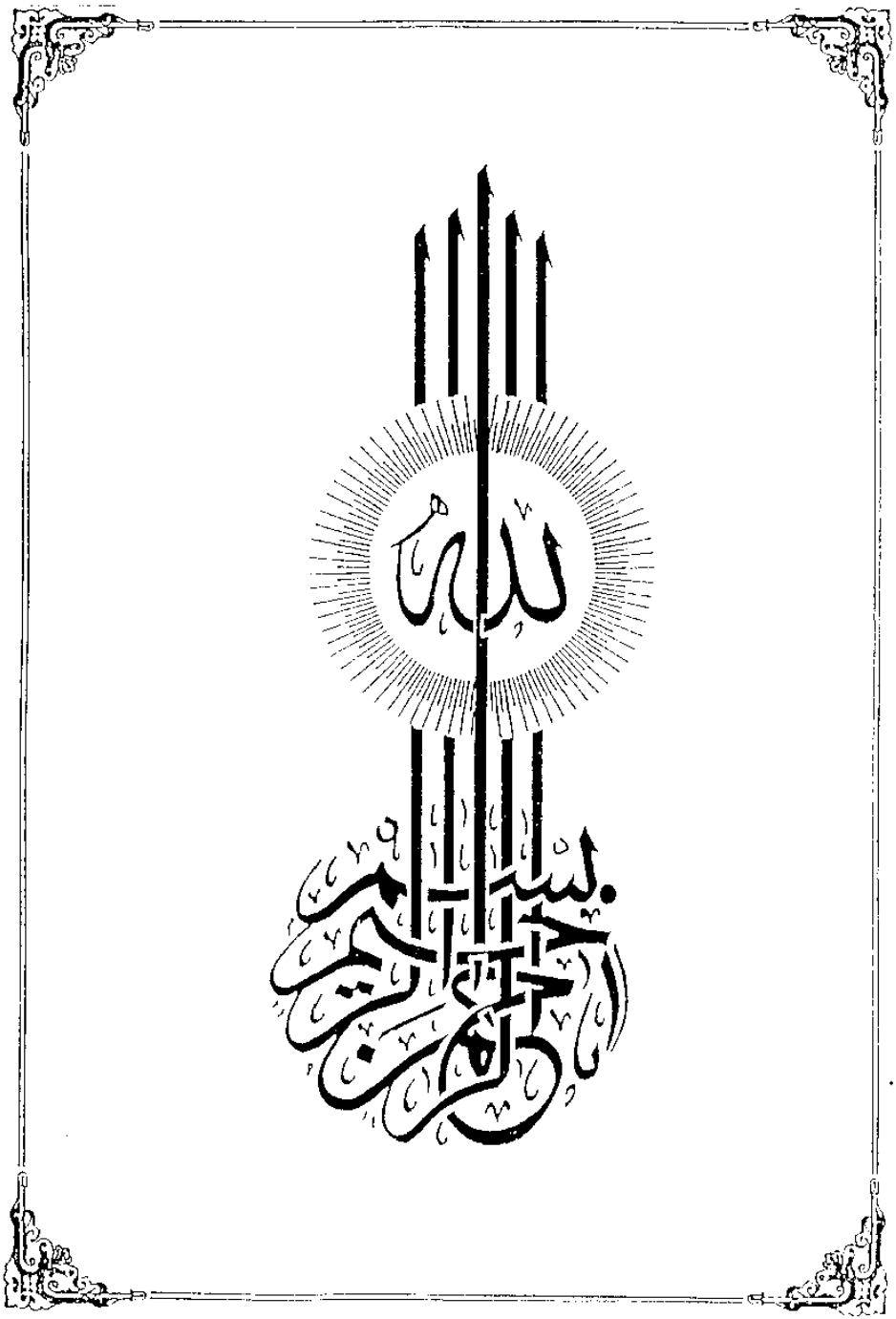
To My Little
Daughter
Christine



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INTRODUCTION

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The heart is a hollow muscular pump which provides the primary source of energy for the movement of blood through the vessel systems.

It is enclosed in a sac, the pericardium, which contains collagen and elastin fibers. The pericardium is lined with mesothelium. The superficial layer of the heart, the epicardium is also covered with a mesothelium.

The two atria and two ventricles are similar in their tissue architecture. The muscle of the atria is separated from the ventricular muscle by sturdy fibrous rings. These rings are called annuli fibrosi and are composed of dense (Type I) collagen fiber bundles. They surround the atrioventricular ostia and form the center portion of the so-called cardiac skeleton.

Similar fibrous rings surround the origin of blood vessels entering into and leading from the atrio and ventricles. The dense collagen bundles of the rings prevent distortion of the vessel openings when the heart contracts.

Type I collagen fiber bundles continue from the annuli fibrosi to the atrioventricular valves. The fibrous rings and the collagenous interventricular septum thus provide the scaffold to which cardiac muscle and valves are anchored.

The inner layer of the heart is called the endocardium. It is lined by endothelial cells with an underlying network of supporting collagen and elastin fibrils and a few smooth muscle cells.

A large group of collagen diseases affect the heart and cause permanent cardiac lesions.

One interesting aspect of connective tissue changes within this group of diseases is the similarity of many of the pathologic lesions. Furthermore, identification of the etiologic cause of the cardiac involvement at the bedside has often been difficult. For example, aortic insufficiency observed in rheumatic spondylitis, was frequently considered rheumatic fever in origin.

Now, the nature of cardiac and vascular lesions in collagen diseases is well known.

ETIOLOGY AND PATHOGENESIS OF COLLAGEN DISEASES

Etiology and Pathogenesis of Systemic Lupus Erythematosus

Kaposi's original description of acute lupus erythematosus in 1872 referred to some of the extra-cutaneous symptoms of the disease. Subsequent dermatologic investigators added further observations, which were well summarized by Jadassohn at the turn of the century. Nevertheless it was generally accepted that acute lupus erythematosus was merely a cutaneous disease.

The general constitutional symptoms such as fever, prostration, typhoid state as well as the local morbid phenomena such as joint pain and swelling ulceration of mucous membranes, glandular swelling and albuminuria were vaguely interpreted as the manifestations of a severe toxic state induced by the severe involvement of the skin.

Autopsy reports of this period mentioned the occurrence of pneumonia, pleuritis, parenchymatous nephritis, occasionally T.B. and degeneration of the parenchymatous organs. Pernet in 1908, referred to small vegetations on the mitral valve in his case (Klemperer, 1948).

Tuberculous Etiology:

In the question of etiology, main emphasis was placed

upon the role of T.B. Indead, up to recent years, the tuberculous etiology of acute lupus erythematosus has been seriously considered, finally it was disproved by Keil in 1933.

During the first two decades of this century, an increasing number of well observed cases was reported by competent clinicians from the broader view point of internal medicine. Acute lupus erythematosus thus came to be recognized as a clinical entity in which the cutaneous lesions were merely part of a serious systemic malady. However, attempts to define the disease in terms of morbid anatomy were less successful because the observations at autopsy were not characteristic and mostly disclosed only the terminating events of a grave systemic disorder (Klemperer, 1948).

Libmann and Sacks' report (1924) of an unusual form of endocarditis in cases with the characteristic clinical symptom complex, constitutes the first significant contribution to the comprehension of the morbid anatomy of acute lupus erythematosus. Subsequently, these observations were confirmed and amplified by Gross (1940). These disclosures indicated that lupus erythematosus should be defined anatomically as primary cardiac disease.

In 1935, several investigators called attention to conspicuous and widespread lesions of blood vessels and to frequent involvement of serous membranes. They then tried to correlate clinical symptoms with these structural alterations. They thought that the co-existing endocardial, vascular, serosal and joint involvement must be the manifestations of a primary injury of the endothelial cells and that acute lupus erythematosus could be explained as the result of the action of an endotheliotropic injurious factor.

Microscopic examination revealed not only vascular lesions but other tissue alterations which had not been noticed previously. Restudy of the old material disclosed that identical changes had been present but had eluded attention. These histologic findings were fully described and illustrated in 1941 by (Klemperer et al.) and a detailed account can therefore be omitted. Microscopic observations showed the presence of a widespread alteration of the connective tissue, affecting the heart, serous membranes, vasculature, lymph nodes, skin and mediastinal and retroperitoneal area (Klemperer, 1948).

Bacterial infection:

Bacteriologic examination during the life of the patients

and of the tissues after death have failed to disclose bacteria as the immediate cause of the disease.

Yet, the acute and subacute fibrile course and the severe toxic symptoms still suggest an infectious process (Klemperer, 1948).

Hypersensitivity:

Hypersensitivity to bacteria or bacterial products was proposed as a probable cause. This hypothesis is strengthened by the fact that fibrinoid collagen changes have been found as a conspicucous feature of the morbid anatomy of acute lupus erythematosus. It is generally accepted that fibrinoid collagen alterations occur in allergy. This was first demonstrated by Gerlach and Klinge in animal experiments. Its occurrence in diseases with an obvious allergic background such as periarteritis nodosa and serum sickness and in drug hypersensitivity supply further evidence for a pathogenetic relationship. The allergic hypothesis of the etiology of rheumatic fever certainly deserves serious considerations.

Yet, we must not loose sight of the fact that collagen alterations hardly distinguishable microscopically from those seen in allergy can be observed in situations which bear no relation to hypersensitivity. It has long been known

that fibrinoid collagen alterations occur in a variety of acute bacterial infections; this fact has been stressed even by Schosing, a student of Klinge, the most ardent advocate of the significance of collagen alterations in allergy. Identical changes can be observed in inflammations due to chemical or physical irritation. In experimental hypertension, conspicuous vascular lesions simulating periarteritis nodosa have been reported repeatedly. The alteration which is so often found in collagen fibres in the base of a peptic ulcer or the vicinity of acute pancreatic necrosis is strinkingly similar to fibrinoid collagen changes. Finally Wu Tsai Tong showed that simple squeezing of the skin of rats results in collagen alterations indistinguishable from fibrinoid changes. These observations seem to justify the general conclusion that fibrinoid collagen alteration must not be interpreted solely and invariably as an expression of hypersensitivity. Consequently it is doubtful to accept the doctrine that any disease anatomically characterized by such connective tissue lesions is persumably of allergic origin. Also, there is no direct clinical evidence in support of hypersensitivity in acute lupus erythematosus. An allergic hypothesis rests, therefore, upon the histologic features alone and it must be stressed that these anatomic facts have not yet been

analysed sufficiently to permit a final pathogenetic synthesis.

The morbid process of acute lupus erythematosus and scleroderma affects the collagenous tissue systems of the body in a conspicuous manner, but we can not comprehend its nature, because even the normal structure of this matrix is still incompletely understood.

Examination of the connective tissue fibres with the aid of electron microscope and roentgen - ray difraction have disclosed their molecular structure; but very little is known of altered collagen fibres. In particular, the fibrinoid metamorphosis which is so conspicuous in acute lupus erythematosus and allied conditions, requires more adequate definition. It has not yet been ascertained whether the peculiar appearance of the collagen fibre is due to material alteration or merely to impregnation with true fibrin or possibly the result of a combination of both factors.

Viral infection:

In recent years, several investigators have described non specific myxovirus - like inclusions in capillary endothelial cells of the glomerulus and the peritubular capillaries of the kidney, skin, and muscles of patients

with systemic lupus erythematosus.

In 1969, Gyorkey found tubular structures in five consecutive cases and suggested that systemic lupus erythematosus may follow an immune reaction to cells carrying a foreign antigen and that the virus may be the agent inducing the intimal injury by which autoimmune mechanisms are initiated.

In the same year, Norton conducted a prospective study of seven patients with systemic lupus erythematosus in order to gain information concerning the nature of the microvascular injury. Twelve biopsy specimens from five patients showed characteristic inclusions within endothelial cells that persisted as long as 9 months. These are not specific for systemic lupus erythematosus; they have been observed in other connective tissue diseases as well as in Goodpasteur's syndrome.

The findings are compatible with a common viral cause or with a nonviral mechanism of tissue injury.

Direct and indirect immunoflourescent studies with the use of antimyxovirus sera were negative. Norton concluded that if the inclusions were viral, it seemed unlikely they were coincidental since they were found in all active lesions of systemic lupus erythematosus.

Later Labowitz and Schumacker (1971) identified