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Editorial

Acute myocarditis: a diagnostic dilemma

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Myocarditis, an inflammatory process affecting the myocardium, may be caused by any bacterial, viral, rickettsial, mycotic, or parasitic organism. In Europe and in the United States, however, most cases of acute myocarditis seem to be caused by viruses. It is often difficult to prove the viral aetiology in cases of myocarditis and such cases are often referred to as idiopathic myocarditis. The Coxsackie B enterovirus is especially cardiotropic in man, although Coxsackie pericarditis is thought to be more common than Coxsackie myocarditis. Coxsackie virus infections commonly appear as epidemics, particularly in the summer and autumn. Coxsackie virus types B1 to 5 and A4 and 16 are the strains most commonly implicated. The echovirus group of enteroviruses, especially types 9, 11, and 22, can also cause acute myopericarditis. Even when a causative organism is isolated it is often not known whether direct invasion and tissue damage by the infectious agent or a toxic, allergic, or hypersensitivity response to this agent is responsible for the clinical, electrophysiological, haemodynamic, and morphological manifestations of myocarditis.[1] Although raised titres of neutralising antibody in the serum may suggest viral myocarditis they are not necessarily diagnostic. Also viral particles have never been seen unequivocally in the myocardium except cytomegalovirus in immunocompromised hosts. The clinical diagnosis of myocarditis is difficult, if not impossible. For this reason, the incidence and course of the disease have not been established. Some published reports suggest that myocarditis improves when immunosuppressive agents are given; however, others suggest that steroid treatment may increase the adverse effects of myocarditis or even accelerate its course.

If treatment is to be attempted accurate diagnosis of myocarditis becomes even more important. The widespread use of multiple endomyocardial biopsies raised hopes that it would be possible to diagnose myocarditis more accurately if a histopathological examination showed a definite inflammatory infiltration of the myocardium. Unfortunately, it now appears that the use of the endomyocardial biopsy in the diagnosis of acute myocarditis may have raised more problems than it has solved.

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The role of the endomyocardial biopsy in viral myocarditis

Endomyocardial biopsy is now an established and safe procedure in experienced hands[2 3] and should be well suited to the definitive morphological diagnosis of myocarditis. The role of the biopsy, which seemed obvious and exciting, may be summarised as: (*a*) to identify the inflammatory infiltrate within the myocardium; (*b*) to rule out any other causes of myocardial disease which might clinically mimic viral myocarditis, such as sarcoidosis, hypersensitivity reaction (eosinophilic myocarditis), or idiopathic dilated cardiomyopathy; (*c*) to follow the development of a dilated cardiomyopathy in cases of confirmed viral myocarditis (a sequence of events long suspected, but apart from anecdotes, never satisfactorily proved); and (*d*) to investigate the effect of treatment, particularly the controversial one of immunosuppression.

Pitfalls of endomyocardial biopsy in acute myocarditis

There are many reasons why interpretation of myocarditis by endomyocardial biopsy is difficult. Some, such as variation in sample size owing to the use of different bioptomes, obvious sampling error, and the failure to take into account other causes of lymphocytic infiltrates in the myocardium have already been noted.[4] Patients dying of myocarditis were

known to have a fulminant interstitial infiltrate of inflammatory cells, usually a mixed cell infiltrate together with necrosis of the myocardium, but the early morphological stages of this disease were unclear. The question of whether focal clusters of inflammatory cells represented "early" myocarditis became an issue. This question was partially resolved when several large necropsy series on young accident victims (presumed to be healthy) revealed lymphocytic infiltrations in 4–10% of cases.[5-7]

As well as the normal occurrence of lymphocytes in the heart, small collections of inflammatory cells with focal myocyte necrosis are known to be a result of the "catecholamine" effect of stress or vasopressor agents. Some pathologists felt that in the setting of "clinical" myocarditis these focal collections of inflammatory cells were important and myocarditis was diagnosed even though it is known that a classical history and symptoms of myocarditis are frequently spurious. More important, however, was the fact that most endomyocardial biopsies were performed on patients who presented in left heart failure, which is unlikely to be caused by focal aggregates of inflammatory cells even if focal myocyte damage is present. There is now a vast experience (over 10 000 endomyocardial biopsy specimens in our own centre alone) with biopsy specimens from cardiac allograft recipients with acute rejection, which is morphologically indistinguishable from viral myocarditis and which is therefore a good model of viral myocarditis. From this experience we have learned that focal myocyte necrosis and inflammatory infiltrates do not result in heart failure. In fact, it is clear that only fulminant, diffuse infiltrates that are present in every biopsy fragment lead to heart failure. This experience makes a strong case against labelling focal infiltrates as myocarditis; if the patient is already in heart failure another cause should be looked for. Small focal collections of acute or chronic inflammatory cells in isolated microscopic fields must not be over emphasised if clinical credibility is to be retained.[8]

Dilated congestive cardiomyopathy may present suddenly in young athletic patients without previous symptoms but with a history of "flu" symptoms resembling acute myocarditis. Cardiac biopsy specimens from these patients also may show a considerable number of lymphocytes in the myocardium. In one study 25% of biopsy specimens from patients with dilated congestive cardiomyopathy contained considerable numbers of lymphocytes,[9] and 87% of 108 hearts from patients with end stage cardiomyopathies who were undergoing transplantation showed foci of mononuclear cells.[10] Biopsy specimens from patients with dilated congestive cardiomyopathy have been mistakenly diagnosed as myocarditis because pathologists have failed to recognise the "background" of the pronounced hypertrophy with large bizarre shaped nuclei and fibrosis that distinguishes biopsy specimens from patients without coronary disease who have dilated congestive cardiomyopathy.

The last two paragraphs summarise some of the more important reasons why there is overdiagnosis of acute viral myocarditis in many endomyocardial biopsy specimens. The reported frequency of "biopsy proven" myocarditis from various centres ranges from 3% to 41% and 63%[11 12] or even higher. This causes difficulties not only for clinicians treating these patients but also because the results of studies undertaken on patients supposed to have "biopsy proven" myocarditis may be misinterpreted. Concern about such misinformation, together with the need to do a good randomised multicentre study on the possible beneficial effect of immunosuppression on myocarditis, led to a meeting in Dallas, Texas, in March 1984 of eight cardiac pathologists with experience and interest in the interpretation of endomyocardial biopsy specimens. The Dallas criteria for a histopathological definition and classification of myocarditis were formulated at this meeting.

The Dallas classification

Because the clinical symptoms of acute myocarditis can be mimicked by other cardiac diseases entry into any trial of immunosuppressive treatment for acute myocarditis must depend on an endomyocardial biopsy specimen that shows acute myocarditis. Because there were no uniform diagnostic criteria for acute myocarditis it was necessary, for the purposes of the trial, to attempt a classification that any pathologist could follow. In brief, the goals of the group were (*a*) to produce a morphological definition of myocarditis, (*b*) to develop histopathological criteria for the diagnosis of myocarditis, (*c*) to establish a simple reproducible working classification, (*d*) to outline the problems and pitfalls of establishing the diagnosis of myocarditis, (*e*) to assess the applicability and reproducibility of the classification system itself, and (*f*) to make this information available to other pathologists and clinicians. This goal was attained and a working classification and definition was published.[4]

There are three diagnostic categories of myocarditis at initial biopsy:

(a) Active myocarditis (with or without fibrosis).—Both an inflammatory infiltrate and damage of the adjacent myocytes are required for this diagnosis. The damage may be frank necrosis but

but may consist of vacuolisation, irregular cellular outlines, and cellular disruption with lymphocytes closely applied to the cell surface. The uninvolved myocardium often appears normal.

(b) Borderline myocarditis (not diagnostic, requires repeat biopsy).—This term implies that the inflammatory infiltrate is too sparse or that myocyte damage is not seen on light microscopy. Additional cuts of the original biopsy specimens may demonstrate diagnostic changes, in which active myocarditis can be diagnosed without a repeat biopsy.

(c) No evidence of myocarditis.

Three categories will be used to classify the results of subsequent biopsies:

(a) Ongoing (persistent) myocarditis.—This diagnosis is made when the degree of abnormality is the same or worse than that of the original biopsy specimen.

(b) Resolving myocarditis.—This diagnosis is made when the inflammatory infiltrate is less than in (*a*) and reparative changes are evident.

(c) Resolved myocarditis.—No inflammatory infiltrate remains and there is no evidence of ongoing cellular necrosis.

It must be emphasised that this exercise was prompted, convened, and executed by pathologists in the multicentre trial. It was not meant to establish a definite classification of acute myocarditis; rather the purpose was to test some of the problems of diagnosis—for example are small foci of inflammatory cells in the heart a manifestation of myocarditis?

The Dallas criteria, however, have been misunderstood and misrepresented as a classification that sometimes is used as a *sine qua non* of the histological diagnosis of myocarditis. But, as clearly stated in the report, our goal was to "establish a simple reproducible working classification" in order to "assess the applicability and reproducibility of the classification system." Further it was stated that the purpose of the report was to present a purely morphological classification and definition of myocarditis that would be workable and simple for those participating in the multicentre trial. We also stated that "histology itself may prove not to be the 'gold standard' for the diagnosis of myocarditis and that other features such as physiologic, biologic, biochemical, or immunologic parameters in the future may be shown to be more accurate in assessing the presence, prognosis, and treatment of the disease."

Pathologists using the Dallas classification should be aware that it was devised to achieve more uniform diagnosis and that the classification itself has yet to be tested. Until the Multi-Centre Myocarditis Trial is finished, assuming that sufficient myocarditis positive specimens are collected, we will not know whether the small focal myocardial lesions are indeed harbingers of myocarditis or whether they resolve spontaneously without sequelae. Only then can we assess the value of the Dallas classification.

Endomyocardial biopsy, carefully performed and intelligently examined, is a useful diagnostic tool for the study and management of many cardiac disease states. Many new and useful facts have emerged from the use of the biopsy and there is still much more to be learned from it. We must take care not to jeopardise the credibility of cardiac biopsy by trying to use it inappropriately and by not being mindful of its limitations.

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