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Editorial

How can myocarditis be diagnosed and should it be treated?

Myocarditis remains an enigma. On one hand it is a diagnosis which is suspected clinically when sudden cardiac failure or arrhythmias or both follow a febrile 'flu-like illness. On the other hand, myocarditis has a defined histological appearance with evidence of myocyte damage and a lymphocytic interstitial inflammatory infiltrate. The similarity between this histological picture and acute rejection led naturally to the suggestion that immunosuppression might be a useful treatment.[1] Regrettably the clinical and pathological facets of the disease often do not coincide, and the reported frequency of a biopsy positive confirmation of the clinical diagnosis has at best been variable. Leaving this difficulty aside it was unclear whether any form of treatment influenced the ultimate outcome.

Clinical experience showed that in the short-term some patients recovered spontaneously, others died. Longer term follow up showed that some patients had impaired left ventricular function and some late deaths occurred. Individual clinicians did not see enough cases to assess the impact of steroid or immunosuppressive treatment.

A large trial was initiated by Jay Mason at the University of Utah Medical Center to answer specifically the question of whether immunosuppression improved prognosis. A panel of international experts in the histology of myocarditis met in Dallas, and laid down strict criteria for the diagnosis and terminology used in reporting on the biopsy specimens.[2] The preliminary results of the trial were reported to the American College of Cardiology meeting in Dallas in April 1992 and were discussed in the ACCEL (American College of Cardiology Extended Learning) programme for May 1992.

As its starting point the trial recruited patients with a short history (<2 years) of unexplained congestive heart failure. All underwent cardiac biopsy, and a patient could only enter the trial if a biopsy specimen showed acute myocarditis and the ejection fraction was less than 45%. The first point of major interest was that in over 2000 subjects fitting the clinical criteria the local pathologist reported myocarditis by histological criteria in only about 200. Only 111 of these were available for randomisation: the others were excluded because they had good left ventricular function or because they refused to take part in the trial. Patients who consented to the trial were randomised to treatment with cyclosporin and prednisone with heart failure treatment over 24 weeks or to treatment for heart failure alone. A third arm to the trial using azathioprine was stopped at 14 months owing to the low patient recruitment rate and the need to reduce sample size requirements. Sixty four patients were treated with immunosuppression and 47 controls were given conventional treatment for heart failure. Many patients in both groups showed an improvement in left ventricular function but this was not significantly different in those treated with immunosuppression and those who were not. Death rates at one and two years were not significantly different. A further interesting aspect of the trial was that when all the biopsy specimens were reviewed by the Dallas panel of pathologists only about two thirds were confirmed as showing histological acute myocarditis. The most significant clinical improvement occurred in those with histologically confirmed myocarditis, whether or not they had been treated with immunosuppression.

The trial showed that histologically confirmed acute myocarditis is rare. Previous pathological studies that suggested that the disease was more common may either have coincided fortuitously with an outbreak of a particularly cardiotoxic virus infection in the community or have used less rigorous diagnostic criteria than the Dallas panel. A major difficulty in histological interpretation is the identification of the nature of small round dark cells in the interstitial tissues. Only if these cells can be identified as lymphocytes by immunohistochemistry is the diagnosis of myocarditis justified. In future the standard minimum criterion for acute myocarditis should be an infiltrate of interstitial cells that are shown to be T lymphocytes by immunohistochemical marking.

The second message of the trial is that many patients recover with a considerable improvement of left ventricular function. Treatment with cyclosporin and steroids is neither harmful nor beneficial.

The study does raise interesting and unanswered questions that the fuller reports of the trial may in part answer. If most patients did not have histological myocarditis, what was suppressing left ventricular function? It may be that the histological appearances used to diagnose myocarditis are too rigorous. Could a virus infection suppress myocardial function without inducing myocyte necrosis and inflammation? The use of in situ hybridisation to demonstrate viral genomes, when probes are available for all the viruses known to be cardiotoxic, may answer this point. Could humoral antibody mediated damage rather than cellular immunity be present, with the short-term deposition of immune complexes in the myocardial microvasculature? The more detailed report of the myocarditis trial may show whether immune activation in the myocardium indicates subgroups that are either at higher risk or would respond to immunosuppression.

Many of the subjects without histological myocarditis did have abnormal biopsy specimens showing myocyte hypertrophy and interstitial fibrosis. These features suggest a process that is more longstanding than indicated by the clinical history. Thus it seems that some subjects in whom a dilated cardiomyopathy is already established remain well for long periods before sudden undergoing decompensation. It may be that the acute myocarditic phase is short, and that in many patients this phase was over before a biopsy specimen was taken.

What do these findings mean in practice in a patient with a clinical diagnosis of acute myocarditis? Diagnostic biopsy, if it is undertaken solely to establish myocarditis by routine histological methods with a view to starting immunosuppression, is now not justified—because the findings will not influence treatment.

The trial should not be used to discredit the overall practice of performing cardiac biopsies. Biopsy specimens are useful in many conditions and are essential to the management of cardiac transplantation. Biopsies are an integral part of investigating restrictive cardiomyopathies and the only way to confirm cardiac amyloid.[3] The amount

of fibrous tissue in the myocardium can give some prognostic information in cardiomyopathies. The aquisition of myocardial tissue for immunological and virological studies is vital if the pathogenesis of human myocarditis is to be unravelled. Biopsy specimens should continue to be taken as part of a formal research protocol: the value of the Mason trial may lie in what is learnt about the mechanisms of immunological damage to the myocardium. What is no longer necessary, and indeed hard to justify, is occasional cardiac biopsy for the sole purpose of making a tissue diagnosis of myocarditis.

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