Diagnostic endomyocardial biopsy – still useful after all these years

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Diagnostic endomyocardial biopsy seems to have fallen out of clinical favour and, in most centres, is no longer a common procedure. In the past, endomyocardial biopsies were used for diagnosis and monitoring of anthracycline drug toxicity, with treatment decisions guided by the degree of cardiomyocyte damage (1). Currently, such decisions are usually made with noninvasive monitoring and imaging. Endomyocardial biopsies continue to be the gold standard for monitoring cardiac transplant allograft rejection; however, even this application is being challenged with the advent of serum biomarkers.

If one asks clinicians why they no longer do diagnostic endomyocardial biopsy procedures, issues of nonspecific pathological diagnoses and a significant complication rate are mentioned. In a skilled operator's hands, the complication rate is low (1). With decreasing performance of the procedure, and the resulting lower expertise, such a cycle will be self-perpetuating. Pathologists could also lose their expertise in the interpretation of the biopsies.

With this in mind, the article by Luk et al (pages e48-e54 of this issue of *The Canadian Journal of Cardiology*) demonstrates the continued usefulness of diagnostic endomyocardial biopsy in the appropriate clinical situation. An endomyocardial biopsy generally has low utility and is not indicated in the workup of conventional ischemic heart disease. In the workup of nonischemic cardiomyopathy, biopsy may have utility in selected patients. Luk et al found a 17% overall clinical misdiagnosis rate; with omission of the ischemic patients, there was a 30% misdiagnosis rate in cases of nonischemic cardiomyopathy. This rate is remarkably similar to that previously noted in a study originating from Johns Hopkins Hospital in Baltimore, Maryland (USA) (2). Misdiagnoses, risk management and medical error are interesting topics from a pathologist's viewpoint, but these important matters will not be discussed in the present editorial.

In many cases, a clinical misdiagnosis would have little significance because clarification of the diagnosis would be apparent by pathological examination of the explanted heart. However, not all patients are transplant candidates, and there are clinical situations in which a diagnosis missed may be an opportunity missed. A cardiac transplant is not curative, and the patients may have considerable morbidity and complications from the procedure and subsequent immunosuppression. With a shortage of donor organs and imperfect ventricular assist devices, therapies that attenuate or decrease cardiac disease, and perhaps delay transplant might be beneficial. Diagnostic endomyocardial biopsy might influence management and thus allow this delay for certain diseases.

Endomyocardial biopsy is beneficial for the diagnosis of primary and secondary cardiomyopathic changes. However, it has little ability to differentiate between primary dilated cardiomyopathy, hypertrophic cardiomyopathy and noneosinophilic restrictive cardiomyopathy. All primary cardiomyopathies may look identical, with the same histological abnormalities. Myocyte disarray, an indicator for diagnosing hypertrophic cardiomyopathy, is a common finding in biopsies taken from the right ventricle apex and apical septum. Disarray is an expected finding in this location and should not be used to make a specific diagnosis of primary hypertrophic cardiomyopathy (1).

Endomyocardial biopsy for a sarcoidosis diagnosis has a low yield. Sarcoidosis tends to involve the base of the heart, which is not the area biopsied in the usual right ventricle endomyocardial biopsy procedure. (3) The utility of a biopsy for the diagnosis of arrhythmogenic cardiomyopathy depends on where the biopsy is taken. Free-wall and infundibulum biopsies would have a higher utility than those from the ventricular septum. With ventricular wall thinning and fatty infiltration, such a procedure may be deemed too risky for free-wall perforation. Noninvasive evaluation may be more prudent in such a patient.

So, after such criticism with respect to what biopsies are not good for, just what is an endomyocardial biopsy still good for?

The biopsy is useful for differentiating chronic cardiomyopathy changes from myocarditis in the setting of an episode of acute heart failures. Many such patients may actually have an acute exacerbation of a chronic condition. Biopsy may demonstrate chronic cardiomyopathic changes with fibrosis and hypertrophy (1). Although not always specific for a type of cardiomyopathy, such a finding has implications for patient prognosis, reversibility, likelihood of recovery and, perhaps, a treatment plan. If the patient has myocarditis, giant cell myocarditis can produce a severe acute clinical picture and may be successfully treated by immunosuppression. Giant cell myocarditis may also recur in a transplanted graft.

Endomyocardial biopsy may also be useful for the differentiation between constrictive pericarditis versus restrictive cardiomyopathy. If the hemodynamics or imaging studies are not clear, an endomyocardial biopsy may demonstrate a myocardial cause for restriction – eosinophilic and noneosinophilic primary restrictive cardiomyopathy, amyloidosis or iron storage. In constrictive pericarditis, such a biopsy would be normal or the cardiomyocytes might show atrophy.

The endomyocardial biopsy may also be used for diagnosis of iron overload in the myocardium, which is important because the patients

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can be treated, potentially decreasing their heart failure or delaying transplantation. Iron is not normally found in the cardiomyocyte; therefore, any myocyte iron deposit found by the pathologist is abnormal (4). If iron overload is sufficient to cause congestive heart failure, the biopsy should be informative.

With a myocardial biopsy, amyloidosis may also be diagnosed and typed, with treatment implications. It is important to note that an amyloid may be deposited solely in the heart, so a negative extracardiac biopsy (such as a fat aspirate or rectal biopsy) does not rule out cardiac amyloidosis. Differentiating the amyloid type is also important, and may be done by the pathologist (5,6). Amyloid light-chain amyloids are seen in primary amyloidosis and may be due to plasma cell dyscrasia, including myeloma. Cardiac transplantation in such individuals usually does not have a good outcome, unless the underlying plasma cell problem is also aggressively treated. Without treatment, the amyloid slowly recurs in the cardiac graft, but morbidity and mortality occur due to the extracardiac deposits, with renal failure and gastrointestinal tract pathology (7). Transthyretin-type amyloidosis is often age-related. With aging of the population, such amyloids are becoming more commonly noted but are mainly incidental. However, this type of amyloid may cause heart failure and be localized solely to the heart. The post-transplant outcome would be anticipated to be much better than that of amyloid light-chain amyloidosis.

Storage diseases, including Fabry's disease, may also be diagnosed by endomyocardial biopsy. Fabry's heterozygotes may have unexplained left ventricular hypertrophy and there may be cardiac-predominant Fabry's. With enzyme replacement therapy available, such a diagnosis may have implications for therapy and disease course (8). Neoplasms and drug toxicity, such as chloroquine toxicity, may also be diagnosed by endomyocardial biopsy (3). Both right- and left-sided neoplasms may be biopsied, allowing diagnosis and treatment planning. Avoiding sternotomy in an unresectable tumour may be a humane option. Altering or cessation of a drug that is causing or contributing to heart failure would be of benefit.

Endomyocardial biopsies may be of increasing interest for evaluating primary dilated cardiomyopathy, especially in cases thought to follow myocarditis. Although the Myocarditis Treatment Trial (9) had a negative result, it is generally recognized that at the time, there was little ability to distinguish which cases were associated with viral replication and which were autoimmune-associated. With developing molecular biology techniques, this distinction using biopsy tissue may be of importance to help decide whether antiviral or immunosuppressive therapy is indicated (10).

Knowledge concerning the genetics and molecular biology of primary cardiomyopathies is also evolving. Much of the genetic diagnosis will almost certainly be possible by peripheral blood analysis, but somatic mutations do occur, as illustrated by the recent discovery of somatic mutations in cardiac connexins in atrial fibrillation (11).

As will be evident from the brief discussion above, the diagnostic endomyocardial biopsy procedure should not be discarded. It is important to maintain some level of clinical interest and expertise in this procedure and the specialized interpretation of the pathology. Pathologists need to have good communication and interaction with the clinicians to ensure the best interpretation of the material. As with many aspects of medicine, a team approach is optimal. Future clinical applications are promising and the current judicious use of this procedure remains an important contributor to the care of our patients.

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