Gene expression profiling: time to file diagnostic uncertainty in inflammatory heart diseases?

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This editorial refers to ‘Improved diagnosis of idiopathic giant cell myocarditis and cardiac sarcoidosis by myocardial gene expression profiling’¹, by D. Lassner et al., on page 2186.

Gene expression profiling allows us to assess the expression of numerous genes simultaneously. In oncology, this novel technique contributed greatly to better classification, improved prognostic stratification, and specifically tailored treatment approaches for many cancers. In heart diseases, however, gene expression profiling has not yet found its way into routine diagnostic work-up. The appearance of heart-infiltrating cells, their composition, their morphological differentiation, as well as resolution of active inflammation or fibrotic remodelling are tightly and specifically regulated processes in myocarditis and inflammatory dilated cardiomyopathy (IDCM). Thus it seems obvious to expect specific gene expression patterns orchestrating time- and disease-specific cytokine production, adhesion molecules, and activation states of pro- and anti-inflammatory intra-cellular pathways.

Despite low sensitivity, endomyocardial biopsies (EMBs) are still the diagnostic gold standard for inflammatory heart diseases. Analysis of biopsies by conventional histology, immunohistochemistry, and reverse transcription–quantitative PCR (RT–qPCR) aiming at viral genomes provides not only a quite specific diagnosis but also prognostic and therapeutic clues.¹ Lymphocytic myocarditis is the most common histological form of active inflammatory heart disease, and usually results from viral infection or virus-triggered heart-specific autoimmunity. Other typical histological patterns include eosinophilic and idiopathic giant cell myocarditis (IGCM). IGCM represents a rare but distinct entity of unknown origin with unfavourable prognosis.² Typical IGCM histology shows myocyte damage, eosinophils, foci of lymphocytic infiltrates, and multinucleated giant cells. IGCM is certainly a rare form of myocarditis, but the patchy distribution of inflammatory infiltrates and hence the possible sampling error in detecting multinucleated giant cells further impairs diagnostic sensitivity and may contribute to an underestimation of its true incidence.

Cardiac sarcoidosis (CS) affects at least 25% of patients with systemic disease, but may be limited to the heart only.³ In the latter cases, diagnosis is achieved by systematic work-up, including biopsies of heart failure patients. The presence of non-caseating granuloma and marked fibrosis in myocardial biopsies strongly argues for sarcoidosis. The sensitivity for histological detection of non-caseating granuloma, however, is moderate in heart biopsies of CS patients. Moreover, histological patterns are sometimes overlapping in CS and IGCM. Giant cells, for example, are present in both diseases, and histiocites and even fibrosis may be observed in CS as well as in IGCM. Thus, it is not surprising that there have been concerns regarding whether IGCM and CS really represent different disorders.³

From a clinical point of view, several lines of evidence suggest a better prognosis for individuals with CS. In CS, patients present with atrioventricular (AV) block, arrhythmias, sudden cardiac death, or congestive heart failure.³,⁴ Congestive heart failure and arrhythmias dominate the clinical picture in IGCM, but affected patients have a shorter time from symptom onset to death or transplantation. Whereas early and aggressive immunosuppressive treatment appears to be critical for IGCM, steroids alone may be sufficient to control CS.³,⁴ In contrast, immunosuppression is not warranted for patients with active myocarditis and evidence for viral genomes in the molecular analysis of heart biopsy samples.⁵ Obviously, a precise histological and molecular diagnosis determines the optimal treatment approach in patients with inflammatory heart disease. As pointed out above, however, conventional analysis of heart biopsies lacks sensitivity, and somehow specificity. Therefore, any method improving diagnostic accuracy might be a major step forward in the management of inflammatory heart diseases.

Lassner et al. now present a novel approach to overcome diagnostic uncertainty in the distinction between CS and IGCM (Figure 1).⁶ The authors analysed EMB specimens of 4738 consecutive patients...
way to conceive this specific ‘inflammatory cardiac microenvironment’ and to use it for diagnostic purposes.

The methodological approach of Lassner and colleagues is straightforward, clear, and technically convincing. There are, nevertheless, several issues to be clarified before gene expression profiling really finds its place in routine heart biopsy evaluation. First, and despite the large numbers of screened samples, biopsies from only 10 patients with CS and from 10 patients with IGCM contributed to the gene expression profile data. Secondly, the authors’ research team refers to profound and well-recognized technical expertise in the work-up of iDCM patients and heart biopsies. As stated by the authors, generation of valid gene expression data from small tissue samples requires optimal specimen procurement, appropriate sample storage, and pre-amplification techniques for specific gene sets with reverse transcription of cellular RNA into cDNA immediately after biopsy processing. Careful sample work-up should provide sufficient RNA from 1–2 EMBs to perform reliable expression profiling studies in archived samples. This process works in a specialized research facility. Transfer of this patented gene expression profiling approach into routine diagnostics, however, requires that the authors’ findings can be reproduced with appropriate and comparable quality on more samples from more patients in different centres.

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References

Figure 1 Gene expression profiling might be useful to overcome high sampling error due to patchy distribution of characteristic histological patterns and diagnostic decisive cell subsets, such as giant cells, for example.