INTERLEUKIN-10: BIOMARKER OR PATHOLOGIC CYTOKINE IN FULMINANT MYOCARDITIS?

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"...science, I am told, may go astray; the doctors [are] not able to discriminate between the counterfeit and the real."

Fyodor Dostoevsky, The Brothers Karamazov, 1879

Sensitive and specific serologic markers for myocardial infarction (MI) and heart failure (HF) are now being incorporated into routine clinical practice with a great influence on physicians’ decision making. To have such serologic markers for myocarditis is a worthy goal because the diagnosis depends on a non-specific clinical history and findings, exclusion of other cardiovascular diseases, and/or endomyocardial biopsy, a highly invasive procedure that has poor sensitivity (1–3). Indeed, discrimination between patients with a favorable prognosis and those without is currently more in the realm of art than science.

In this issue of the Journal, Nishii et al. (4) addressed a challenging question: “are there serologic biomarkers that will predict the prognosis of patients with fulminant myocarditis?” This is a particularly important question because it has been demonstrated that despite the severity of disease at presentation, a high percentage of patients will survive and completely recover once they overcome the acute phase (5).

Given the effectiveness of cardiac assist devices in patients falling into the category of severe HF who are being treated with high doses of catecholamines, it would be valuable to have serologic markers that would identify those patients who are most likely to need mechanical support and those who are not. To address these questions, the authors studied 22 consecutive patients that fit the definition of fulminant myocarditis: a distinct onset of HF after flu-like symptoms requiring high-dose catecholamines with histologically proven myocarditis (5,6). The patients were then classified into three groups: group 1—patients who had already lapsed into cardiogenic shock requiring mechanical cardio-

pulmonary support on admission; group 2—patients who unexpectedly lapsed into cardiogenic shock requiring mechanical cardiopulmonary support more than two days after high-dose catecholamine treatment had started; and group 3—patients who required only high-dose catecholamines without mechanical cardiopulmonary support.

Of the alterations that were observed in serum cytokines and C-reactive protein (CRP), the most striking finding was that the admission serum interleukin (IL)-10 level discriminated patients who would require mechanical cardiopulmonary assistance after admission to be discriminated from those who would not require such assistance. In addition, those who would ultimately die from their disease had the highest levels of IL-10. Importantly, average serum IL-10 levels were higher in patients with fulminant myocarditis than in patients with acute MI who also required mechanical cardiopulmonary support, and none of the patients with either fatal or non-fatal MI requiring mechanical support had IL-10 levels as high as those that died of fulminant myocarditis. These findings indicate that IL-10 might be a useful prognostic marker in patients with fulminant myocarditis, whereas other inflammatory markers such as tumor necrosis factor alpha and serum CRP were not as predictive for mortality and the need for mechanical support in this study. In addition, these data demonstrate that inflammatory markers such as IL-10, tumor necrosis factor alpha, and CRP are higher in patients with fulminant myocarditis than in severely ill patients with acute MI. Although this is not particularly surprising, given the inflammatory nature of myocarditis, it sheds a ray of hope that there may be a profile of serologic biomarkers that will discriminate myocarditic from non-inflammatory causes of cardiac dysfunction. Their findings provide meaningful prognostic and diagnostic information that could be useful in the management of patients with fulminant myocarditis.

PROGNOSIS OF FULMINANT VERSUS ACUTE NON-FULMINANT MYOCARDITIS

If we focus on acute myocarditis only, a somewhat paradoxical observation has been reported: patients with fulminant myocarditis have an excellent long-term prognosis despite very severe hemodynamic compromise upon presentation. A clinicopathologic classification using both histologic and clinical features has been published that provides prognostic information in patients with acute myocarditis (6). Based on this classification, a prospective study was performed that demonstrated that 93% of patients with fulminant myocarditis were alive without heart transplantation 11 years after diagnosis, compared with only 45% of those with acute non-fulminant myocarditis (5). These observations strongly support aggressive therapy, including mechanical cardiac...
support, when necessary, in patients with fulminant myocarditis (7–10).

**POTENTIAL IMPACT OF SERUM IL-10 LEVELS ON CLINICAL MANAGEMENT**

The cause of myocarditis in a given patient has been very difficult to define; however, pertaining to fulminant myocarditis, the article by Nishii et al. (4) suggests that IL-10 levels could facilitate the management of patients with fulminant myocarditis by predicting those that are likely to develop severe hemodynamic compromise requiring a ventricular assist device. Although the data do not address whether early implantation of a cardiac assist device would be beneficial in patients with high levels of IL-10, they do suggest that more intense monitoring and management could be appropriate in these patients. For example, in the setting of high IL-10 levels, surgeons could be notified of the patient’s status, and preparations for potential implantation of a ventricular assist device could be undertaken. Alternatively, in the setting of lower IL-10 levels, a less aggressive management strategy may be appropriate.

**A PATHOGENIC ROLE FOR IL-10 IN MYOCARDITIS?**

The data presented in the study by Nishii et al. (4) demonstrate that IL-10 might be used as a prognostic biomarker in myocarditis; however, the strong association between IL-10 and prognosis raises the question of whether IL-10 levels may have a pathogenic role in the course of myocarditis as well. It is known that both direct viral injury and the immune response of the host can have important roles in myocarditis (11). Results from experiments in murine models of myocarditis indicate that although the immune response has an important protective role, it also may have deleterious effects on the host. The balance between these protective and deleterious effects may ultimately determine the course of disease after enteroviral infection.

Interleukin-10 generally is thought of as an immunosuppressive cytokine (12), but its exact role in myocarditis is not clear. It has been demonstrated that IL-10 has a protective role in experimental autoimmune myocarditis (13). Alternatively, it is conceivable that induction of an IL-10 immunosuppressive effect could decrease the host defense against viral infection and thus be detrimental to the host. An example of where this appears to be true is in relation to the Epstein-Barr virus, which has incorporated a copy of IL-10 known as viral interleukin (vIL)-10 into its genome (14). Because Epstein-Barr virus has evolved with vIL-10 in the genome, it is likely that it is beneficial to viral replication.

Although the data presented by Nishii et al. (4) do not define a pathologic role for IL-10 in myocarditis, the data do suggest the testable hypothesis that high levels of IL-10 could have a role in the pathogenesis of the disease: a mechanism that could have implications on its diagnosis and treatment.

**FUTURE DIRECTIONS**

On the basis of this initial result, consideration should be given to a multi-center study employing a larger population to confirm the significance of serum IL-10 levels in patients with both fulminant and non-fulminant myocarditis, including chronic active or persistent myocarditis. Given the difficulty of diagnosis of myocarditis, it would be valuable if a “footprint” of myocarditis could be defined using serum markers in place of myocardial biopsy. Ideally, this should include prognostic and etiologic markers of the disease. Although these goals may seem to be out of reach, it was not long ago that the best biomarker for MI was measurement of lactate dehydrogenase and serum glutamic oxaloacetic transaminase, enzymes that are expressed at high levels in the liver. Now, serum levels of highly specific and sensitive markers of MI are available that provide valuable prognostic information. We can only anticipate that consistent steady progression of knowledge from bench to bedside will facilitate diagnostic and prognostic breakthroughs in this seemingly invincible disease, thus providing a scientific tool that will discriminate between real myocarditis and its counterfeits.

**REFERENCES**