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EDITORIAL COMMENT

Biomarkers for Immune Checkpoint Inhibitor–Induced Myocarditis

Caution Needed*

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Immune checkpoint inhibitors (ICIs) improve cancer outcomes and are generally well tolerated.[1] There are, however, complications associated with therapy.[2] These include dermatitis, myositis, colitis, endocrinopathies, hepatic dysfunction, and myocarditis.[2] Myocarditis has been recognized usually in its most overt form.[3] In general, myocarditis can be acute and severe, with marked increases in cardiac troponin,[4] or asymptomatic and relatively indolent, with minor increases.[5] Unfortunately, often the diagnosis rests on increases in biomarkers alone, as electrocardiographic changes and symptoms are highly variable. The diagnosis of ICI myocarditis is one clinicians do not want to miss because of its high mortality when severe.[2] Presently, it is thought that the immune responses are not unique to the heart and that there can be a variety of associated abnormalities, such as hepatic function abnormalities and myositis concomitantly. These also are diagnoses that rely on biomarker determinations.

For these reasons, investigators at the University of Michigan searched their databases to identify biomarker profiles that would facilitate diagnosis.[6] They included in their studies 27 patients, 18 of whom were diagnosed with "possible" myocarditis. The classification used in this study relied on biopsy and cardiovascular magnetic resonance (CMR) for definite myocarditis and suggestive CMR findings with symptoms and other clinical and/or biochemical criteria for probable myocarditis. Possible myocarditis could occur with an increased high-sensitivity cardiac troponin T (hsTnT) value alone, and it may be that an increased troponin led to the diagnosis in the absence of other overt etiologies for the increase. It is important to remember that this "possible" group included 18 of the 27 patients reported. The investigators then evaluated biomarkers. Understandably, markers such as hsTnT were not obtained in a reproducible manner; they were obtained when the patients presented clinically and when testing was needed clinically. The sampling frequency was a conglomerate of varying times, and probably because of the complexity and frequency and variability, these times were not well described. Accordingly, the investigators have done their best to make sense of how the biomarkers might help diagnostically. Given the heterogeneity of the sampling, this was likely a daunting task. The variability between a value obtained 2 hours after the initial sample and one obtained 6 weeks later may be different, and it is likely that most of the biomarkers were obtained when there was diagnostic ambiguity or when patients got worse, so the ability to really define changes in biomarker patterns was problematic. It is also unclear whether the other biomarkers that were probed, which included hepatic biomarkers as well as creatine kinase (CK) were obtained separately or "as needed." The investigators did attempt to confirm their analyses by studying an additional 30 patients from another institution with ICI myocarditis, but again, this was likely a very high specificity group.

In addition, as with all patients who are elderly, these patients had comorbidities of a variety of sorts, and there was a relationship between coronary artery disease and the development, at least in this cohort, of ICI myocarditis.[6] Unfortunately, baseline samples

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for biomarkers were not available. It is known that a large percentage of patients with cancer will have baseline biomarker abnormalities, including increases in cardiac troponin.[7] In contrast to these researchers, who suggested only a 5% incidence of increased hsTnT in their "control group," Pavo et al[7] found detectable values (>5 ng/L) in more than 50% and found them to be dramatically prognostic. Thus, some the increases potentially attributed to ICI might be chronic ones. Whether these increases reflect prior disease or the direct effects of cancer biology on the cardiovascular system itself is unclear. This is a critical issue that the field has yet to definitively address. This is a circumstance in which an early study probing biomarkers might lead to confusion unless these critical caveats are appreciated.

What may be important is that patients had increases in biomarkers of hepatic function and of skeletal muscle damage (CK) on presentation, in addition to diagnoses of ICI myocarditis. This finding may stand the test of time in patients with overt disease. However, although a control group was present, it is unclear what percentage of that group had increases in these analytes. These are, after all, older patients with cancer who may well have comorbidities related to cancer alone or to prior disease. In addition, although in the acute setting these findings might be common, they may not be common early on, and/or they may not be common in more benign cases. In addition, once treatment was initiated, probably with mostly high-dose steroids,[8] it did appear that the hepatic function abnormalities, particularly CK, were relatively rapid responders, at least compared with hsTnT. When modeling was used, because hsTnT was one of the key determinants of the diagnostic cascade, it was present ubiquitously, but a change in CK also appeared to at least herald the overt cases. Hepatic function abnormalities were also common. What these investigators then attempt to do is interpret all of this, and this is quite difficult. Likely there are caveats and some misinterpretations from probing such a problematic database. What is clear is that troponin is a good marker in this circumstance, although as noted later, hsTnT alone needs to be interpreted cautiously rather than being considered a maker specific for myocarditis.

Every field progresses slowly, and a study such as this is a first step. However, several additional studies are necessary.

First, patients started on ICIs should undergo baseline troponin assessment, and if levels are increased, some scrutiny would be advised to determine the etiology of the cardiac injury. This may identify groups that are at high risk for ICI myocarditis and also aid in the interpretation of hsTnT when subsequent values are found to be elevated. This is particularly important for patients with coronary artery disease, who constituted the group more apt to develop ICI myocarditis in this analysis. Ischemic heart disease also elaborates larger signals in hsTnT, similar to those seen with fulminant myocarditis.

Second, following patients with serial assessment is suggested. It may well be that there is some low-level myocardial involvement that occurs transiently, and it is only a subset of patients who have some additional abnormalities or events that evolve into more robust clinical syndromes. In addition, serial sampling will also provide insights into how to properly interpret biomarker values after a diagnosis of ICI myocarditis. Because some of the persistent elevations in troponin that exist may be attributable to underlying disease, if that were known, one might understand that increases after treatment may still persist for that reason.

Third, given the idea that there is often more diffuse involvement, including with hepatic and skeletal muscle involvement, baseline surveillance if one is measuring troponin levels to evaluate these markers would be strongly advised.

Fourth, analytical abnormalities can occur with all testing. With troponin we are beginning to see what are called macrotroponins, which are immune complexes linked to troponin. They can cause false positive abnormal results.[9] This is not the only analytical issue that can occur. However, this one is occurring as we are stimulating increases in the immune response to a variety of infectious abnormalities. One unintended consequence could be an increased number of analytical false positive troponin measurements. Such increases can occur with cardiac troponin T, although they are more common with high-sensitivity troponin I.[9] This possibility is worthy of consideration. We need to embrace the idea that if the diagnosis rests solely on troponin and is not consistent with clinical signs and symptoms, at least evaluation for some sort of false positive should be entertained. This may also be a reason why an increase in the frequency of postvaccination diagnoses of myocarditis has occurred (ie, by relying on troponin alone, which in some instances might be increased artifactually).[10] This is not a common circumstance, but it may occur in as many as 1% of individuals, and in a group that is as large as those receiving ICIs, it may well be something that on occasion will be observed.[9]

The investigators have provided a start. If that pushes us to more comprehensive evaluations of biomarkers, we may in the long run begin to

develop insights into the diagnosis, treatment, and pathogenesis of ICI myocarditis. For now, there are some nuggets of clinical information that are helpful, but the large number of gaps require that all of us, in dealing with these patients, be aware that there is no solely reliable biomarker or test short of a biopsy or CMR to confirm myocarditis. Myocarditis is a hard diagnosis, and we all need to be cautious in how we use these biomarker data moving forward.

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Dr Jaffe presently or in the past has consulted for most of the major diagnostic companies, including those that make the assays used in this study.

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