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What Is the Evidence of the Diagnostic Criteria and Screening of Immune Checkpoint Inhibitor–Induced Myocarditis?

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Immune checkpoint inhibitors (ICIs) reduce the risk of death and recurrence of many cancers. While use of these agents is expanding, immune-related adverse events (irAEs) is of concern. Myocarditis, one of the most serious, has reported fatality rates from 25% to 40%. Although rare (1% to 2%), myocarditis occurs more frequently with combination therapy and early. Death can occur secondary to cardiovascular causes, but also due to cancer progression if ICI therapy must be stopped. Treatment is generally high-dose corticosteroids followed by intensified immunosuppressive therapy.[1] Given the severity of this complication, recommendations have been proposed to guide clinicians in the diagnosis and screening of ICI-related myocarditis.[1-3] This paper provides a brief overview of recent evidence and challenges that reflect the current approach to this topic.

WHAT ARE THE DIAGNOSTIC STRATEGIES?

Myocarditis is an inflammatory condition of the myocardium most often related to viral infection. The diagnosis is suspected based on clinical context, symptoms, and associated test abnormalities including electrocardiogram (ECG), and circulating and imaging markers of myocardial injury. Because such findings are not specific for myocarditis, other causes of myocardial injury (eg, acute coronary syndrome [ACS]) must be excluded. Endomyocardial biopsy (EMB) can confirm the diagnosis by demonstrating inflammatory infiltrations with or without myocyte degeneration or necrosis of non-ischemic origin.[4] EMB is not routinely performed because of the risk of procedural complications and a sensitivity that varies widely according to pretest probability, timing, sampling site, myocarditis type, and analytic methods. Cardiac MRI (CMR) is considered the best noninvasive imaging modality for the diagnosis of myocarditis based on the 2018-Lake Louise (2018-LL) criteria, which identify major criteria, including edema and nonischemic myocardial injury. Myocardial edema is evidenced by global or regional T2 elevation or hypersignal on T2-weighted sequences. Nonischemic myocardial injury is demonstrated by late enhancement (LGE), global or regional native T1 elevation, and/or extracellular volume fraction in a nonischemic distribution. In the presence of 2 major criteria, the sensitivity and specificity of 2018-LL criteria are 88% and 96%, respectively.[5]

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HIGHLIGHTS

- Myocarditis is a rare, but serious, complication of immune checkpoint inhibitor therapy.
- The diagnosis of immune checkpoint inhibitor–induced myocarditis is sometimes challenging because of clinical, biological, and imaging features.
- Diagnostic criteria have been proposed to help clinicians, but have never been validated to date.
- Some guidelines now recommend early detection by repeated troponin and ECG testing, but its role has not yet been clearly demonstrated.

WHAT ARE THE UNIQUE FEATURES OF ICI-INDUCED MYOCARDITIS?

A question is whether these findings and the diagnostic strategy, which have been established mainly in viral myocarditis, also apply to ICI-induced myocarditis (ICI-M). One consensus statement has recommended a myocarditis diagnosis with ≥1 symptoms associated with ≥1 diagnostic criteria or ≥2 diagnostic criteria if the patient is asymptomatic.[4] These recommendations were established before the era of ICI-M, which may have heterogeneous clinical presentations secondary to noncardiovascular irAEs or asymptomatic elevations of cardiac troponin (cTn). Although cases of ICI-M without elevated cTn have been reported, ongoing injury is detectable in most of patients, particularly with the use of highly sensitive assays.[1] However, the specificity of biomarkers has been questioned, with some raising the possibility that isolated myositis may theoretically lead to elevated cTnT or creatine kinase-MB, whereas cTnI may be more specific for myocardial injury.[1] Additional data are needed to support this hypothesis.

CMR with ICI-Ms also has its own particularities. Two studies from an international registry analyzed CMR results of patients with a diagnosis of ICI-M based on histopathological data or the presence of diagnostic criteria.[6,7] Although LGE is typically present in 80% of cases of non-ICI-M, in these studies, LGE was observed in 48% to 56% of all patients and in 38% of patients whose myocardial biopsy showed lymphocytic infiltration. Moreover, the presence of LGE varied with the time from admission to CMR. Considering the 2018-LL main criteria, nonischemic myocardial injury was present in 90% of biopsy-proven cases, while myocardial edema was present in 63% of biopsy-proven cases. All patients fulfilled at least 1 main 2018-LL criterion, and the presence of both main criteria had a sensitivity of 53% in biopsy-proven cases. The lower rate of LGE and the lower sensitivity of the 2018-LL criteria in ICI-M than in viral myocarditis was confirmed in a recent study.[8] Several hypotheses may explain these results, including lack of standardization of CMR protocols and ICI-M definition, small sample size of biopsy-proven cases, and the early initiation of corticosteroid therapy, which may have affected the diagnostic performance of CMR.[7] Finally, CMR results may be influenced by the patient characteristics. Patients with ICI-M are older and have more cardiovascular comorbidities than patients with viral myocarditis. Thus, the specificity of 2018-LL criteria could be lower in patients with previous myocardial damage or to the toxicity of other cancer treatments administered before or in conjunction with ICIs. Recently, 1 study showed that 10% of patients scheduled to receive ICI had prevalent LGE.[8]

HOW DO WE DEFINE ICI-M IN CLINICAL PRACTICE?

The strategy for diagnosing ICI-M is therefore potentially more complex than that for myocarditis from other etiologies. Its impact on patient outcomes is considerable given its implication on management. Underdiagnosis may lead to a lack of or a delay in the initiation of corticosteroid therapy and major cardiovascular events (MACE). Overdiagnosis may lead to permanent discontinuation of ICI and cancer progression. Bonaca et al[2] have provided a uniform definition of cancer therapy-associated myocarditis to facilitate case ascertainment, particularly in clinical trials testing ICI. This hierarchical definition classifies diagnoses of ICI-M into definite, probable, and possible based on clinical symptoms/signs and histopathology, ECG, biomarker, and cardiac imaging data. However, these definitions were established to facilitate the adjudication of events in trials and were not intended for clinical use. A lack of therapeutic strategy for probable or possible ICI-M may lead to inappropriate management. Another definition of ICI-M has been recently proposed by the International Cardio-Oncology Society (IC-OS).[3] This is binary and based on major and minor criteria, to facilitate clinical management. Definitions of severity and recovery

ABBREVIATIONS AND ACRONYMS

2018-LL = 2018-Lake Louise
ACS = acute coronary syndrome
CMR = cardiac magnetic resonance
cTn = cardiac troponin
ECG = electrocardiogram
EMB = endomyocardial biopsy
ICI = immune checkpoint inhibitor
ICI-M = immune checkpoint inhibitor–induced myocarditis
IC-OS = International Cardio-Oncology Society
irAE = immune-related adverse event
LGE = late gadolinium enhancement
MACE = major cardiovascular events

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TABLE 1 International Cardio-Oncology Definition for Immune Checkpoint Inhibitor Myocarditis

Diagnosis
Either pathohistological diagnosis: Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy of cardiac tissue samples
Or clinical diagnosis[a,b]
A troponin elevation[c] (new, or significant change from baseline) with 1 major criterion or a troponin elevation (new, or significant change from baseline) with 2 minor criteria after exclusion of acute coronary syndrome or acute infectious myocarditis based on clinical suspicion
Major criterion
• CMR diagnostic for acute myocarditis (modified Lake Louise criteria)
Minor criteria
• Clinical syndrome (including any one of the following: fatigue, muscle weakness, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnea
• Lower extremity edema, palpitations, light-headedness/dizziness, syncope, cardiogenic shock)
• Ventricular arrhythmia and/or new conduction system disease
• Decline in cardiac (systolic) function, with or without regional WMA in a non-Takotsubo pattern
• Other immune-related adverse events, particularly myositis, myopathy, myasthenia gravis
• Suggestive CMR (meeting some, but not all, of the modified Lake Louise criteria)

[a]Clinical diagnoses should be confirmed with cardiac magnetic resonance imaging (CMR) or endomyocardial biopsy if possible and without causing delays of treatment. [b]In a patient that is clinically unwell, treatment with immunosuppression should be promptly initiated while awaiting further confirmatory testing. [c]Both troponin I and troponin T can be used; however, troponin T may be falsely elevated in those with concomitant myositis.

WMA = wall motion abnormality.

have been also proposed (Table 1). Compared with the Bonaca definition, the IC-OS definition includes noncardiovascular irAEs as a minor criterion, does not consider positron emission tomography, and gives a central place to cTn. A cTn elevation associated with ≥1 major or ≥2 minor criteria make a definite diagnosis. This raises the issue of diagnosing chronic inflammatory cardiomyopathy, which is not always associated with cTn elevation. In addition, ICI-M may be inappropriately diagnosed in some circumstances such as cardiothyreosis following ICI-induced hyperthyroidism or exacerbation of heart failure during ICI-induced pneumonitis. These complex situations may be managed by performing an EMB and analyzing the evolution of the cardiovascular status after resolution of the noncardiovascular irAE. Similarly, thresholds for cTn elevation are challenging for patients with an elevated baseline level.

Both the Bonaca and IC-OS definitions suggest the use of the 2018-LL criteria to interpret CMR, but we must use them with caution, given their limitations in ICI-M. For these reasons, some experts have recommended a wider use of the EMB. Nevertheless, we still lack evidence to adopt this invasive diagnostic strategy, especially in patients with few or no symptoms who would have a low pretest probability of an EMB. The value of repeat CMR is also not established. Finally, we do not know the true accuracy of these definitions, as none have been validated in clinical studies.

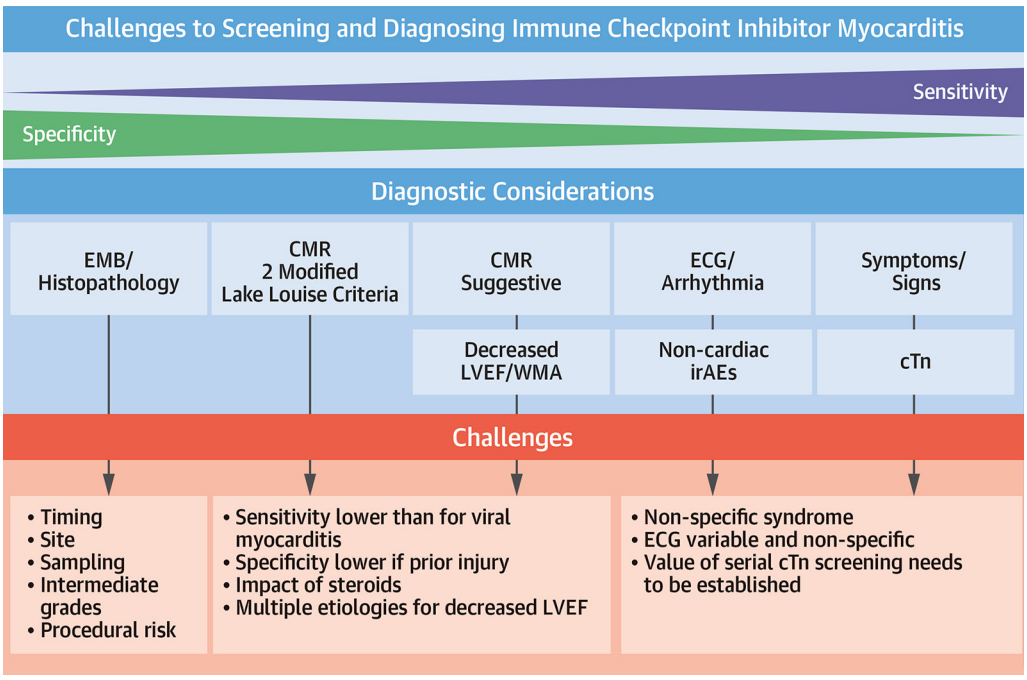
Both definitions require excluding another cause of myocardial injury, especially ACS by coronary imaging. In clinical practice, the situation is sometimes challenging when ICI-M and coronary artery disease are combined. Recent data also suggest that ICI therapy may lead to worsened atherosclerotic disease and ACS. Takotsubo-like syndromes have also been described, making diagnoses even more challenging.[1]

WHAT ARE THE SCREENING STRATEGIES?

Given the potential high morbidity and mortality with ICI-M, experts have considered a screening strategy that would lead to early diagnosis and management. Some have proposed systematic performance of ECG and cTn testing before and during the first weeks of treatment, especially in cases of combined ICI. This strategy has gradually been adopted by many centers and is now recommended by the European Society of Cardiology guidelines.[1] Nonetheless, this position has led to a significant increase in the number of asymptomatic patients with an isolated mild cTn elevation, in whom the diagnostic of ICI-M is often challenging. In addition, the lack of specificity for cTn for myocarditis may lead to detection for other etiologies (eg, pulmonary embolism, type 2 myocardial infarction) and potentially misdiagnosis when detected through screening for ICI-M.

In a prospective study, which consisted of cTnI monitoring at baseline and every 2 to 4 weeks in 214 patients treated with ICI, 24 patients had an elevated TnI (≥55 ng/L), of which only 3 had ICI-M.[9] Among the remaining 21 patients, the diagnosis was non-ST-segment elevation myocardial infarction in 2 patients, was unknown in 19 patients, and led to delay of ICI treatment in 3 patients. The positive

FIGURE 1 Current Challenges to Diagnose and Screen Immune Checkpoint Inhibitor–Induced Myocarditis



This figure illustrates the low sensitivity/specificity ratio of the clinical features and investigations proposed for suspected immune checkpoint inhibitor–induced myocarditis. It also describes the limitations and challenges for each. CMR = cardiac magnetic resonance imaging; cTn = cardiac troponin; ECG = electrocardiogram; EMB = endomyocardial biopsy; irAE = immune adverse events; LVEF = left ventricular ejection fraction; WMA = wall motion abnormality.

predictive value of cTn elevation was only 12.5% with the ≥55 ng/L threshold. When the 3 cases of ICI-M were analyzed, no patients had an EMB, and the diagnosis was definite according to the Bonaca criteria in only 1 patient. Recently, in patients with advanced renal cell carcinoma receiving avelumab (PD-L1 inhibitor) plus axitinib (VEGF inhibitor) vs sunitinib (VEGF inhibitor), the association between MACE and changes in levels of serum cardiac biomarkers was evaluated.[10] cTn I or T was measured at baseline and serially in the first 16 weeks of treatment. Myocarditis occurred in 1.4% of patients who received ICI and in 0.2% of patients of the other group. Although patients in the ICI arm who had high baseline cTnT values were at higher risk of MACE compared with patients with low values, routine cardiac investigation in asymptomatic patients was not useful for early detection of myocarditis.

Increased cTn reflects myocardial injury, of which there are many potential cardiac and noncardiac etiologies, and is associated with worse outcomes irrespective of the clinical scenario. Therefore, active screening of myocarditis during ICI therapy could lead to a risk of a high rate of false positives and misinterpretation of laboratory testing. The current data would justify cTn testing at baseline before ICI therapy to have a reference value in case of suspicion of ICI-M during the treatment as well as to identify patients at high risk of MACE, especially when ICI is associated with VEGF inhibitors. By contrast, an elevated cTn level at baseline would not specifically predict the risk of ICI-M. Although we and other experts have recommended cTn monitoring during ICI therapy, there are no strong data to support this indication. However, it might be justified in higher-risk patients for ICI-M, of which ICI combination is the most recognized risk factor. The cTn threshold value at which investigations must be conducted and the implications of dynamic changes remain to be determined.

CONCLUSIONS

ICI-M is a serious complication for which data on diagnosis, screening, and treatment strategies are insufficient (Figure 1). Although recommendations

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have been published, most of them are based on expert consensus and will have to be updated promptly with new, rigorous data. Basic and translational research should advance our understanding of mechanisms to inform strategies in the clinic. Finally, focusing on the prediction and detection of myocarditis as the only cardiovascular irAE induced by ICI would be a mistake because other cardiovascular toxicities related to this therapy also exist and should be considered.

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