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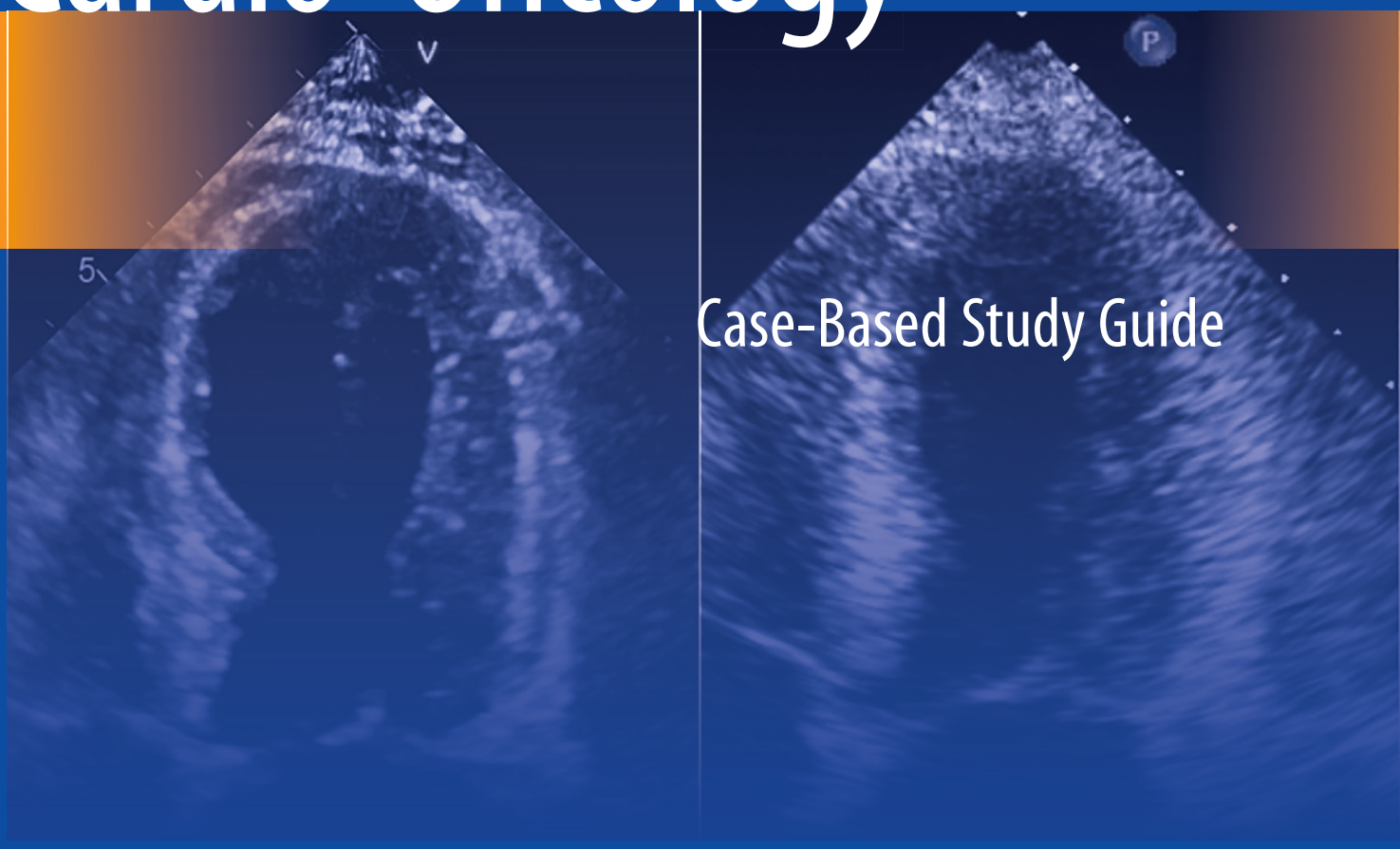
Case-Based Study Guide



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Immune Checkpoint Inhibitor (ICI)-Associated Myocarditis

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Nicolas L. Palaskas, Eric H. Yang, and Tomas G. Neilan

Key Points

- ICIs have revolutionized the treatment of cancers, specifically melanoma, lung, and genitourinary malignancies, with significant improvements in oncologic outcomes.
- The most serious of the immune-related adverse events (irAEs) is myocarditis, with a reported mortality of 25–50%. However, ICI-associated myocarditis is uncommon with an incidence of 1–2% in recent publications.
- The only established risk factor is the use of combination ICI therapy.
- The mainstay of treatment for ICI-associated myocarditis is glucocorticoids.
- The presentation may be non-specific, at times insidious, other times fulminant. Multiple imaging modalities, serial biomarkers, myocardial biopsy, and astute clinical judgement in combination with a high index of suspicion are all required to diagnosis and manage these complex patients.

3.1 Introduction

The observation of an association between the use of immune checkpoint inhibitors (ICI) and the development of myocarditis is relatively recent. Despite the presumed low incidence of myocarditis, increasing use and the expansion of ICI for treating different malignancies have led to an increase in the number of cases being seen in academic centers and the community. Any cardio-oncology practice must be equipped to recognize and treat this potentially fatal disease. The diagnosis of ICI-associated myocarditis is complicated and relies on a combination of clinical, laboratory, imaging, and biopsy findings. All patients with suspected ICI myocarditis should be admitted for assessment. Various treatment regimens have been reported with the mainstay of treatment involving cessation of the ICI and the administration of corticosteroids. The three cases presented below will highlight differences in clinical presentations, diagnostic tests, and treatments followed by an in-depth discussion of these differences.

3.2 Cases

3.2.1 Case 1. Relatively Asymptomatic but Troponin is Elevated

An 80-year-old male presented with a history of coronary artery disease, hypertension, and hyperlipidemia. He underwent coronary artery bypass grafting in 2016 for an acute coronary syndrome. He has been free of cardiovascular symptoms since that time and was physically very active. In late 2018, he was diagnosed with metastatic melanoma and was started on a PD-1 inhibitor in January 2019. He received a single dose. Four weeks later, he presented with new onset of fatigue with exertion. He was without chest pain or shortness of breath. On examination, he had a regular rhythm at 78 beats per minute. His blood pressure was

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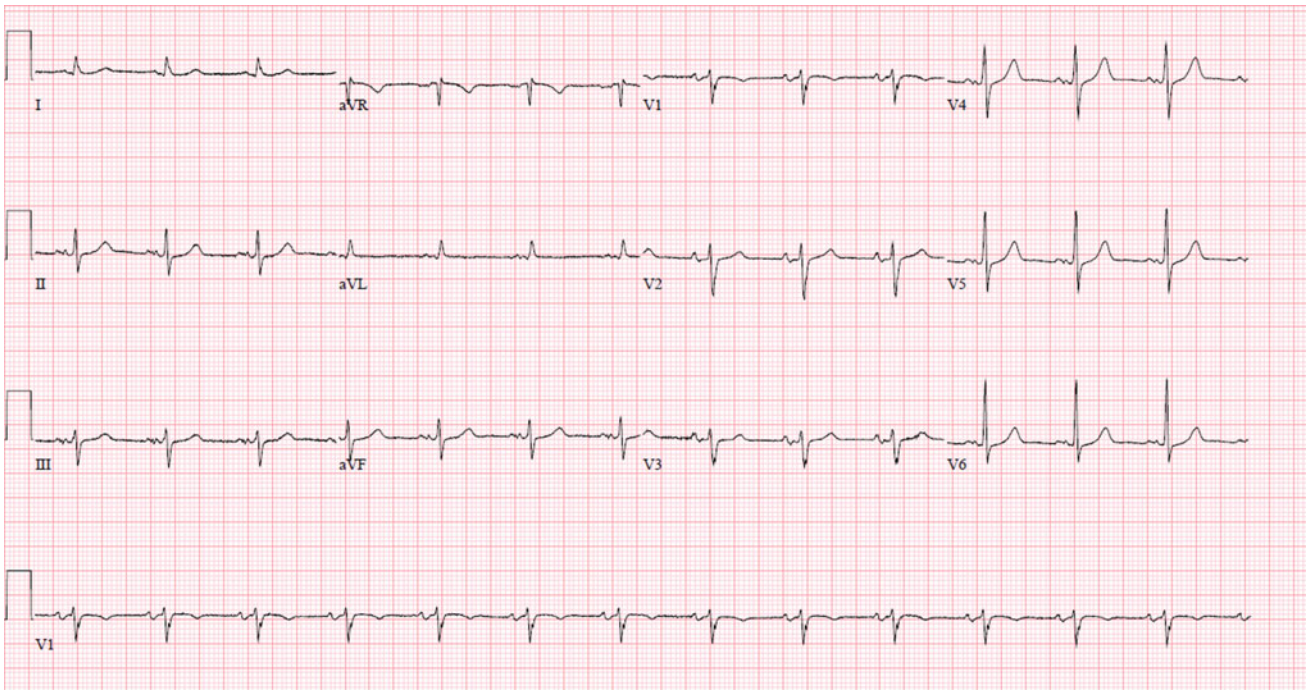

Fig. 3.1 Presentation EKG showing sinus rhythm, a left atrial abnormality, but was otherwise unremarkable

126/72 and he had no signs of heart failure. He had an EKG (Fig. 3.1) which, apart from a left atrial abnormality, was unremarkable. His creatinine kinase was 3,005 U/L (normal <400 U/L). His HsTNT was 369 ng/L (normal <14 ng/L). His ICI was held and he was admitted to the in-patient cardiology service with a consult to the cardio-oncology team. He had a transthoracic echocardiogram (Fig. 3.2, Video 3.1). This echocardiogram showed normal left ventricular (LV) size and ejection fraction (LVEF 72%). There was abnormal interventricular septal motion. The left atrial volume was increased and the pulmonary artery systolic pressure was 42 mmHg. There was no pericardial effusion. He underwent cardiac magnetic resonance imaging. This confirmed normal LV size and EF without significant wall motion abnormality or pericardial effusion. The right ventricle also had a normal volume and function. There was no evidence of myocarditis using late gadolinium enhancement imaging or black blood T2 imaging (Fig. 3.3). Parametric T1

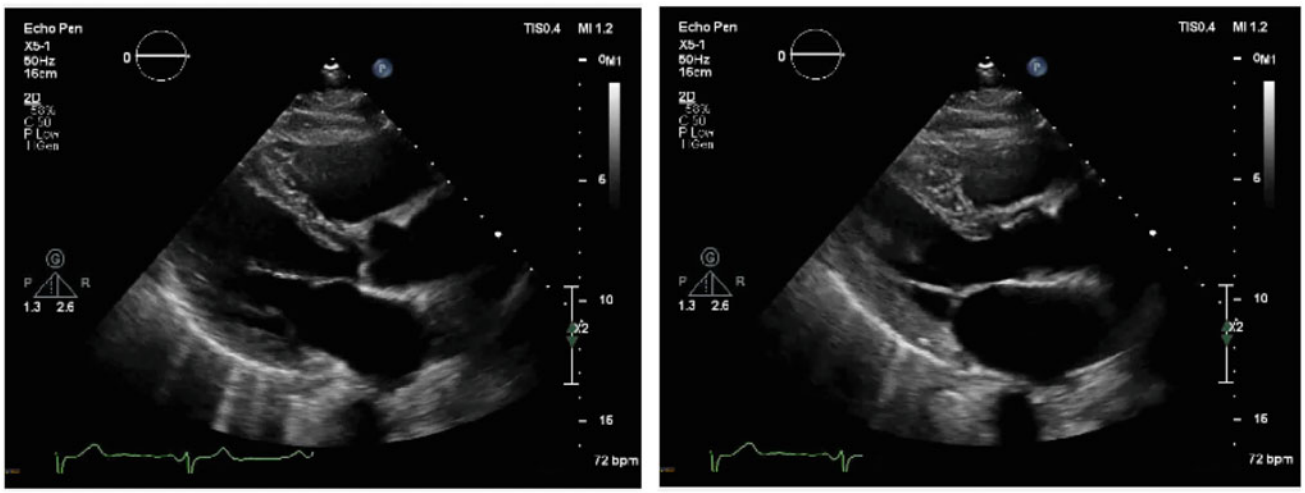

Fig. 3.2 Transthoracic echocardiogram showing normal left ventricular (LV) size and ejection fraction (LVEF 72%). There was abnormal interventricular septal motion. The left atrial volume was increased and the pulmonary artery systolic pressure was 42 mm Hg. There was no pericardial effusion

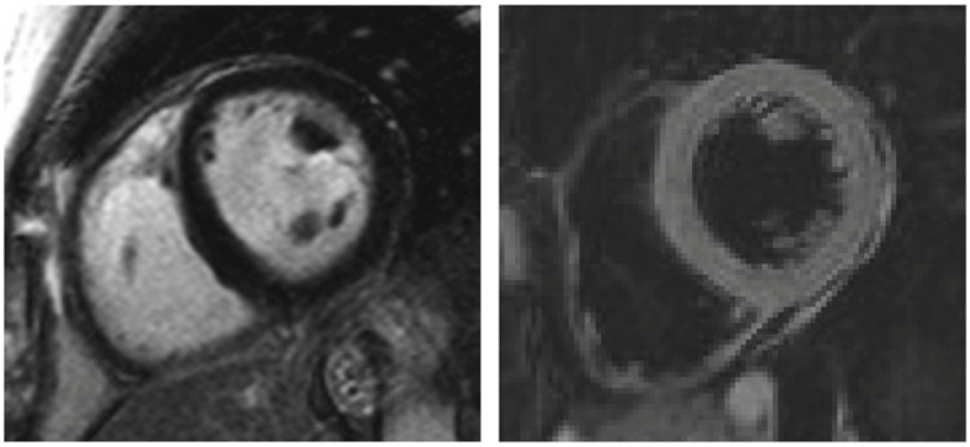

Fig. 3.3 Still images from the cardiac MRI imaging. There was no evidence of myocarditis using late gadolinium enhancement imaging or black blood T2 imaging. Parametric T1 or T2 mapping was not available

or T2 mapping was not available. The troponin-T increased to 563 ng/L on the day of admission while creatine kinase decreased slightly to 2,776 U/L. The patient remained stable but in view of the rising troponin and negative cardiac MRI, an endomyocardial biopsy was performed. This showed focal infiltration by lymphocytes, macrophages, and scattered eosinophils with associated cardiomyocyte injury consistent with myocarditis (Fig. 3.4). He was started on a gram of methylprednisone per day, prophylaxis for pneumocystis pneumonia, and a proton pump inhibitor. His troponin did not decrease. On day 5, he was treated with a single dose of infliximab 5 mg/kg without effect on his serum troponin. On day 7, a repeat dose of infliximab was administered, while he transitioned to 60 mg of oral prednisone per day. The serum troponin increased. The patient remained stable with occasional new frequent episodes of non-sustained ventricular tachycardia (NSVT). Mycophenolate mofetil was added at 750 mg twice a day, rising to 1000 mg twice a day. His troponin began to decline (Fig. 3.5). However, on day 30 of his admission, he developed frequent runs of NSVT and, after a family meeting where several options were presented, it was decided to administer intravenous immunoglobulin. His episodes of NSVT resolved. Six weeks after discharge, he presented with odynophagia, an esophagogastroscopy was performed and biopsies revealed cytomegalovirus esophagitis. His viral load was very elevated and he was treated with ganciclovir and later transitioned to oral valganciclovir. Two weeks after that discharge, he reported bilateral lower extremity edema. He had a lower extremity duplex ultrasound which revealed bilateral deep venous thrombosis and he was started on enoxaparin. One week after that he was admitted with an upper GI bleed. Three weeks later, his oral intake was poor and he was losing weight. He was diagnosed with Candidal esophagitis. He was treated with fluconazole. Thereafter he did well symptomatically, and was ultimately able to exercise for 2 hours daily. He presented eight months later with coffee-ground emesis and was found to have a large submucosal mass in the gastric body with pathology consistent with metastatic melanoma. He had a gastric wedge resection and is well and cancer-free 19 months after his initial presentation.

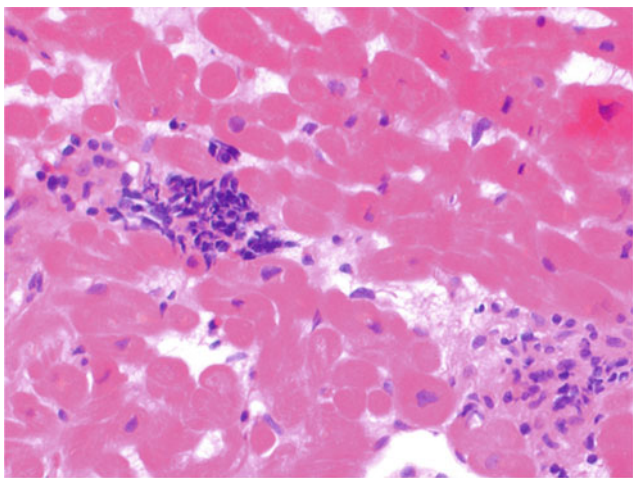

Fig. 3.4 Pathological images from endomyocardial biopsy showing focal infiltration by lymphocytes, macrophages, and scattered eosinophils with associated cardiomyocyte injury consistent with myocarditis

3.2.2 Case 2. Moderately Symptomatic with Abnormal Imaging

A 67-year-old female with a history of metastatic urothelial carcinoma presented to the emergency room with several weeks of worsening pelvic and abdominal pain related to her malignancy, along with fatigue and weakness. She denied any symptoms of chest pain, dyspnea, fevers, chills, nausea, or vomiting and was debilitated due to severe abdominal pain. Her oncologic history was significant for a diagnosis of

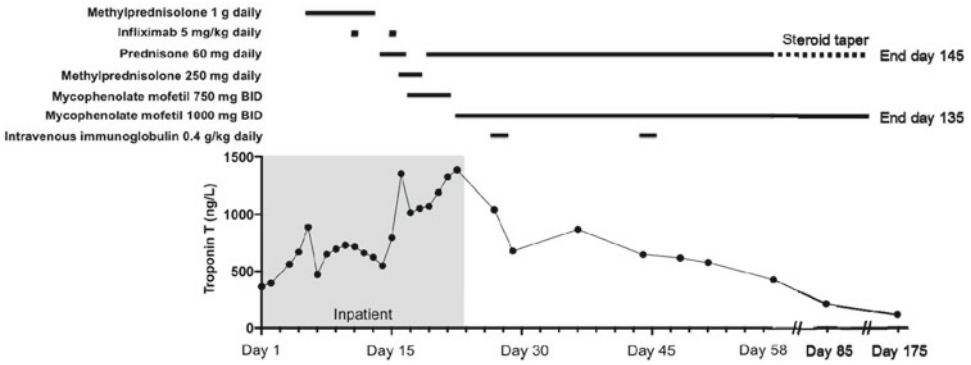

Fig. 3.5 Clinical course of the patient with troponin change over time and each of the treatments that were instituted at each time point and how the troponin responded. The patient was treated with solumedrol, infliximab, mycophenolate, and IVIG at different stages

urothelial cancer with pelvic lymphadenopathy and peritoneal carcinomatosis. She had undergone six cycles of cisplatin and gemcitabine; given a lack of clinical response, she was started on combination immunotherapy with a PD-L1 inhibitor and a T cell immunoreceptor with Ig and ITIM domains (TIGIT) inhibitor. Her first treatment was administered 5 days prior to presentation. Her vital signs were significant for hypotension at 80/63 mm Hg and a heart rate of 116 bpm. She was afebrile with an oxygen saturation of 98% on room air. Her cardiovascular examination was negative for jugular venous distension, peripheral edema, murmurs, rubs, gallops, S3 or S4. Lung auscultation was unremarkable. Her physical examination was only positive for pelvic/abdominal pain on palpation without any signs of acute abdomen. The patient's laboratory results were significant for a leukocytosis of 49.9×10^3/microliter, a hemoglobin level of 14.5 g/dL, and a platelet count of 300×10^3/microliter. Her electrolytes were significant for a potassium of 6.6 mmol/L, and an elevated creatinine of 2.0 mg/dL. Liver enzymes were mildly elevated with an aspartate aminotransferase level of 69 U/L, and an alanine aminotransferase level of 16 U/L. Thyroid-stimulating hormone levels were within normal limits. Her total creatine kinase level was elevated at 596 U/L and troponin-I levels were elevated at 10.4 ng/mL. A 12-lead electrocardiogram (ECG) obtained on admission was significant for sinus tachycardia with diffuse ST segment elevations seen in the precordial and inferior limb leads (Fig. 3.6). A transthoracic echocardiogram (TTE) obtained demonstrated low normal left ventricular ejection fraction (LVEF) of 50–55%, with dyskinetic motion of the mid to distal left ventricle with normal wall motion of all other wall segments (Fig. 3.7, Video 3.2). ECG and TTE prior to ICI treatment were both unremarkable. Coronary angiography and cardiac magnetic resonance imaging were recommended and offered to the patient, but ultimately not performed in line with her goals of care. The wall motion abnormalities noted on TTE were not congruent with the extent of ST segment elevations seen on ECG, nor was it consistent with a myocardial injury pattern with traditional coronary anatomy; thus, the leading diagnosis was stress-induced (Takotsubo) cardiomyopathy (see Chap. 15) and probable perimyocarditis (abnormal cardiac biomarkers and atypical wall motion abnormalities on echocardiography) associated with ICI use. A total of 1 g methylprednisone was given intravenously for 5 days, then switched to oral prednisone 60 mg daily. The patient's troponin-I levels peaked at 26.4 ng/mL on hospital day 2 and down trended afterwards; the patient never had symptoms of myocardial ischemia or heart failure. A repeat TTE done 7 days after admission demonstrated an improved LVEF at 60–65% with resolving—but still present—wall motion abnormalities in the distal left ventricle. Because of the patient's poor prognosis and ongoing severe pain related to her malignancy, and in discussion with the patient and family, the decision was made to transition the patient to hospice and palliative care. The patient passed away on hospital day 17; autopsy was declined by the family.

3.2.3 Case 3. Life-Threatening Myocarditis

A 74-year-old man with metastatic bladder cancer presented with severe fatigue, dyspnea, and lightheadedness 5 days after receiving the second dose of nivolumab (PD-1 inhibitor). The patient had a past medical history of hypertension but notably no history of coronary artery disease, CVA, dyslipidemia, or diabetes. On arrival to the emergency room he had a heart rate of 27 beats per minute and hypotension with blood pressure of 93/61 mmHg. The electrocardiogram revealed complete heart block with a ventricular escape rhythm (Fig. 3.8). A temporary pacemaker was placed at the bedside in the emergency room with improvement in blood pressure and dizziness; however, the patient had continued

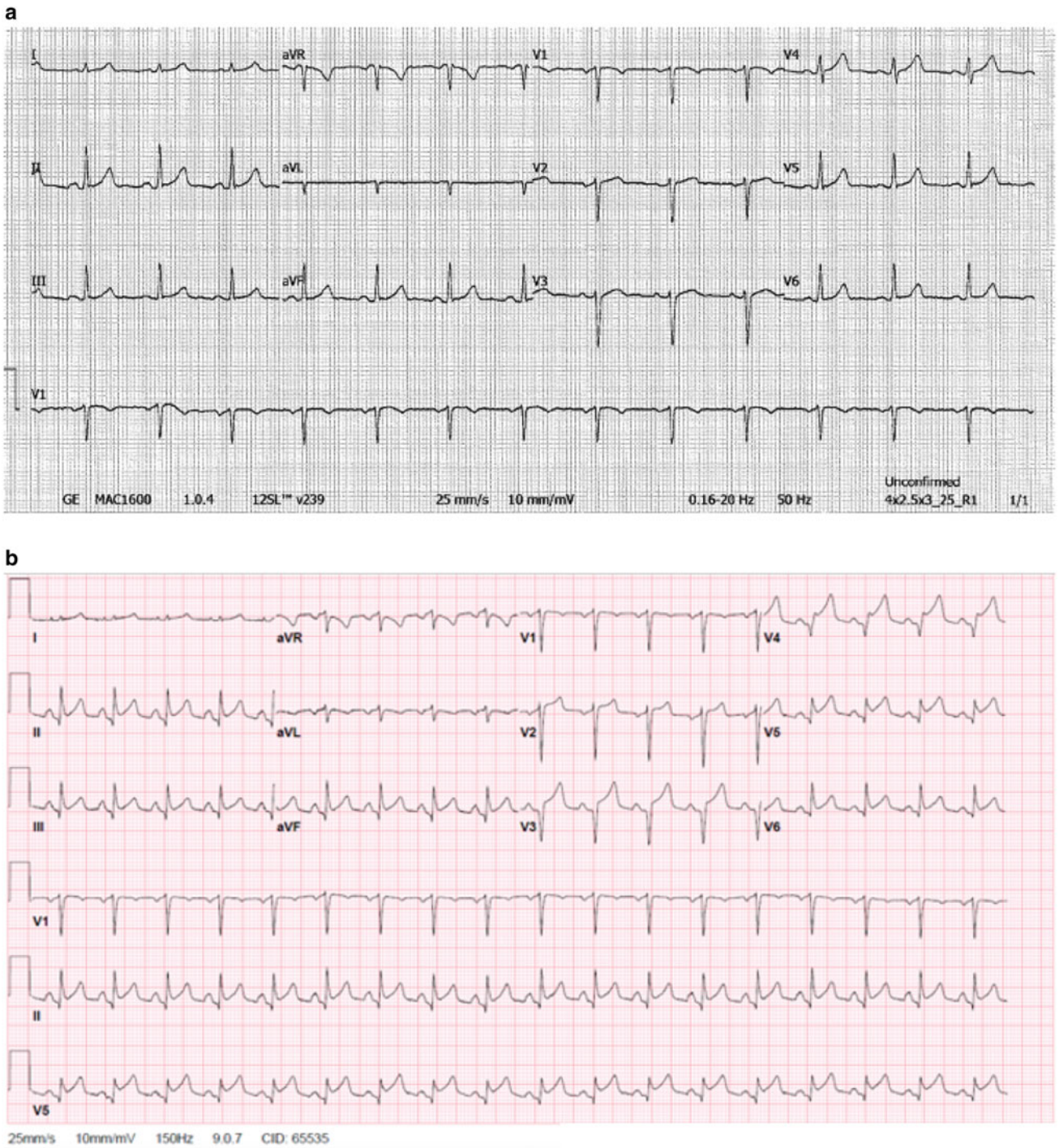

Fig. 3.6. 12-lead electrocardiograms before and during presentation of immune checkpoint inhibitor (ICI) associated myocarditis. Panel A: Normal 12-lead ECG two weeks before ICI treatment. Panel B: 12-lead ECG on admission for suspected ICI-associated myocarditis sinus tachycardia with diffuse ST segment elevations in the precordial and inferior limb leads. PR segment depressions are seen in the precordial leads.

fatigue and dyspnea. The initial troponin-T value was 1085 ng/L and echocardiogram revealed normal left ventricular systolic function with a moderate-sized pericardial effusion (Fig. 3.9). The patient is taken to the catheterization laboratory for left and right heart catheterization with endomyocardial biopsy which ruled out acute coronary syndrome, and biopsy results reveal lymphocytic infiltration with myocyte necrosis consistent with myocarditis

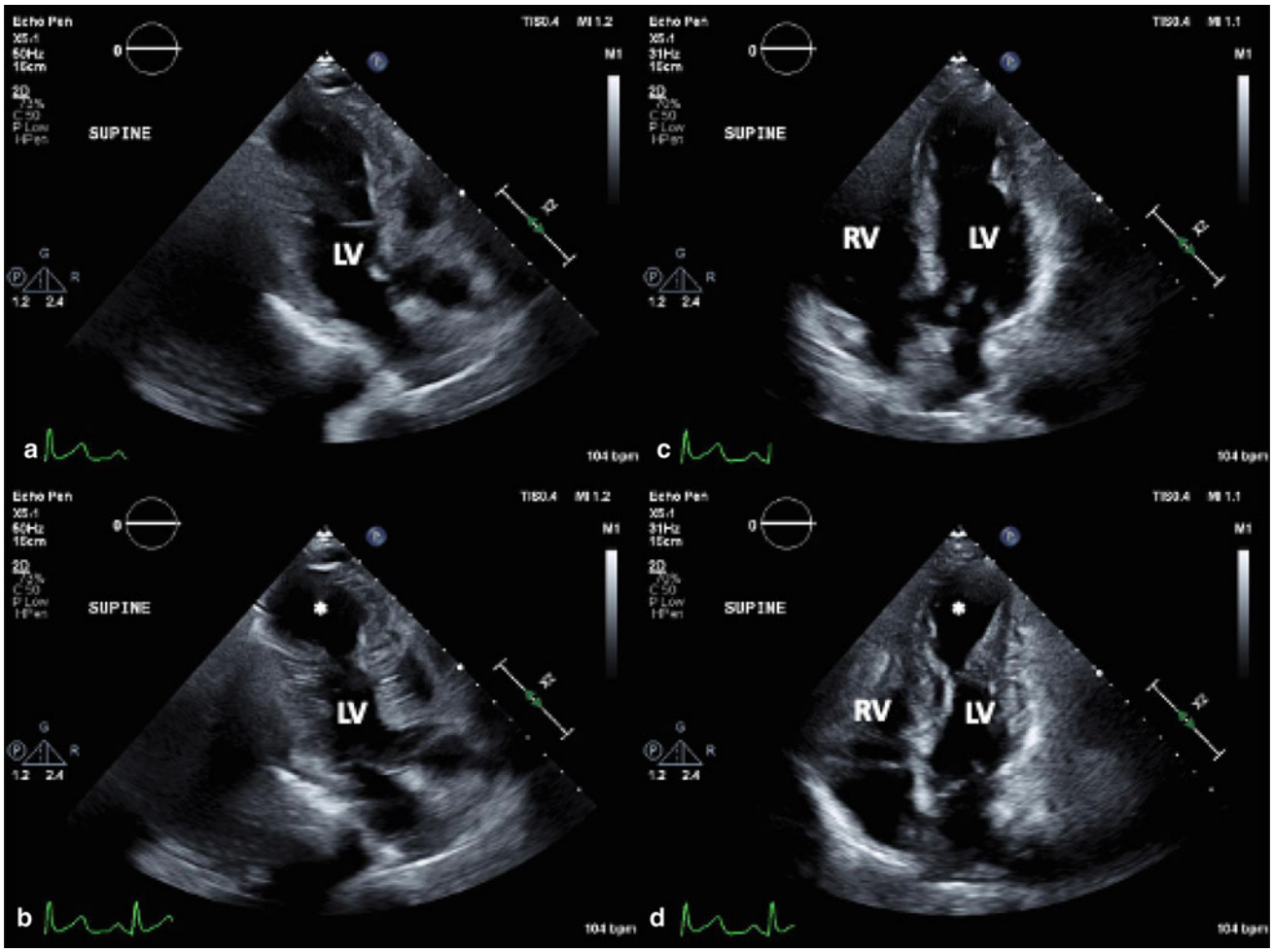

Fig. 3.7 Transthoracic echocardiography on admission. Apical three-chamber views in diastole (Panel A) and systole (Panel B), and apical four-chamber views in diastole (Panel C) and systole (Panel D) demonstrate dyskinesis of the distal left ventricle (*), including the mid to distal lateral, septum, apex, and anterior walls. Because the wall motion abnormalities were incongruous with the extent of the diffuse ST elevations noted on 12-lead electrocardiogram, imaging was suggestive of stress-induced (Takotsubo) cardiomyopathy and peri-myocarditis associated with immune checkpoint inhibitor use. Left ventricular ejection fraction (LVEF) was calculated at 50–55%. Repeat echocardiography 7 days later demonstrated an improvement in LVEF with improved, but persistent distal wall motion abnormalities. LV: left ventricle. RV: right ventricle

(Fig. 3.10). The patient was initiated on high-dose steroids at 1 g solumedrol daily for 3 days followed by 1 mg/kg daily of prednisone with a troponin peak of 1454 ng/L. However, his respiratory status continued to decline and he required intubation for mechanical ventilation. Therefore, second-line therapy was initiated with plasmapheresis (5 sessions) followed by intravenous immunoglobulin for three doses with improvement allowing for extubation. The complete heart block persisted and he required permanent pacemaker implantation. The troponin levels decreased to 291 ng/L but never became normal. He continued a corticosteroid taper over the next 6 weeks. The patient did not have any other therapeutic options for his metastatic bladder cancer, and therefore, a decision was made to pursue hospice and he passed away 6 months after discharge.

3.3 Discussion

3.3.1 Background

ICIs have revolutionized the treatment of cancers, specifically melanoma, lung, and genitourinary malignancies, with significant improvements in oncologic outcomes [1]. They are a form of immunotherapy that is relatively new with the first ICI being approved by the United States Food and Drug Administration (FDA) in 2011. Ipilimumab was the first ICI developed and is a cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor. Since then, there have been six additional FDA-approved ICI which are all programmed cell death protein 1 (PD1) or programmed death-ligand 1

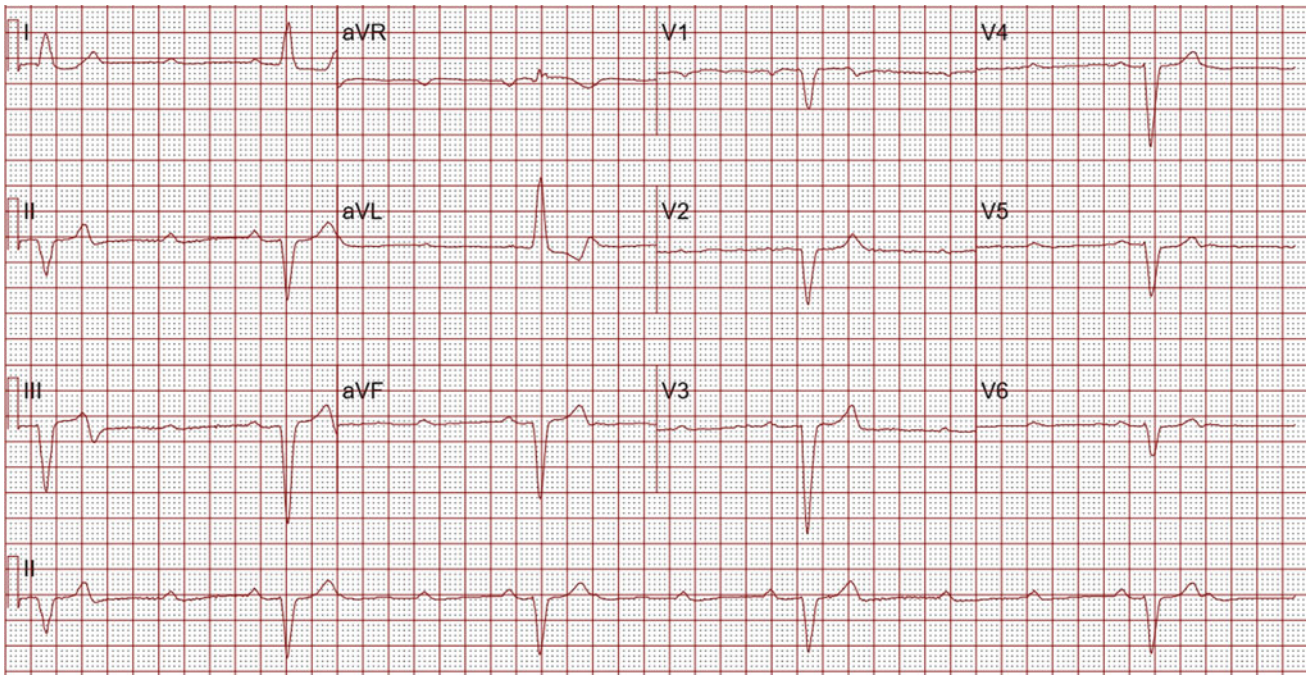

Fig. 3.8 12-lead electrocardiogram showing complete heart block and ventricular escape rhythm at 27 beats per minute

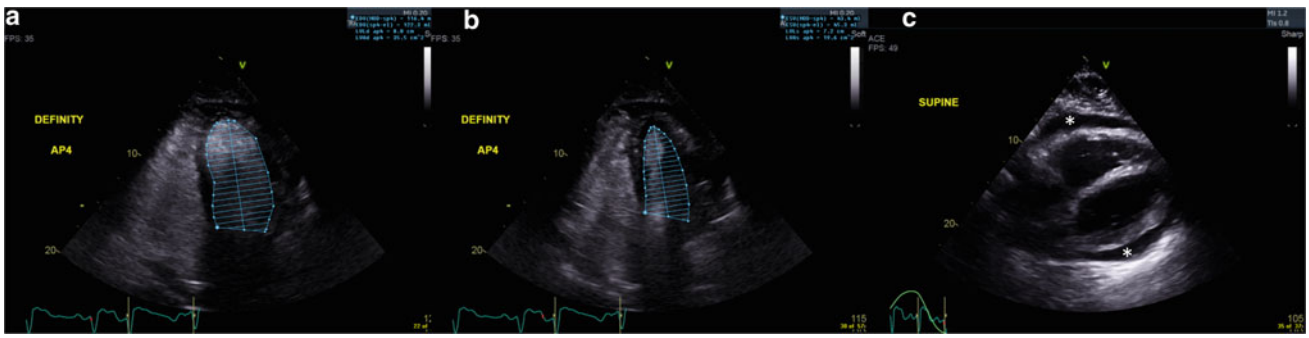

Fig. 3.9 Echocardiographic images showing normal left ventricular ejection fraction, 55% per biplane modified Simpson's, and a moderate-sized pericardial effusion. **a** Apical four-chamber view with micro-bubble-enhanced image showing modified Simpson's end-diastolic volume measurement. **b** Apical four-chamber view with micro-bubble-enhanced image showing modified Simpson's end-systolic volume measurement. **c** Subcostal image showing circumferential moderate-sized pericardial effusion (white asterisks)

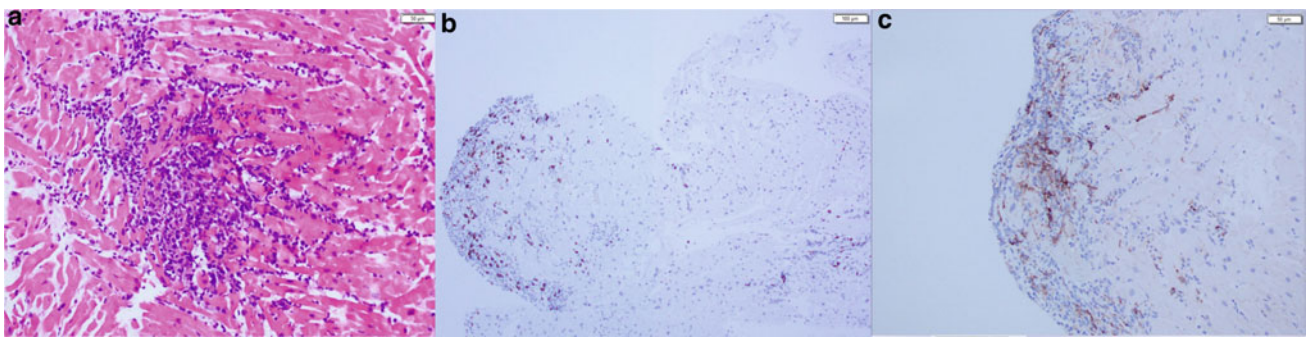

Fig. 3.10 Endomyocardial biopsy pathology slides showing inflammatory infiltrate and myocyte loss consistent with myocarditis. **a** Hematoxylin and eosin stain showing inflammatory infiltrate with myocyte loss. **b** Immunohistochemical stain for CD8+ T cells showing patchy infiltration of the myocardium. **c** Immunohistochemical stain for programmed death ligand 1 (PD-L1) showing increased uptake in the areas of inflammatory infiltrate

(PD-L1) inhibitors. There are numerous other classes of ICI currently in development with notable targets, including lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin, ITIM domain (TIGIT), and V-domain Ig suppressor of T cell activation (VISTA). It was anticipated that leveraging the immune system would be associated with immune-related adverse events (irAEs) affecting multiple parts of the body from the thyroid to the joints [2]. The most serious of the irAEs is myocarditis with a reported mortality of 25–50% [3–6]. However, ICI-associated myocarditis is uncommon with an incidence of 1–2% in recent publications [4]. The cases presented above highlight several important aspects of myocarditis: the varied clinical presentation, various modalities used for diagnosis, and evolving treatments.

3.3.2 Pathophysiology

Malignant cells can evade the immune system by immune checkpoints which abrogate the activation of immune cells [7]. T cell activation requires co-stimulation with both antigen presentation to T cell receptors and activation of CD28 receptors by B7 molecules on antigen presenting cells [8, 9]. Immune checkpoints such as CTLA-4 bind to B7 molecules with higher affinity than CD28 receptors and thus suppress T cell activation [10]. By inhibition of immune checkpoints or of their ligand, PD-L1, T cells can recognize tumor cells and attack the cancer. However, releasing the brakes on the T cell activation can result in unwanted off-target effects such as T cells attacking normal tissues. Endomyocardial biopsies of patients with ICI-associated myocarditis reveal predominantly T cell infiltration of the myocardium that resembles acute cellular rejection in transplanted hearts [3, 11]. The proposed mechanism is via molecular mimicry and shared epitopes between antigens of tumor cells and substructures of the myocardium [3]. Further research is needed to confirm this as the mechanism of ICI cardiotoxicity.

3.3.3 Clinical Presentation

Beyond combination immune therapy, the risk factors for ICI-associated myocarditis are incompletely understood. Additional risk factors suggested include age, pre-existing cardiovascular disease, and hypertension [12, 13]. Patients with ICI-associated myocarditis present with a myriad of symptoms and there is a spectrum of clinical presentations ranging from smoldering to fulminant [3, 14, 15]. Some of the more common symptoms are non-specific, including fatigue, dyspnea, and weakness which makes the diagnosis difficult. Patients may also present in heart failure with orthopnea, paroxysmal nocturnal dyspnea, and volume overload or present with chest pain similar to an acute coronary syndrome [16–19]. The most concerning presentations are those of fulminant myocarditis in which patients present in shock with hemodynamic instability either from hypoperfusion due to cardiac failure, complete heart block, or ventricular tachycardia/sudden cardiac death [3, 18]. Initial reports of myocarditis suggested that this was a rare disease occurring in 0.06% of those with monotherapy and 0.27% of those on combination therapy [3]. It is likely that these were capturing only the fulminant cases of myocarditis [20]. As recognition of this disease entity has improved, less severe clinical presentations have been diagnosed as myocarditis and the incidence has increased to approximately 1% [4]. Most commonly, myocarditis will occur within the first 2 months after initiation of ICI, however, late presentations up to 454 days after starting ICI have been described [4].

The only established risk factor is the use of combination ICI therapy as opposed to monotherapy with smaller reports suggesting the possibility of female sex, obesity, and increased neutrophil to lymphocyte ratio at baseline as potentially additional risk factors [3]. It is worth noting that traditional cardiac risk factors for anthracycline cardiotoxicity such as age, hypertension, diabetes, coronary artery disease, and congestive heart failure do not appear to be risk factors for developing ICI-associated myocarditis. In addition, multiple irAE can occur in patients at the same time. The most common irAE to overlap with ICI-associated myocarditis are myasthenia gravis and myositis [2], with the overlap associated with a higher mortality. It can be difficult to differentiate whether symptoms of dyspnea and fatigue are due to myocardial involvement of myocarditis versus neuromuscular junction or muscle cell involvement of myasthenia gravis or myositis.

3.3.4 Diagnosis

The diagnosis of ICI-associated myocarditis is dependent on a combination of the clinical presentation, laboratory data, non-invasive imaging, and/or endomyocardial biopsy [11, 21]. Each test has its limitations in making a diagnosis of myocarditis which will be discussed below. Therefore, a combination of several tests in addition to the clinical presentation and ruling out more common cardiac conditions such as acute coronary syndrome or ischemic heart disease [19] is necessary prior to making the diagnosis of ICI-associated myocarditis. Bonaca et al. proposed diagnostic criteria for myocarditis in the setting of cancer therapeutics that separated the diagnosis into three categories

(definite myocarditis, probable myocarditis, or possible myocarditis) based on combinations of the clinical presentation and diagnostic tests. The criteria include [22]:

1. Definite Myocarditis: presence of at least one of the following
   a. Pathology consistent with myocarditis
   b. Diagnostic CMR, clinical syndrome of myocarditis, and positive biomarker or EKG
   c. Echo with wall motion abnormality, clinical syndrome of myocarditis, positive biomarker, positive EKG, and negative angiography for CAD
2. Probable Myocarditis:
   a. Diagnostic CMR without clinical syndrome of myocarditis, positive EKG, or positive biomarker OR
   b. Suggestive CMR with one of the following:
      i. Clinical syndrome of myocarditis
      ii. Positive EKG
      iii. Positive biomarker OR
   c. Echo with wall motion abnormality and clinical syndrome of myocarditis with either positive EKG or biomarker OR
   d. Clinical syndrome of myocarditis with PET scan evidence and no alternative diagnosis
3. Possible Myocarditis
   a. Suggestive CMR without clinical syndrome of myocarditis, positive EKG, or positive biomarker OR
   b. Echo with wall motion abnormality and clinical syndrome of myocarditis or positive EKG OR
   c. Elevated biomarker with clinical syndrome of myocarditis or positive EKG and no alternative diagnosis.

Laboratory data: Cardiac biomarkers such as troponin-I and troponin-T are typically elevated in cases of myocarditis. Elevations in troponin have prognostic value, as Mahmood et al. showed that troponin-T values above 1.5 g/dL were associated with a fourfold increased risk of major adverse cardiovascular events [4]. Elevations in troponin are non-specific findings and more common causes such as acute coronary syndrome and demand ischemia due to sepsis, for example, must be excluded prior to making the diagnosis of ICI-associated myocarditis. Troponin-I is preferred over troponin-T due to cross-reactivity of troponin-T with skeletal muscle [22]. Often creatinine kinase (CK) and creatinine kinase-muscle/brain (CK-MB) are also elevated during myocarditis; however, given the overlap with myositis and myasthenia gravis, additional workup for these irAEs should be considered when significant elevations are observed in CK and CK-MB out of proportion to troponin elevation. Some institutions have implemented routine cardiac biomarker surveillance strategies during ICI therapy; however, it is unknown whether there is benefit to performing such surveillance due to the low incidence of myocarditis. Chuy et al. attempted this strategy in 76 patients with weekly biomarker surveillance for the first 6 weeks after starting ICI but no cases of myocarditis were observed [23]. Baseline troponin values have not been shown to be predictive of ICI myocarditis but can be helpful as a comparison if symptoms develop and there is suspicion of myocarditis after initiation of ICI [4].

Electrocardiogram: Various electrocardiogram (EKG) abnormalities have been described in patients presenting with ICI-associated myocarditis. The most concerning EKG findings that warrant immediate intervention and workup include advanced atrioventricular block and ventricular tachycardia or increased runs of non-sustained ventricular tachycardia/premature ventricular complexes. These abnormalities have been described in fulminant myocarditis and carry a high mortality [3]. Of course, other more common causes of these arrhythmias may need to be excluded. More subtle EKG changes such as prolonging PR or QRS intervals can be harbingers of myocarditis and patients with these changes should have a myocarditis workup performed. After admission for suspected myocarditis, it is common to place patients on telemetry to monitor for arrhythmias that may occur early in the disease course. Baseline EKGs are not predictive of subsequent myocarditis events [4] and similar to cardiac biomarkers, EKG surveillance strategies are of unknown benefit due to the low incidence of myocarditis [23].

Echocardiograms: Typically, with viral myocarditis, a dilated cardiomyopathy is observed. With ICI-associated myocarditis patients can present with preserved or reduced left ventricular ejection fraction [21]. Mahmood et al. described 51% of patients presenting with preserved left ventricular ejection fraction, but despite maintaining a normal left ventricular ejection fraction 38% developed major adverse cardiovascular events [4]. Supporting findings of ICI-associated myocarditis on echocardiograms include the development of a pericardial effusion and a reduction in global longitudinal strain [21]. Similar to electrocardiograms, the baseline echocardiogram before the start of ICI therapy has not been predictive of subsequent ICI-associated myocarditis [4]. In contrast to anthracycline cardiotoxicity, a depressed left ventricular ejection fraction is not necessarily a contraindication to ICI therapy.

Cardiac Magnetic Resonance Imaging: The best non-invasive diagnostic test for myocarditis is cardiac magnetic resonance imaging (CMR) because of its superior ability to characterize tissue. In the setting of viral myocarditis, CMR has shown good correlation with endomyocardial biopsy results [18]. The updated Lake Louise criteria are used for the CMR diagnosis of

myocarditis and apply a combination of myocardial edema and fibrosis [24]:

1. Main criteria (2 out of 2): If both myocardial edema and non-ischemic myocardial injury are identified, then CMR is highly suggestive of myocarditis with greater specificity. Having only one main criterion may still support the diagnosis of myocarditis in the correct clinical setting.
   a. **Myocardial edema**:
      i. Abnormal findings in T2 mapping or T2-weighted images
   b. Non-ischemic myocardial injury:
      i. Abnormal findings on T1, LGE, or ECV
2. Supportive criteria (Helpful, suggestive, not definitive):
   a. Pericarditis
      i. Evidence of pericardial effusion, or abnormal LGE/T2 or T1 findings in pericardium
   b. Left ventricular systolic dysfunction
      i. Regional or global wall motion abnormalities.

The correlation of CMR with endomyocardial biopsy in ICI-associated myocarditis is not robust. Zhang et al. found that in 103 patients with known ICI myocarditis and CMR studies, only 48% had late gadolinium enhancement. The presence of late gadolinium enhancement was found more commonly if the CMR was performed greater than 4 days after admission [11]. A limitation of this study was the lack of parametric mapping. While it has its limitations, CMR remains the best non-invasive diagnostic test for ICI-associated myocarditis and can make a definitive diagnosis of myocarditis when used in combination with the clinical presentation and/or cardiac biomarkers.

Endomyocardial biopsy: The gold standard diagnostic test for myocarditis is endomyocardial biopsy. The pathologic diagnosis is based on the Dallas Criteria which require the presence of inflammatory infiltrate and myocyte necrosis [25]. Immunohistochemical staining of the inflammatory infiltrate has shown a predominant T cell infiltration with CD8+ and CD4+ inflammatory cells, however, myeloid cells with CD68+ inflammatory cells have also been observed [3, 26]. There are reports of an antibody-mediated component with peri-capillary C4d+ staining which is seen in heart transplant antibody-mediated rejection [27]. It is recommended to obtain 4–6 biopsy samples due to the patchy nature of myocarditis and sampling error when obtaining biopsies [25]. The most common site for endomyocardial biopsy is the right ventricular septal wall. Despite obtaining 4–6 biopsy samples, ICI-associated myocarditis can have focal involvement of the myocardium, and if the right ventricular septal wall is not involved, then the biopsy will be negative. In addition, endomyocardial biopsies are performed at specialized centers with experience in this procedure and while generally safe do have a risk of major complications such as right ventricular laceration. Patients with cancer also can have thrombocytopenia which limits the ability to perform this invasive procedure.

3.3.5 Treatment

The mainstay of treatment for ICI-associated myocarditis is glucocorticoids [28]. It has been shown that early initiation of high dose glucocorticoids results in lower major adverse cardiovascular events [4, 29]. Guidelines recommend high dose steroids, at least 1–2 mg/kg/day of prednisone but many centers initiate pulse dose methylprednisolone at 500–1000 mg/day for 3 days followed by an oral steroid taper depending on the clinical response. Various tapers have been suggested, but the American Society of Clinical Oncology clinical practice guidelines recommend a taper over at least 4–6 weeks [28]. If clinical deterioration continues despite corticosteroids, then other immunomodulators have been shown to have varying success in case reports. These include mycophenolate [30], antithymocyte globulin [31], intravenous immunoglobulin [30], plasmapheresis [32], infliximab [32], alemtuzumab [33], and abatacept [34]. Given the high mortality of ICI-associated myocarditis, it is recommended to permanently discontinue ICI therapy after an episode of myocarditis [28].

3.4 Conclusion

With the increasing use of ICIs for cancer treatment, it is necessary for oncologists, general cardiologists, and cardio-oncologists to work together to promptly diagnose and treat ICI-associated myocarditis. Understanding the various benefits and limitations of available diagnostic tests and their use in combination with the clinical presentation will help guide the diagnosis and the treatment. Ongoing research will help to better standardize treatment regimens and societal guideline recommendations.

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