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Cardiac adverse reactions associated with cancer immunotherapy

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About the Expert

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This review is intended as an educational resource for healthcare professionals who encounter patients with adverse reactions while receiving immune checkpoint inhibitor (ICI) therapy for cancer. It summarises the impact, diagnosis, and management of cardiac immune-related adverse reactions (irARs) in these patients, using current clinical consensus. The review also presents and discusses two cases of ICI-associated myocarditis with very different outcomes. This publication has been created with an unrestricted educational grant from AstraZeneca, MSD and Roche. The content is entirely independent and based on published studies and the author's opinion.

Introduction

Immune checkpoint inhibitors (ICIs) are biologic agents used in cancer immunotherapy to enhance the patient's anti-tumour immune response.[1,2] ICIs targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death-1 (PD-1) and PD ligand-1 (PD-L1) have approval in New Zealand for a number of indications, including head and neck cancers, lung cancers, melanoma, renal cell carcinoma and urothelial carcinoma.[3]

Patients receiving ICIs can experience immune-related adverse reactions (irARs) across any organ or system in the body.[2,4] Cardiac irARs are rare but can have serious clinical consequences, including death.[4-6] Symptoms of cardiac irARs may be masked by other irARs, malignancy symptoms or comorbid conditions.[4] Early identification of cardiac irARs and prompt intervention by a multidisciplinary team is needed to ensure optimal patient outcomes.[7,8]

Cancer immunotherapy

Immune checkpoint inhibitors available in New Zealand

In New Zealand, the ICIs atezolizumab, durvalumab, ipilimumab, nivolumab and pembrolizumab are available for the treatment of several advanced or metastatic cancers, as either first- and/or second-line therapy as well as combination therapy in some cases (see **Table 1**).[3,9-13] For full details of these ICIs, please review the respective Data Sheets at www.medsafe.govt.nz.

Mechanism of action

CTLA-4 and PD-1 receptors are immune checkpoint proteins expressed on the surface of naive and cytotoxic T cells.[1] These receptors interact with their ligands CD80/CD86 (in the case of CTLA-4) and PD-L1 (in the case of PD-1), facilitating cancer cell evasion from cytotoxic T-cell-mediated death.[1,14] ICIs prevent binding of the receptors and ligands and disrupt these signalling pathways.[4]

Despite the clinical benefits, new toxicities related to the mechanism of action have been identified in patients treated with ICIs.[14] The underlying mechanisms of irARs are not fully understood, but may involve cellular autoimmunity, autoantibodies, complement activation, cytokine/chemokine release, genetics and alterations of the gut microbiome.[14]

The impact of irARs across organs

Any organ or system in the body can be affected by irARs.[2,4,6] These can occur after the first ICI infusion, after several infusions or even after active treatment has stopped.[1,2] In contrast, adverse events to chemotherapy usually occur early and repetitively during the treatment course.[1] Moderate to severe irARs may cause a severe decline in organ function, quality of life and even death.[4]

Cardiac irARs include myocarditis, pericarditis, vasculitis, acute coronary syndrome, conduction disease (including complete heart block), atrial and ventricular arrhythmias, Takotsubo syndrome, non-inflammatory left ventricular dysfunction and symptomatic heart failure.[4,15]

Cardiac irARs are thankfully rare, with a reported incidence from clinical trials of <1%.[5,6,8] However, the true incidence is likely to be higher given cardiac assessments were not routinely performed in trial patients.[5,7,15] The risk may be increased with combination ICI therapy compared with monotherapy.[2,4] Myocarditis is the most common cardiac toxicity and one of the most serious irARs overall, with a mortality rate of 30-50%.[2,6,8,16]

Myocarditis, pericarditis, vasculitis and cardiac conduction disease usually present within the first 4 cycles of ICI therapy;[15] median time to onset of myocarditis has been reported to be approximately 30 days after treatment initiation.[2,8] Non-inflammatory heart failure usually appears after ≥3 months of ICI therapy, most commonly after 6 months.[15] Acute coronary syndrome and arrhythmias may occur throughout ICI therapy.[15] Atrial tachycardias may be either primary or secondary to acute thyrotoxicosis, acute systemic inflammatory syndromes or other irARs associated with significant electrolyte imbalance.[15]

Immunotherapy	Target antigen	Therapeutic areas where indicated
Atezolizumab[9] Tecentriq®	PD-L1	Monotherapy: non-small cell lung cancer, urothelial carcinoma Combination therapy with bevacizumab: hepatocellular carcinoma Combination therapy with bevacizumab, paclitaxel and carboplatin: non-small cell lung cancer Combination therapy with chemotherapy: small-cell lung cancer Combination therapy with paclitaxel/nab-paclitaxel and carboplatin: non-small cell lung cancer Combination therapy with nab-paclitaxel: triple-negative breast cancer
Durvalumab[10] Imfinzi®	PD-L1	Monotherapy: non-small cell lung cancer, urothelial carcinoma Combination therapy with chemotherapy: biliary tract cancer, small-cell lung cancer
Ipilimumab[11] Yervoy®	CTLA-4	Monotherapy: melanoma Combination therapy with nivolumab: malignant pleural mesothelioma, melanoma, renal cell carcinoma Combination therapy with nivolumab and chemotherapy: non-small cell lung cancer
Nivolumab[12] Opdivo®	PD-1	Monotherapy: classical Hodgkin Lymphoma, head and neck squamous cell carcinoma, hepatocellular carcinoma, melanoma, non-small cell lung cancer, oesophageal cancer or gastro-oesophageal junction cancer, oesophageal squamous cell carcinoma, renal cell carcinoma, urothelial carcinoma Combination therapy with cabozantinib: renal cell carcinoma Combination therapy with chemotherapy: gastric cancer, gastro-oesophageal junction cancer, oesophageal adenocarcinoma Combination therapy with ipilimumab: malignant pleural mesothelioma, melanoma, non-small cell lung cancer, renal cell carcinoma Combination therapy with ipilimumab and chemotherapy: non-small cell lung cancer
Pembrolizumab[13] Keytruda®	PD-1	Monotherapy: classical Hodgkin lymphoma, colorectal cancer, head and neck squamous cell carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, urothelial carcinoma Combination therapy with axitinib: renal cell carcinoma Combination therapy with chemotherapy: head and neck squamous cell carcinoma, non-small cell lung cancer, oesophageal cancer, triple-negative breast cancer Combination therapy with chemotherapy and paclitaxel with or without bevacizumab: cervical cancer Combination therapy with lenvatinib: endometrial cancer, renal cell carcinoma

Table 1. Indications of immune checkpoint inhibitors available in New Zealand.[3,9-13]
CTLA-4 = cytotoxic T-lymphocyte antigen-4; PD-1 = programmed cell death-1; PD-L1 = PD ligand-1.

Diagnosis of cardiac irARs

Presenting symptoms of cardiac irARs include progressive fatigue, myalgia or weakness, palpitations, chest pain, presyncope or syncope, shortness of breath and peripheral oedema.[4] In severe cases, such as fulminant myocarditis, patients can present with cardiogenic shock or sudden death.[2,4] Symptoms may be masked or coincide with other irARs, such as myositis, pneumonitis and hypothyroidism, or pulmonary symptoms related to malignancy or comorbid conditions.[4] Approximately 30% of myocarditis cases are associated with myositis and 10% with myasthenia gravis.[2]

Initial work-up for patients with symptoms of cardiac irARs should include electrocardiography (ECG) and a cardiac troponin assay.[2,4] Creatine phosphokinase should be measured to rule out concurrent myositis, especially in patients receiving combination ICI therapy, and other causes of troponin elevation should be ruled out.[4] A brain natriuretic peptide (BNP) assay, chest x-ray, and an echocardiogram are also recommended.[2,4] Other diagnostic tests should be guided by a cardiologist and include cardiac stress testing, cardiac catheterisation, and cardiac magnetic resonance imaging (MRI).[2,4] Endomyocardial biopsy should be considered for patients who are unstable or in whom diagnosis remains unclear after cardiac MRI or cardiac positron emission tomography-computed tomography (PET-CT).[4,15]

Myocarditis

The International Cardio-Oncology Society has proposed new diagnostic criteria for ICI-associated myocarditis (see **Table 2**).[15,17] Timely diagnosis of this cardiac irAR is critical, as prompt initiation of immunosuppressive therapy improves outcomes.[17,18]

Pathohistological diagnosis: multifocal inflammatory cell infiltrates in endomyocardial biopsy with overt cardiomyocyte loss by light microscopy
OR
Clinical diagnosis: cardiac troponin elevation (new or significant change from baseline) with 1 major criterion or 2 minor criteria after exclusion of ACS and acute infectious illnesses
Major criterion: cardiac MRI diagnostic for acute myocarditis
Minor criterion: clinical syndrome (including fatigue, myalgia, chest pain, diplopia, ptosis, shortness of breath, orthopnoea, lower extremity oedema, palpitations, light-headedness or dizziness, syncope, muscle weakness, and/or cardiogenic shock)
Minor criterion: ventricular arrhythmia and/or new conduction system disease
Minor criterion: decline in cardiac function with or without regional wall motion abnormalities in a non-Takosubo pattern
Minor criterion: other irARs, particularly myositis, myopathy and myasthenia gravis

Table 2. Diagnostic criteria for ICI-associated myocarditis.[15,17]
ACS = acute coronary syndrome; irAR = immune-related adverse reaction; MRI = magnetic resonance imaging.

EXPERT COMMENT

irARs have an increasing impact on medical services with the expanding use of ICI therapy. Prompt recognition of a possible cardiac irAR is important and should be considered in all patients on these agents. A thorough history is paramount. A low threshold for investigation and involvement of the local Cardiology service is important if the patient presents to Oncology or General Medical teams, and often a combined management approach is needed for these complex patients.

Baseline investigations in patients prior to these treatments is important. A baseline troponin and transthoracic echocardiogram can be vital, especially when patients present with non-specific symptoms – serial measures can often be helpful.

The diagnosis of a cardiac irAR can be clouded by other comorbidities, including that of the primary cancer. Simple tests such as an ECG, the troponin and BNP level and a transthoracic echocardiogram can usually be quickly obtained. This helps guide the need for coronary angiography, cardiac MRI and/or PET-CT, and if performed early can allow clinicians to institute immunosuppression treatment, if indicated. It should also be remembered that many of these patients also have the usual risk factors for cardiac problems and can also present with a 'standard' cardiac problem such as an acute coronary syndrome.

Management of irARs

Communicating with patients

Potential irARs should be discussed with patients prior to initiation of ICIs, and patients should be advised to contact their treating healthcare professional if they experience any adverse reactions.[4,15] Risk factors for cardiac irARs include prior cardiovascular disease, chronic diseases such as kidney disease, diabetes and autoimmune conditions, as well as concurrent use of other cardiotoxic agents.[19]

It is important to ask patients about the type of treatment prescribed (immunotherapy, chemotherapy, targeted therapy), and also the specific ICI(s) they are receiving.[1] Patients should have been provided with information at treatment initiation; asking for a patient alert card or other material may assist healthcare professionals with diagnosis.[1] Healthcare professionals must be aware of the potential delay in presentation of irARs; consider asking about past treatments in patients with a recent history of cancer.[1] Patients should be reassured that irARs are manageable in most cases.[1]

Multidisciplinary collaborations

A high level of suspicion, early diagnosis and prompt intervention by a multidisciplinary team is essential to achieving optimal outcomes in patients with irARs (see **Figure 1**).[2,8] Consistent communication is needed between members of the multidisciplinary team.[1,2]

Healthcare professionals should all be aware of the wide range of clinical manifestations of irARs, as well as the Common Terminology Criteria for Adverse Events (CTCAE) grading system used to establish severity.[2,8]

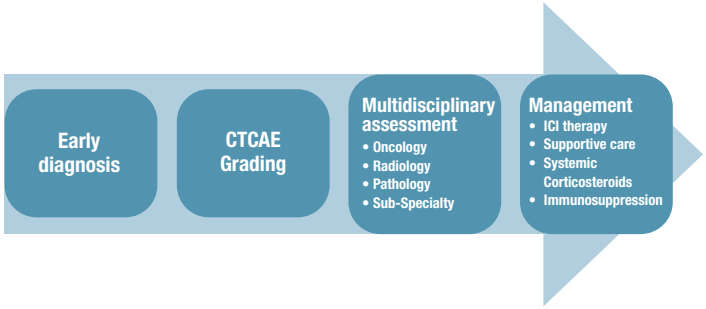

Figure 1. Management recommendations for immune-related adverse reactions (reproduced from Connolly C, et al. Front. Oncol. 2019 Jun 20;9:530).[8]

CTCAE = Common Terminology Criteria for Adverse Events; ICI = immune checkpoint inhibitor.

CTCAE grade	Level of care	Management	ICI therapy
1. Asymptomatic or mild	Ambulatory	Observation	Continue ICI therapy with close monitoring
2. Moderate	Ambulatory	Systemic corticosteroids (0.5-1 mg/kg/day of prednisone or equivalent)	Temporary hold; resume when grade ≤1
3. Severe but not immediately life-threatening	Inpatient	High dose systemic corticosteroids (1-2 mg/kg/day prednisone or methylprednisolone); consider additional therapies if no response within 48-72 hours	Temporary hold; resume when grade ≤1 in discussion with patient
4. Life-threatening	Inpatient +/- intensive care unit	High-dose corticosteroids (1-2 mg/kg/day prednisone or methylprednisolone); consider additional therapies if no response within 48-72 hours	Permanent discontinuation, with the exception of endocrinopathies managed by hormone replacement

Table 3. Common Terminology Criteria for Adverse Events (CTCAE) grading.[8]

ICI = immune checkpoint inhibitor.

CTCAE grading

CTCAE severity grading is shown in **Table 3**.[8] However, as this grading system is not specifically tailored towards irARs, it should be supplemented with the clinical judgement of healthcare professionals familiar with irARs.[8] Higher grade toxicities require more urgent medical intervention.[1]

The incidence of grade ≥3 irARs is 7-12% in patients treated with anti-PD-1/PD-L1 monotherapy, 20–25% in those treated with anti-CTLA-4 monotherapy, and 35–50% in those treated with ICI combinations.[2]

Clinical practice guidelines

Organ-specific guidelines for the management of irARs from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were updated in 2021 and 2022, respectively.[4,15] The guidelines take account of new literature published since the original guidelines were released in 2017 and 2018.[4,15]

ESMO 2022 guidelines note that the management of cardiac irARs has three components:

- Treatment of the cardiac complication according to cardiology guidelines
- Immunosuppression for myocarditis, pericarditis or vasculitis
- Temporary or permanent interruption of ICI therapy, according to the nature and severity of the cardiac irAR.[15]

Temporary interruption of ICI therapy is recommended in all cases of suspected cardiac toxicity until the diagnosis has been confirmed or refuted.[15] Patients with suspected myocarditis should receive immunosuppressive treatment while awaiting definitive diagnosis via cardiac MRI or cardiac PET-CT.[15] Significantly reduced rates of major cardiac events have been reported in patients with ICI-associated myocarditis who were treated with high-dose corticosteroids within 24 hours of presentation compared with delayed treatment and/or treatment with lower-dose corticosteroids.[15,18]

A summary of key recommendations from ESMO for the management of ICI-associated cardiac toxicities is shown in **Table 4**.[15]

Management of cardiac toxicities
Myocarditis
Suspected cases of ICI-associated myocarditis should be admitted to level 2 or 3 care with ECG monitoring and resuscitation facilities
Other causes of troponin elevation should be ruled out, including acute coronary syndrome if appropriate
ICI therapy should be interrupted, and in most cases permanently discontinued if myocarditis is confirmed
A diagnostic cardiac MRI with inflammatory sequences and cardiac troponin is recommended for cases of suspected ICI-associated myocarditis
If cardiac PET-CT is not available, endomyocardial biopsy should be considered for suspected myocarditis cases where diagnosis remains uncertain after cardiac MRI and troponin, before restarting ICI therapy
IV methylprednisolone 500-1000 mg/day should be administered for 3 days and then reviewed in confirmed cases of myocarditis
Conversion to oral prednisolone 1 mg/kg/day (maximum 80 mg/day) is recommended if troponin has fallen to normal or <50% of peak after 3 days of IV methylprednisolone, and the patient is clinically stable. Prednisolone dose should then be reduced by 10 mg/week, with troponin monitoring, provided cardiovascular stability continues
A multidisciplinary team discussion is recommended before restarting ICI therapy in patients with mild, clinically uncomplicated myocarditis
Pericarditis
A diagnostic cardiac MRI with inflammatory sequences and cardiac troponin is recommended for cases of suspected ICI-associated pericarditis
Oral prednisolone and colchicine (500 µg twice daily) are recommended for uncomplicated pericarditis
IV methylprednisolone (500-1000 mg) and colchicine (500 µg twice daily) are recommended for pericarditis complicated by moderate or large pleural effusion, along with temporary interruption of ICI therapy. Large pericardial effusions with or without tamponade physiology require urgent percutaneous pericardiocentesis
Heart failure or cardiogenic shock
Should be treated according to European Society of Cardiology heart failure guidelines

Table 4. Summary of ESMO recommendations for the management of ICI-associated cardiac toxicities.[15]

CT = computed tomography; ECG = electrocardiogram; ICI = immune checkpoint inhibitor; IV = intravenous; MRI = magnetic resonance imaging; PET = positron emission tomography.

ASCO 2021 guidelines include definitions of severity grades for ICI-associated cardiac toxicities (see **Table 5**).[4] Cardiac irARs of any grade should be investigated and managed, given the potential for severe clinical consequences.[4] A summary of recommendations for the management of ICI-associated cardiac toxicities is shown in **Table 5**.[4]

Myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure, vasculitis
Grading
Grade 1: Abnormal cardiac biomarker testing without symptoms and with no ECG abnormalities
Grade 2: Abnormal cardiac biomarker testing with mild symptoms or new ECG abnormalities without conduction delay
Grade 3: Abnormal cardiac biomarker testing with either moderate symptoms or new conduction delay
Grade 4: Moderate to severe decompensation, IV medication or intervention required, life-threatening condition
Management
All grades warrant workup and intervention, given the potential for cardiac compromise
Hold ICI therapy for grade 1 elevated troponin and recheck level 6 hours later. Resumption of ICI therapy may be considered once troponin level has normalised or if the change is not considered related to ICI therapy
Hold ICI therapy and discontinue for grade ≥2 events
Consider early initiation (i.e., within 24 hours) of high-dose corticosteroids (1-2 mg/k/day of prednisone, oral or IV depending on symptoms) for patients with grade ≥2 events
Admit patient for cardiology consultation
Management of cardiac symptoms according to American College of Cardiology/American Heart Association guidelines and with guidance from cardiology
Consider immediate transfer to a coronary care unit for patients with elevated troponin or conduction abnormalities
Consider a pacemaker for patients with new conduction delay
Consider early institution of corticosteroids at cardiac transplant rejection doses (methylprednisolone 1 g/day) for patients without an immediate response to high-dose corticosteroids, with the addition of either mycophenolate mofetil, infliximab or antithymocyte globulin. Consider abatacept or alemtuzumab as additional immunosuppression in life-threatening cases

Table 5. ASCO guidelines for the management of ICI-associated cardiac toxicities.[4]

ECG = electrocardiogram; ICI = immune checkpoint inhibitor; IV = intravenous.

ESMO 2022 guidelines recommend baseline measurement of cardiac troponin along with ECG for all patients scheduled to receive ICI therapy.[15] Baseline echocardiography, as well as BNP and cardiac troponin assays, may also be considered for patients with a history of cardiac abnormalities and those receiving combination anti-PD-1/CTLA-4 therapy.[15] However, ASCO 2021 guidelines state there is no clear evidence for routine baseline cardiac troponin and ECG measurement in patients receiving ICI therapy.[4]

EXPERT COMMENT

Patients with irARs often have multiple comorbidities and should ideally be managed jointly with Cardiology and Oncology teams. This may be impractical in smaller centres when the Oncology team may only visit from a tertiary institution. Early discussion with Oncology is still important in these cases. Imaging with MRI or PER-CT and invasive investigation such as angiography may not be possible in some centres and patients may need to travel for these tests or be transferred to the tertiary Cardiology centre for ongoing management. This can potentially delay the start of treatment for these patients.

CASE STUDIES

The case studies presented in **Table 6** and **Table 7** highlight the need for early recognition, evaluation, treatment and triage to decrease morbidity and mortality in patients experiencing cardiac irARs.[1,7,8] In patients receiving ICIs, clinical suspicion should be elevated, but other more common aetiologies (infection, other medications, metastasis) must be ruled out.[1] Patients presenting with irARs should have an oncology follow-up within 1-3 days, as toxicity may continue to develop over days and weeks due to the prolonged kinetics of ICIs.[1]

Patient with ICI-associated myocarditis and myositis	
Clinical presentation	Male patient aged 75 years with stage IV melanoma presented with fatigue, weight loss, back and neck pain and truncal and limb girdle weakness 20 days after receiving a single dose of pembrolizumab
Diagnostic evaluations and results	Initial CK was 13,025 U/L and hs-TNT was 2978 ng/L Cardiac MRI showed mid-wall late gadolinium enhancement in the basal septal and inferoseptal segments without subendocardial enhancement Transthoracic echocardiography showed preserved left ventricular ejection fraction and there were no clinically significant ECG findings, meaning there was no suggestion of acute coronary syndrome Pulmonary function test excluded respiratory muscle involvement
Management	IV pulse methylprednisolone was administered at 1 g/day for 3 days, then at 1 mg/kg for 7 days before transitioning to oral prednisolone Oral mycophenolate mofetil (up-titrated to 1.5g twice daily) was introduced 3 weeks later when hs-TnT and CK remained persistently elevated at 113 ng/L and 513 U/L, respectively CK and hs-TnT normalised 6 weeks after myocarditis diagnosis Prednisolone was weaned over 8 weeks and mycophenolate mofetil was stopped after 6 months

Table 6. Case study of a patient with ICI-associated myocarditis and myositis.[7]
CK = creatine kinase; ECG = electrocardiogram; hs-TNT = high-sensitivity troponin T; MRI = magnetic resonance imaging.

EXPERT COMMENT

This case highlights the non-specific symptoms that patients can present with. A high degree of suspicion is needed – it would be easy in a case such as this to omit any cardiac investigations. Cardiac MRI is a very important imaging tool in suspected myocarditis and should be performed if at all possible, even if patients have to travel for the investigation. The transthoracic echocardiogram here had reportedly showed normal left ventricular function, but the troponin T level was markedly elevated; the cardiac MRI then confirming cardiac involvement. In this case, the cardiac MRI result will have affected the length of the immunosuppressive treatment.

Patient with ICI-associated myocarditis	
Clinical presentation	Male patient aged 65 years with advanced RCC presented with chest pain and dyspnoea following 1 cycle of combination ipilimumab/nivolumab therapy
Diagnostic evaluation	Patient was diagnosed with marked fluid overload and pulmonary oedema Diagnostic workup noted non-specific ST-segment changes on ECG, marked elevation of cardiac markers and new reduced ejection fraction on transthoracic echocardiogram Cardiac MRI noted myopericarditis with late gadolinium enhancement overlying the basal left ventricular lateral wall
Management	Patient was transferred to the Cardiac Care Unit under the care of the cardiology team ICI therapy was permanently discontinued Patient was monitored on continuous telemetry and treated with IV methylprednisolone 1 g/day and diuretic therapy The patient developed complete heart block that was managed with transvenous pacing, however, progressive clinical deterioration followed, resulting in cardiac arrest from which he could not be resuscitated

Table 7. Case study of a patient with ICI-associated myocarditis.[8]
MRI = magnetic resonance imaging; ICI = immune checkpoint inhibitor; RCC = renal cell carcinoma.

EXPERT COMMENT

Sad cases such as this do occasionally occur. Despite the diagnosis being made and appropriate treatment being instituted, the patient died from fulminant myocarditis. ICIs clearly have major clinical benefit. The two cases discussed here, however, serve as a reminder that these treatments do have associated morbidity and mortality. Early recognition and management of potential irARs will minimise their impact.

TAKE-HOME MESSAGES

- Healthcare professionals must be aware that irARs can develop or worsen at any time during ICI therapy, even after treatment has been discontinued[1,2]
- Cardiac irARs are rare but can have serious clinical consequences, including death, meaning that events of any grade must be thoroughly investigated and managed[4-6]
- Treatment for cardiac irARs includes management of cardiac symptoms, immunosuppression for myocarditis, pericarditis or vasculitis, and temporary or permanent interruption of ICI therapy[15]
- Temporary interruption of ICI therapy is recommended for all suspected cardiac irARs until the diagnosis has been confirmed or refuted[15]
- Patients with suspected myocarditis should receive immediate immunosuppressive treatment while awaiting definitive diagnosis[15]
- Early identification of irARs and prompt intervention by a multidisciplinary team is necessary to ensure optimal patient outcomes.[7,8]

EXPERT CONCLUSIONS

The two clinical cases illustrate the diagnostic difficulties with the use of ICIs in terms of cardiac complications. There are several challenges faced. Education of the medical teams is vital so irARs are not overlooked. A multidisciplinary approach to patient management is usually necessary. Access to basic and more advanced investigations is needed. Given the geography of the country, many patients will have to travel for investigations and treatment.

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