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CASE REPORT
Cardiovascular imaging

Steroid-dependent pericarditis following anti-PD1 immunotherapy in a metastatic melanoma patient: a case report

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Background Immune-related adverse events are increasingly prevalent in the oncologist's practice. Cardiac adverse events are rare but can be life-threatening. Case reports of immune checkpoint inhibitor (ICI)–related pericarditis are scarce and so is the scientific evidence for its management. This is the first report of a steroid-dependent pericarditis.

Case summary We present a case of a woman with lung metastatic melanoma who developed pericarditis after two infusions of pembrolizumab. The initial response to steroids and colchicine was favourable, and steroids were successfully tapered, after which the immunotherapy was reintroduced. A complete metabolic remission was achieved after six cycles of pembrolizumab, but pericarditis symptoms recur each time the steroid dose is lowered below 10 mg. After introduction of azathioprine, steroids were successfully tapered over the course of 6 months.

Discussion Because of the chronicity of the pericarditis, it was hypothesized that an underlying auto-immune pericarditis was triggered by the checkpoint inhibitor and the general guidelines for recurrent idiopathic pericarditis were followed, successfully adding azathioprine to taper steroids to stop.

Keywords Immune-related adverse events • Pericarditis • Immune checkpoint inhibitors • Cardiotoxicity • Case report

ESC Curriculum 6.6 Pericardial disease • 6.9 Cardiac dysfunction in oncology patients

Learning points

- Awareness of the possibility of immune checkpoint inhibitor–induced pericarditis is essential for timely diagnosis and management.
- Immune-related pericarditis is reversible in 75% of cases, but a mortality rate of up to 21% is reported.
- Multidisciplinary discussion between cardiologist and oncologist is critical for optimal adverse event management.

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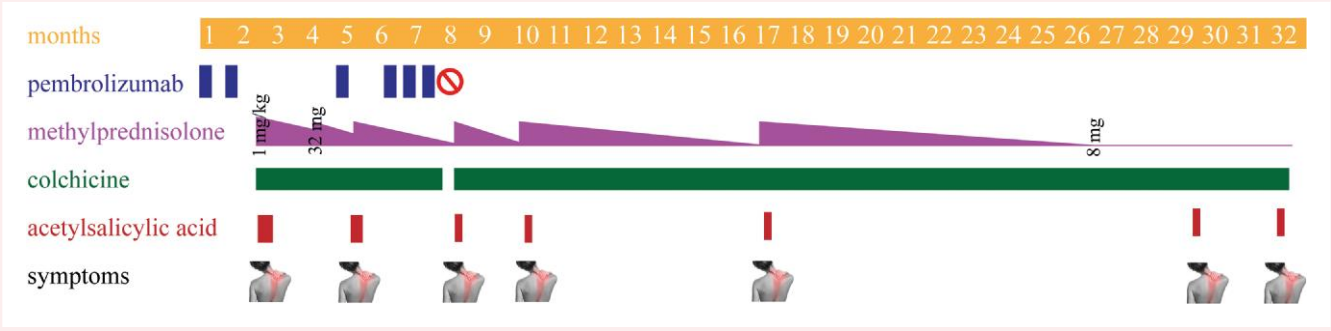
Introduction

Immune checkpoint inhibitior (ICI) can induce autoinflammatory phenomena that can affect any organ system. In addition, it may render subclinical autoimmune syndromes symptomatic. Cardiac adverse events are rare but potentially fatal.[1] We report a case of recurrent pericarditis triggered by ICI.

Timeline



Time course of immunotherapy, pericarditis relapses, and treatment over 32 months. Pembrolizumab administrations are depicted as blue bars. Red stop sign illustrates permanent cessation of pembrolizumab. Steroid courses are shown as purple triangles illustrating taper. Colchicine treatment is shown as green bar and acetylsalicylic acid courses are shown as red bars.

Case presentation

A 50-year-old woman with no significant past medical history was diagnosed in 2014 with a lung, bone, and skin metastatic v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) V600E–mutated melanoma and was treated with *BRAF*/mitogen-activated protein kinase kinase enzyme (*MEK*) inhibition and zoledronic acid. Four years later, positron emission tomography–computed tomography (PET–CT) confirmed progressive disease and she was switched to anti–protein cell death protein 1 (PD-1) therapy (three-weekly pembrolizumab 200 mg).

Shortly after the second administration, the patient presented to the emergency department with pleuritic chest pain radiating to the interscapular and cervical region. She was afebrile, haemodynamically stable, and saturating normally. Clinical examination was unremarkable. An electrocardiogram (ECG) showed a sinus rhythm without conduction or ST abnormalities. Blood work showed a moderate C-reactive protein (CRP) rise of 39 mg/L (normal <5 mg/L) without leucocytosis. D-dimers were low. A chest X-ray showed no acute changes. High-sensitive troponin T levels were elevated at 27.9 ng/L (normal <14 ng/L) with serial values 3 h later not increasing (26.3 ng/L). A viral infection was assumed, and she was discharged home.

The following night, she was readmitted because of worsening symptoms, with sharp chest pain in a recumbent position. She now was tachycardic at 109/min. A follow-up ECG showed concave ST elevation in the anterolateral and inferior leads (*Figure 1*). Pulmonary embolism was excluded with computed tomography angiography, which showed a pericardial effusion and progression of the known metastatic lung nodules and bilateral pleural effusion. A transthoracic echocardiography showed a normal systolic function without regional wall motion abnormalities and confirmed a pericardial effusion without haemodynamic significance. High-sensitive troponin T levels increased to 194 ng/L. Autoimmune work-up showed normal antinuclear antibody levels and a slightly elevated rheumatoid factor at 176 IU/mL (normal <15.9 IU/mL). A nasopharyngeal swab was negative for common respiratory pathogens, and serology for cytomegalovirus (CMV), Epstein–Barr virus (EBV), human immunodeficiency virus (HIV), and hepatitis A, B, and C was negative. The working diagnosis of immune-related (IR) perimyocarditis was made, and she was started on acetylsalicylic acid (ASA), colchicine 0.5 mg twice daily, and 1 mg/kg of methylprednisolone. Her symptoms resolved within a day and steroids were tapered over the course of 4 weeks. Troponin levels returned to normal.

Upon reduction of the steroid dose below 20 mg, she experienced a relapse of pain without ECG changes. A cardiac magnetic resonance imaging (MRI) showed a thickened pericardium with diffuse hyperintense signal alterations on short-axis T2-weighted short-tau inversion recovery (STIR) images and diffuse contrast uptake on late gadolinium enhancement (LGE) images, consistent with an acute pericarditis (*Figure 1*). There was no evidence of myocarditis on MRI. Steroids were increased again.

She experienced several symptomatic flare-ups during steroid tapering (*Timeline*), always responding to an increase in methylprednisolone in combination with ASA. After 4 months, steroids were tapered to 4 mg daily and a pembrolizumab rechallenge was attempted. Two weeks later, symptoms recurred, and she was restarted on ASA with increased doses of steroids. After steroid taper, pembrolizumab was restarted for three more cycles. Colchicine was stopped after 6 months. Two weeks after stopping colchicine, her symptoms recurred and steroids, ASA, and colchicine were restarted. A PET–CT showed a complete metabolic remission, and pembrolizumab was not rechallenged. A cardiac MRI after resolution of symptoms showed regression of the pericardial contrast uptake (*Figure 2*).

Since then, the patient has been in follow-up for 3 years without signs of disease progression. Reducing the methylprednisolone dose below 8 mg daily appeared impossible without relapse pericarditis symptoms.

Her case was presented at a Belgian ImmunoTOXicity (BITOX) board meeting, a meeting between oncologists and organ specialists where complex IR toxicities or comorbidities complicating the initiation of immunotherapy are discussed. Because of the chronicity of the pericardial disease continuing years after cessation of ICI, it was hypothesized that this was an underlying autoimmune pericarditis rendered symptomatic by anti–PD-1 therapy. The frequent relapses are consistent with literature findings on steroid therapy in chronic recurrent pericarditis. Azathioprine treatment was initiated at a dose of 2 mg/kg, and steroids were tapered successfully over 6 months. Azathioprine maintenance treatment is considered for 6 months.

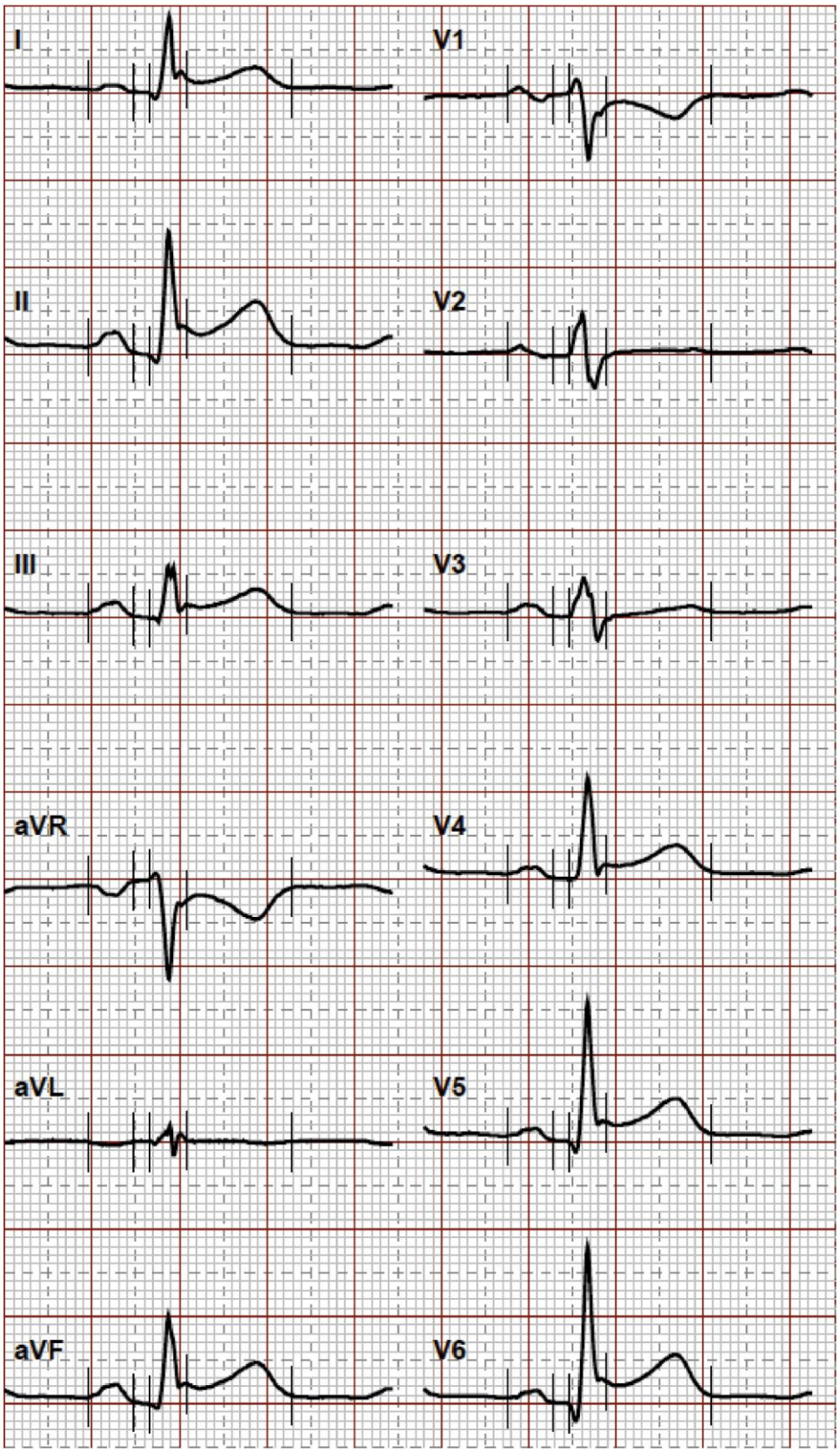


Figure 1 Electrocardiogram showing concave ST elevations in anterolateral and inferior leads.

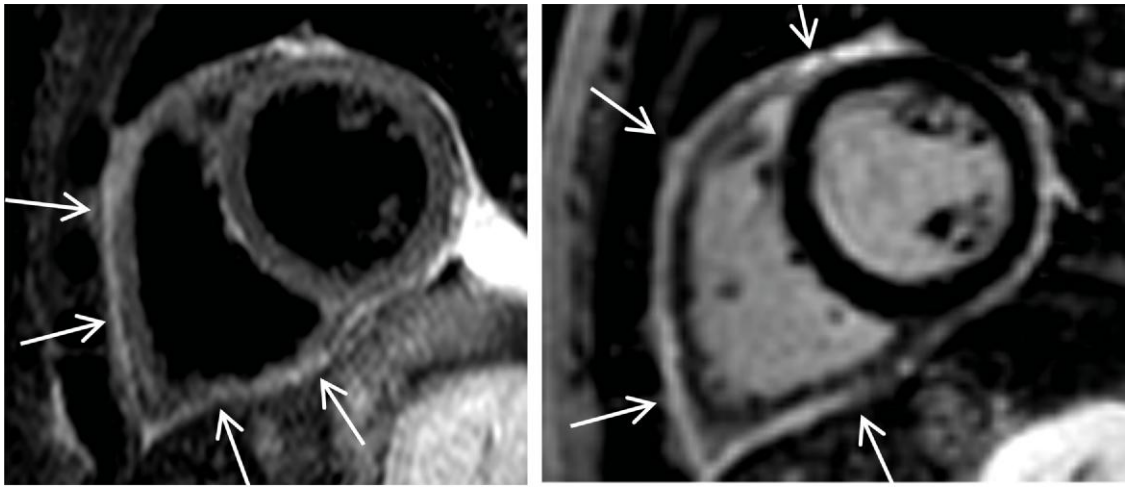


Figure 2 Cardiac magnetic resonance imaging. Left, short-tau inversion recovery images; right, late gadolinium enhancement images. Arrows indicate the thickened pericardium.

Table 1 Published guidelines on management of ICI-related pericarditis of grade 2[a] or higher

ASCO guidelines (eight)	**Acute:** ICI discontinuation, high-dose corticosteroids (1–2 mg/kg/day of prednisone), management of cardiac symptoms according to ACC/AHA guidelines
	Refractory: consider methylprednisolone 1 g, addition of MMF, infliximab, or ATG. Infliximab higher than 5 mg/kg in patients with moderate to severe heart failure is contraindicated. Consider abatacept or alemtuzumab in life-threatening cases
ESMO guidelines (four)	**Acute:** ICI discontinuation, high-dose corticosteroids
	Refractory: infliximab, MMF, or ATG
ESC guidelines (seven)	**Acute:** ICI discontinuation, high-dose corticosteroids with or without colchicine and/or NSAID, pericardiocentesis in case of tamponade
	Refractory: immunosuppressive drugs

ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; ESC, European Society of Cardiology; ICI, immune checkpoint inhibition; ACC/AHA, American College of Cardiology/American Heart Association; MMF, mycophenolate mofetil; ATG, antithymocyte globulin; NSAID, non-steroidal anti-inflammatory drug.
[a]Grading according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 5.0.

Discussion

Imuune Checkpoint Inhibitor-associated pericarditis is a rare but relevant entity. A systematic review of ICI-associated toxicity reports an incidence of 0.3% of pericardial toxicity, defining three presentations (pericarditis, pericardial effusion, cardiac tamponade).[1] A recent safety meta-analysis of 48 randomized controlled trials (all of which consisted of at least 1 ICI arm and 1 control arm) including 29 592 patients reported an incidence of pericardial events as high as 8.3/1000 patients.[2]

A single-centre retrospective study compared 2842 patients who received ICI with 2366 matched patients who did not.[3] The authors report an incidence rate of 1.57 per 100 person-years of pericardial events in the ICI group compared with 0.14 events in the control group, suggesting a four-fold increase in risk after adjusting for potential confounders. Comparing patients on ICI who developed pericardial disease with patients on ICI who did not, they found no difference in baseline cardiovascular risk factors, cancer type, class or combination of ICI, or the number of cycles. Pericarditis seemed to occur more frequently in patients with lung cancer, potentially accounted to prior chest radiotherapy.[4] A systematic review of the published ICI-associated pericardial disease case reports noted reversibility in 75% with a 7% mortality rate,[5] whereas other authors mention mortality rates up to 21%.[1]

Immune-related pericarditis is a diagnosis of exclusion with differential diagnoses being malignant involvement of the pericardial sac and infections. The general diagnostic criteria for pericarditis require at least two of the following: sharp pleuritic chest pain relieved by sitting up and leaning forward, a pericardial friction rub, a widespread ST segment elevation on ECG, and/or a new or worsening pericardial effusion.[6] The most common symptom is shortness of breath.[1] A median time to onset of 30 days [interquartile range (IQR) 85–90] after starting ICI is commonly cited.[7]

There are no prospective studies on management of IR pericarditis. Both the European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines[4,8] group the management of all cardiovascular toxicities, and the European Society of Cardiology (ESC) guidelines are not specific about the type of additional immunosuppressive drug[7] (*Table 1*). In contrast to idiopathic acute pericarditis, where steroids are limited to patients with refractory symptoms or contraindications to NSAIDs, in moderate to severe IR

acute pericarditis, corticosteroids are advised as first-line treatment to counter the autoinflammatory syndrome. Non-steroidal anti-inflammatory drugs and colchicine might suffice in case of asymptomatic or mild (grade 1) pericarditis. The relative risk for invasive management of pericardial effusions seems increased in ICI-treated patients vs. those not receiving ICI.[5]

Considering the hypothesis that the presentation of our patient was compatible with a subclinical autoimmune recurrent pericarditis triggered by ICI, she was treated as 'recurrent idiopathic pericarditis'. Idiopathic pericarditis can become recurrent in about 15–30% of cases. In the absence of specific guidelines on the management of recurrent ICI-related pericarditis, management was based on the 2015 ESC guidelines on chronic and recurrent pericarditis, recommending non-steroidal anti-inflammatory drugs (NSAIDs), colchicine for 6 months, and steroids with a slow taper lowering 1 to 2 mg every 2 to 4 weeks. The use of azathioprine, methotrexate, immunoglobulins, and anakinra in case of refractory symptoms has been reported.[9]

Rechallenging ICI following IR pericardial events can be considered after balancing comorbidities, the risk of recurrent adverse events, the response to therapy, and the alternative treatment options. We strongly advocate multidisciplinary discussion of these cases regarding management and possible ICI rechallenge.[7]

Lead author biography

Marthe is a Belgian medical oncologist in training at the University Hospital of Leuven. She is currently working on a PhD in the University Hospital of Brussels focusing on toxicity of immunotherapy.

Supplementary material

Supplementary material is available at *European Heart Journal—Case Reports*.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The patient provided informed consent for publication in accordance with the Committee on Publication Ethics (COPE) guidelines.

Conflict of interest: None declared.

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