

# Metastatic squamous cell carcinoma to the heart: an unusual cause of ST elevation—a case report

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## Background

Cardiac tumours are typically secondary in nature, and the most common malignancies metastasizing to the heart are cancers of the lung, breast, oesophagus, melanoma, and lymphoma. We present a unique case of squamous cell carcinoma of the tongue, metastasizing to the heart and manifesting with ST elevation in the inferior-leads on electrocardiogram (ECG).

## Case summary

A 25-year-old woman was initially diagnosed with squamous cell carcinoma of the tongue at the age of 23 and treated with hemi-glossectomy with clear-margins. Sixteen months later, the tumour recurred in the oropharynx and the left upper lobe of the lung. She was treated with chemotherapy; however, the tumour progressed. Thus, she was initiated on immunotherapy and radiation therapy. One month later, she presented with chest pain. Electrocardiogram revealed ST elevation in the inferior-leads. Troponin-I was elevated. Transthoracic echocardiogram revealed focal areas of thickening within the left and right ventricular myocardium with associated hypokinesia. These findings suggested ECG changes were likely secondary to infiltrative metastases and not acute-coronary-syndrome. Cardiac magnetic resonance imaging showed infiltrative masses with increased T2-signal and heterogeneous enhancement on perfusion and delayed enhancement sequences. Imaging also demonstrated numerous extra-cardiac metastases. She was treated with analgesics and discharged to home hospice.

## Discussion

Head and neck cancers are a rare cause of cardiac metastasis. ST elevation and troponin release are thought to be due to tumour extension into the myocardium. Cardiac metastases usually present in patients with advanced widespread malignancy. In a cancer patient with cardiac symptoms or ECG changes, it is important to consider a broad differential diagnosis and entertain the possibility of cardiac metastasis.

## Keywords

Case report • Cardiac metastases • Cardiac magnetic resonance imaging • Squamous cell carcinoma • ST elevation myocardial infarction (STEMI) • Cardio-oncology

## Learning points

- Squamous cell carcinoma of the oropharynx can metastasize to the heart. Echocardiogram and cardiac magnetic resonance imaging are useful in establishing a diagnosis of cardiac metastases.
- A clinician should review the differential diagnosis of ST elevation on electrocardiogram in a patient presenting with chest pain, in particular in the context of current or recent malignancy.

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## Introduction

Cardiac malignancies are typically secondary to metastatic disease rather than a primary process.<sup>1</sup> Due to the silent nature of cardiac metastases, the diagnosis is often missed pre-mortem but rather found on autopsy.<sup>2</sup> The most common malignancies spreading to the heart are cancers of the lung, breast, oesophagus, melanoma, and lymphoma. Head and neck cancers are noted to frequently metastasize to the cervical lymph nodes but are rare to cause distant metastasis, including to the heart.<sup>3</sup> We present a unique case of squamous cell carcinoma of the tongue, which metastasized to the heart and manifested with ST-segment elevation in the inferior leads on electrocardiogram (ECG).

## Timeline

October 2015	<ul style="list-style-type: none"> <li>Presented with a painless white papular lesion on the tongue</li> <li>Biopsy positive for moderately-differentiated squamous cell carcinoma</li> </ul>
December 2015	<ul style="list-style-type: none"> <li>Whole body positron emission tomography (PET) scan negative for metastatic disease</li> <li>Underwent surgical resection with clear margins and no involvement of cervical lymph nodes (0/19)</li> </ul>
February 2017	<ul style="list-style-type: none"> <li>Presented with pain and swelling on the right side of the face</li> <li>Underwent removal of a 4.3 cm mass with extracapsular extension and negative lymph node involvement</li> <li>Whole body PET scan showed left peribronchial mass</li> <li>Biopsy of peribronchial mass consistent with metastasis</li> </ul>
March 2017	<ul style="list-style-type: none"> <li>Initiation of chemotherapy with carboplatin, paclitaxel, and cetuximab</li> </ul>
June 2017	<ul style="list-style-type: none"> <li>Found to have metastases to lymph nodes, soft tissues, and bone</li> </ul>
September 2017	<ul style="list-style-type: none"> <li>Started Pembrolizumab</li> </ul>
November 2017	<ul style="list-style-type: none"> <li>Started radiation therapy to the head and neck totalling 4000 cGy over 16 treatments</li> </ul>
8 December 2017	<ul style="list-style-type: none"> <li>Emergency Department presentation for progressively worsening right shoulder and chest pain associated with right arm numbness, cough, and dyspnoea</li> <li>Chest radiography consistent with infiltrate in the left lower lung and worsening of a known left upper lobe cavitary lesion and a new right clavicular lesion</li> <li>Electrocardiogram: ST elevation in the inferior leads with T wave inversion in the inferolateral leads</li> <li>Troponin I peaked at 0.29 ng/L (normal &lt;0.05 ng/L)</li> <li>Differential diagnosis included acute coronary syndrome, myocarditis, and Takotsubo cardiomyopathy</li> </ul>
9 December 2017	<ul style="list-style-type: none"> <li>Transthoracic echocardiogram showed thickening of the right ventricular free wall, mid inferior, and inferoseptal left ventricular myocardium with associated hypokinesis and a highly mobile pedunculated echodensity measuring 0.6 cm × 0.6 cm protruding from a region of inferior wall myocardial thickening</li> </ul>
11 December 2017	<ul style="list-style-type: none"> <li>Cardiac magnetic resonance imaging (MRI) showed infiltrative masses within four separate regions of the left and right ventricular myocardium and a ventricular thrombus</li> <li>Cardiac MRI consistent with metastatic disease to the heart</li> </ul>
15 December 2017	<ul style="list-style-type: none"> <li>Discharged with referral to home hospice</li> </ul>

of the lung. She was treated with a regimen containing carboplatin, paclitaxel, and cetuximab. The tumour progressed to submandibular lymph nodes, soft tissues, and lumbar vertebral body. She was initiated on immune checkpoint inhibitor pembrolizumab and radiation therapy.

A detailed social and family history was taken in an attempt to understand the aggressiveness of her cancer. She worked in a private company involved in the environmental cleaning of lakes and ponds and was exposed to a significant amount of chemicals, including herbicides and pesticides. She has a scant history of smoking: half a pack per day for roughly 1.5 years. She drank alcohol socially on the weekends. Her maternal grandmother died from brain cancer. There was no other family history of cancer. Genetic testing was not performed.

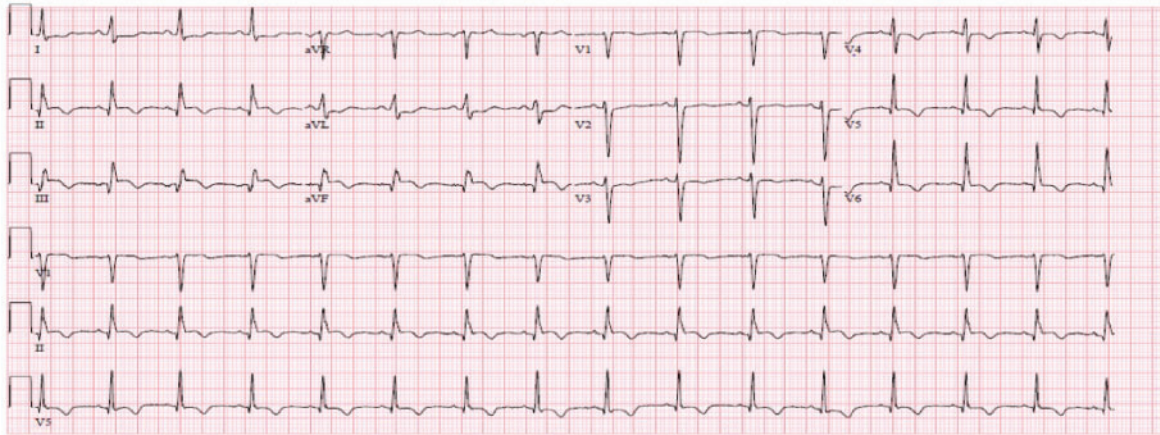
Within 1 month of starting radiation therapy, she presented with progressively worsening severe, sharp, constant pain of the right shoulder and chest associated with right arm numbness, cough pro-

## Case presentation

A 25-year-old Caucasian woman was initially diagnosed with invasive moderately differentiated squamous cell carcinoma of the tongue at the age of 23. She was treated with hemi-glossectomy with clear margins and had no involvement of cervical lymph nodes. Sixteen months later, the tumour recurred in the oropharynx and the left upper lobe

ductive of clear sputum, and dyspnoea on exertion. Pain was exacerbated by right arm movement. She denied any trauma, travel, or oedema of the arm.

On examination, she appeared frail with evidence of weight loss. She had a heart rate of 86 b.p.m. and blood pressure of 121/74. On auscultation, coarse rales and rhonchi were present in the left lower lung field. Cardiac exam revealed a regular rhythm with no murmurs,



**Figure 1** Electrocardiogram revealing ST elevation in the inferior leads and T wave inversion in the anterolateral leads.

gallops, or rubs. She had tender right supraclavicular lymphadenopathy. Additionally, she had swelling in the right suprascapular region and erythema of the overlying skin. Admission ECG showed ST elevation in the inferior leads and T wave inversions in the anterolateral leads (Figure 1). Blood work was significant for an elevated troponin I, which peaked at 0.29 ng/L (normal <0.05 ng/L). The rest of her labs were unremarkable except for Hb 9.2 g/dL (normal 12–16 g/dL), Hct 28.8% (normal 35–47%), total calcium 10.5 mg/dL (normal 8.9–10.4 mg/dL), and ionized calcium 1.51 mmol/L (normal 1.14–1.33 mmol/L). Subsequent ECGs continued to demonstrate ST-segment elevation without resolution. A chest radiograph revealed a retrocardiac opacity concerning for left lower lobe pneumonia, worsening of a known left upper lobe cavitory lesion, and a new right clavicular lesion. Differential diagnosis at this point included myocarditis due to pembrolizumab, acute coronary syndrome (ACS), and Takotsubo cardiomyopathy in a cancer patient.

A transthoracic echocardiogram (TTE) was performed, and it revealed focal areas of myocardial thickening within the basal to mid inferior and inferoseptal myocardium with associated hypokinesis (Figure 2 and Supplementary material online, Video S1). In addition, there was a highly mobile pedunculated echodensity, measuring 0.6 cm × 0.6 cm, which was adherent to and protruding from a region of inferior wall myocardial thickening (Supplementary material online, Video S1). There was thickening of the right ventricular free wall as well. These findings were concerning for metastatic tumour implants within the myocardium with a mobile component within the left ventricular cavity, concerning for thrombus. There was also pericardial thickening and a small pericardial effusion. The TTE findings suggested that the ECG changes were likely secondary to infiltrative cardiac metastases, and as such, ACS was not felt to be the diagnosis. The chest pain was managed with analgesia.

To further characterize the lesions, cardiac magnetic resonance imaging (MRI) was performed. Cardiac MRI revealed infiltrative masses within four separate regions of the left and right ventricular myocardium (Figure 3). These masses demonstrated increased T2 signal and heterogeneous enhancement on perfusion and delayed

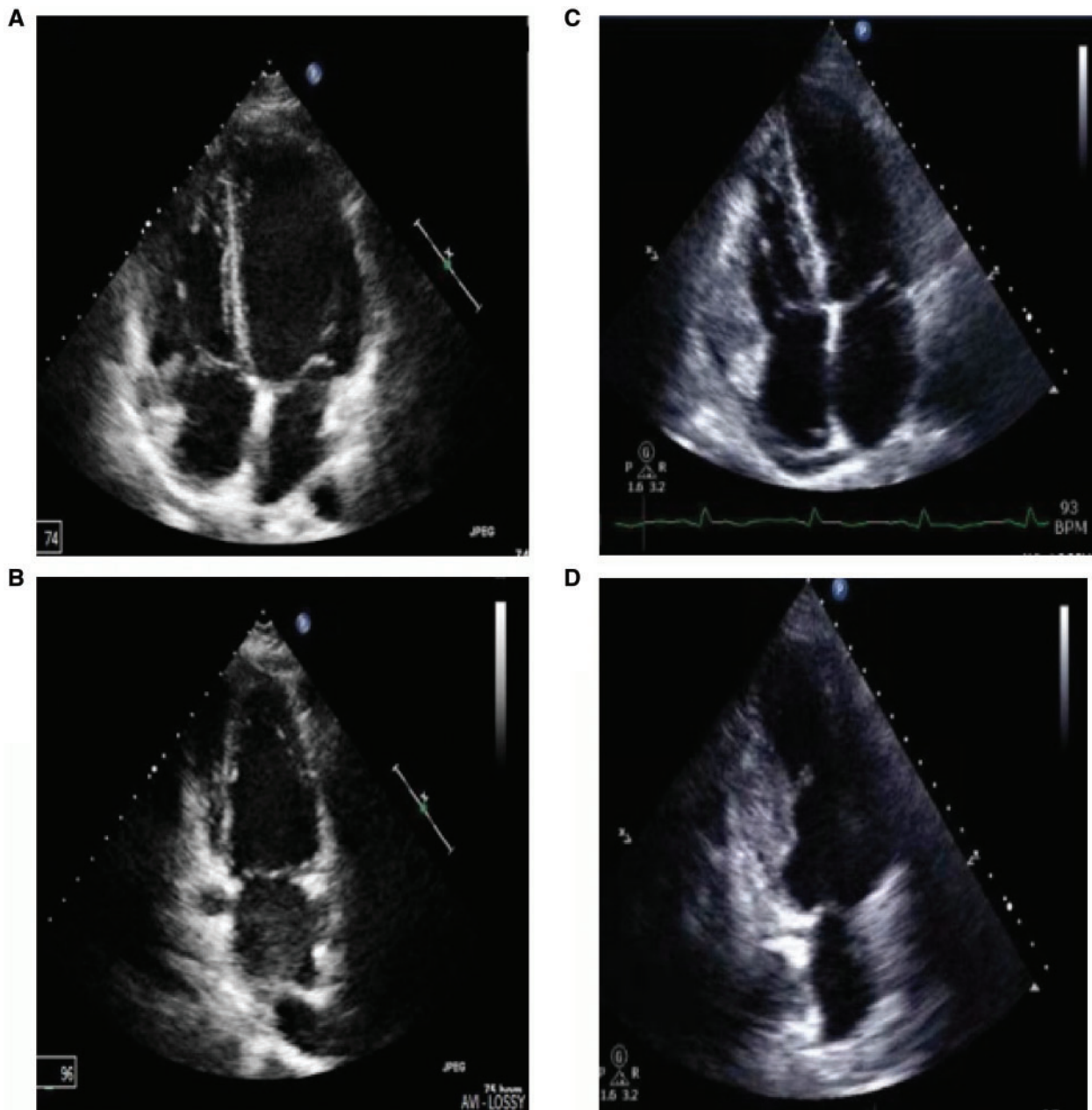
enhancement sequences (Supplementary material online, Figure S1). The areas of infiltrative masses within the myocardium had associated hypokinesis, particularly notable in the inferior wall of the left ventricle. There was a 0.9 × 0.8 cm focus of intraventricular thrombus adherent to the inferior wall.

Further imaging with computed tomography (CT) scan revealed multilobulated, heterogeneous enhancement within the right trapezius muscle, indicative of intramuscular metastatic disease, which likely explained her right shoulder pain. There were lytic lesions within the right clavicle. Metastatic lesions were present in bilateral lung apices. There was interval development of a centrally necrotic 3.7 cm left adrenal mass, indicative of adrenal metastatic disease, which was not present on prior CT scan dated 4 months prior. After treatment of pneumonia and hypercalcaemia, she was referred to home hospice given her poor prognosis.

## Discussion

The most common tumours that metastasize to the heart are cancers of the lung, breast, oesophagus, malignant lymphoma, leukaemia, and melanoma.<sup>4</sup> Head and neck cancers are a rare cause of cardiac metastasis.<sup>3</sup> The mechanism by which oral squamous cell carcinoma spreads to the heart is poorly understood. When it does metastasize to the heart, the following cardiac tissues are affected in decreasing order of frequency: pericardium, myocardium, epicardium, and endocardium. To our knowledge, there have been only 10 other reports whereby metastatic oral squamous cell carcinoma to the heart was diagnosed in living patients.<sup>1, 3–5</sup>

Metastatic involvement of the heart occurs in approximately 8% of patients with a cancer diagnosis as evidenced by post-mortem autopsy.<sup>6</sup> However, this diagnosis is often missed in living patients because of its clinically silent nature.<sup>7</sup> Often, these metastatic lesions are diagnosed on routine surveillance imaging. Symptoms, when present, depend upon the location and size of the mass and usually occur due to the involvement of the pericardium, endocardium, or the



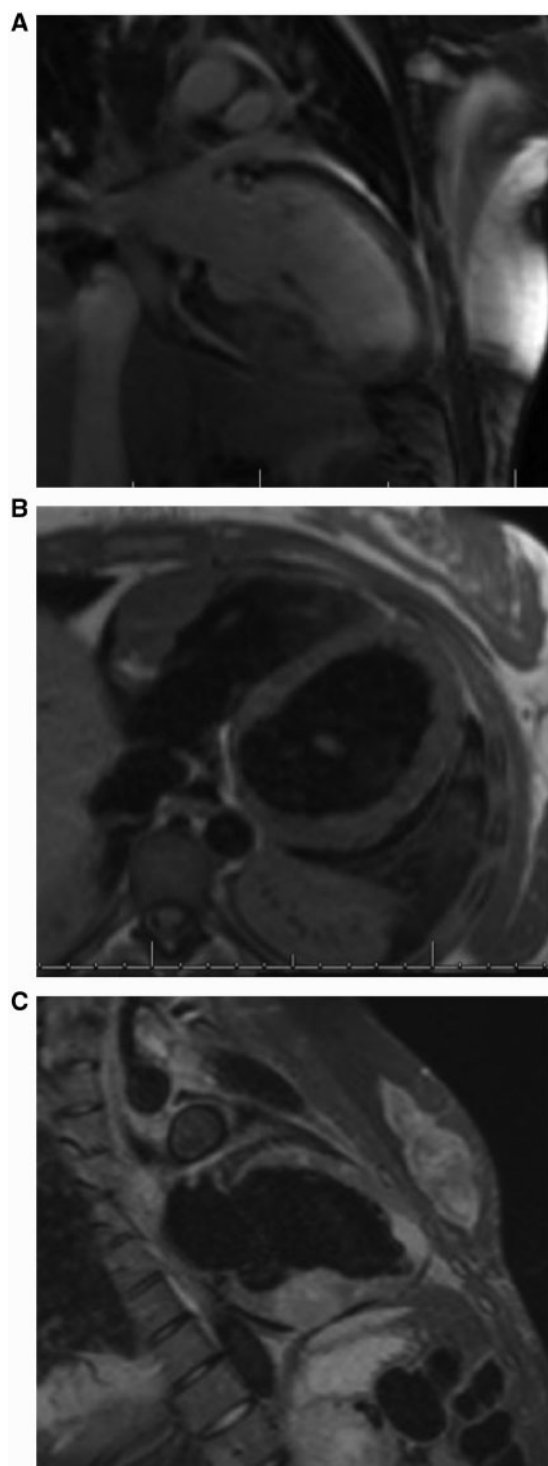
**Figure 2** (A and B) Transthoracic echocardiogram 4 months prior to presentation was a normal study. (C and D) Transthoracic echocardiogram during hospitalization showed focal areas of myocardial thickening and associated hypokinesis with an adherent, mobile echodensity attached to the mid inferior myocardium (\*) (also see [Supplementary material online, Video S1](#)).

intracardiac conduction fibres. A high degree of suspicion is required for the diagnosis of cardiac metastasis since patients are often asymptomatic, particularly in the early stages.

Of the 10 total cases of metastatic oral squamous cell carcinoma to the heart reported, three were found incidentally on routine surveillance imaging.<sup>1, 3–5</sup> As the tumours progress in size within the heart, patients may present with chest pain, valvular abnormalities, heart failure, cardiogenic shock, or tamponade.<sup>5</sup> Electrocardiogram

changes may occur, including ST-segment changes along with troponin elevation due to tumour extension in the myocardium.<sup>4</sup> If the tumour invades into the conduction system, tachy- or bradyarrhythmias may develop.<sup>2</sup> Other complications of cardiac metastasis have been reported to include emboli to the brain or lung.<sup>2</sup> The size and location of the tumour within the heart determine symptom manifestation.<sup>2</sup> Among the cardiac manifestations, pericardial metastases are often diagnosed first due to the development of





**Figure 3** Cardiac magnetic resonance imaging. Left [two-chamber steady-state free precession (SSFP) sequence], middle (T2-weighted inversion recovery image in vertical long axis), and right (axial T1-weighted image) demonstrate infiltrative soft tissue masses within the myocardium (also see [Supplementary material online, Figure S1](#)). Various lesions are noted: A:  $2.6 \times 3.7$  cm mass within the inferior and inferoseptal wall of the left ventricle; B:  $2.2 \times 1.4$  cm mass in left ventricular apex; C:  $2.3 \times 4.2$  cm mass within the lateral free wall of the right ventricle towards the base.

pericardial effusion and clinical tamponade.<sup>2, 7</sup> Unfortunately, the presence of cardiac metastases is usually the result of widespread advanced disease. Even when surgery is offered, treatment is customarily palliative.<sup>6</sup> Given the lack of evidence, there is an unclear role for chemotherapy or radiation in the setting of cardiac metastasis.<sup>4</sup>

When a cancer patient presents with ST elevation on ECG, it is important to consider a wide range of differential diagnoses (*Table 1*). First, ACS must be considered because a cancer patient has an increased risk for acute myocardial ischaemia. The factors accounting for the elevated risk in a cancer patient are as follows: the inflammatory and pro-coagulant milieu of cancer, coronary ischaemia induced by certain cancer drugs, possible radiation-induced injury to coronary arteries, and underlying cardiovascular risk factors.<sup>6, 8–10</sup> The cancer drugs that have been reported to cause myocardial ischaemia include 5-Fluorouracil (5-FU), capecitabine, cisplatin, tyrosine kinase inhibitors (TKI), and vascular endothelial growth factor inhibitors. The pathophysiology of 5-FU-induced myocardial ischaemia is not entirely understood. Proposed mechanisms involve endothelial damage, impaired NO production, coronary vasospasm, and increase in von-Willebrand factor, which enhances platelet aggregation and thrombotic occlusion.<sup>8</sup> Cisplatin, a platinum based chemotherapy, has been reported to cause vascular injury by direct endothelial damage, decreased activity of protein C (anticoagulant), increased von-Willebrand factor, and hypomagnesemia. Certain TKI, such as nilotinib and ponatinib, have been associated with vascular toxicity by causing endothelial damage and exhibiting pro-atherogenic and anti-angiogenic effects coupled with pro-coagulant effects via platelet activation.<sup>9</sup> Vascular endothelial growth factor inhibitors may lead to decreased microvascular density, apoptosis of cardiac myocytes and depressed cardiac function.<sup>10</sup>

Reports of Takotsubo cardiomyopathy associated with chemotherapy have been described in the literature. In particular, 5-FU, capecitabine, bevacizumab, rituximab, and TKI (such as axitinib and sunitinib) have been associated with reversible cardiac dysfunction in the pattern of Takotsubo cardiomyopathy.<sup>11</sup> Electrocardiogram findings in patients with Takotsubo cardiomyopathy mimic those seen in anteroapical ST elevation myocardial infarction (STEMI). However, reciprocal ST depressions are often absent.<sup>12</sup> In one study of Takotsubo cardiomyopathy, T wave inversions were more common (60%) than ST elevations (13.3%).

The differential diagnosis of ST elevation in a cancer patient also includes myopericarditis. Immunotherapy drugs such as anti-CTLA-4 (ipilimumab) and anti-PD-1 (pembrolizumab, nivolumab) have been associated with the development of myopericarditis.<sup>13</sup> PD-1 is known to have protective effects against tissue inflammation and myocyte damage.<sup>13</sup> Inhibiting PD-1 has been shown to increase inflammation and cytotoxic activity via CD8+ T cells. PD-1 deficiency has also been shown to increase the incidence of spontaneous myocarditis in mice.<sup>13</sup> Radiation-induced myopericarditis is due to protein-rich exudative fluid that accumulates within the pericardial cavity.<sup>6</sup> Cardiac myocytes initiate an inflammatory response via activation of macrophages when exposed to radiation.<sup>6</sup> Radiation-induced myocardial fibrosis can also be seen as a later complication, usually months to years later. The pathophysiology involves the increased number of myofibroblasts, which enhance collagen synthesis and deposition within the myocardium.<sup>6</sup> Typical ECG changes of pericarditis are diffuse ST elevation without reciprocal ST depressions.<sup>12</sup> The ST elevation is concave

**Table 1** Differential diagnosis of ST elevation in a cancer patient

Differential diagnosis	Mechanism	ECG features
STEMI (ST elevation myocardial infarction)	Increased thrombogenesis, chemotherapy or targeted drug side effect, radiation-induced injury to coronary arteries, and predisposing CAD risk factors <i>Potential aetiologic agents:</i> 5-FU, capecitabine, cisplatin, tyrosine kinase inhibitors, and vascular endothelial growth factor inhibitors	a. ST elevation convex upward, fuses with T wave to form a dome b. Reciprocal ST depression
Takotsubo cardiomyopathy	Physiologic or emotional stress, chemotherapy or targeted drug side effect, or surgery leading to an increase in catecholamines and a reversible contractile dysfunction <i>Potential aetiologic agents:</i> 5-FU, capecitabine, bevacizumab, rituximab, and tyrosine kinase inhibitors (i.e. axitinib and sunitinib)	a. ST elevation in the anterior leads (V2–V4) typically without reciprocal changes b. T wave inversion
Myopericarditis	Immunotherapy: Inhibiting PD-1 has been shown to increase inflammation and cytotoxic activity via CD8+ T cells. Radiation therapy can cause pericardial and myocardial inflammation/adhesion/fibrosis <i>Potential aetiologic agents:</i> pembrolizumab, nivolumab, and ipilimumab	a. PR depression >1 mm b. Diffuse ST elevation without reciprocal changes
Myocardial metastasis	Tumour spreads haematogenously and produces tumour implants in the myocardium, causing transmural myocardial damage	Persistent ST elevation without typical evolutionary changes of infarct
Hyperkalaemia	Rapid destruction of tumour cells during chemotherapy causing excess potassium to escape from the intracellular compartment leading to hyperkalaemia	a. Narrow-based, peaked T waves pulling the ST segment b. Widening of the QRS c. ST elevation in V1–V3, often downsloping
Pulmonary embolism	Hypercoagulable state due to increased generation of pro-coagulant factors by tumour cells. Certain chemotherapy, surgery, post-operative period, and central venous catheters increase risk <i>Potential aetiologic agents:</i> thalidomide, lenalidomide, bevacizumab, and erythropoiesis-stimulating agents	a. T-wave inversion in V1 and V2 plus at least one of the following: T wave inversion in lead III, the precordial lead with the deepest T wave inversion is V1 or V2 b. ST elevation in aVR and ST depression in lead I; ST elevation in V1–V3 and/or ST depression in V4–V6

upward, and T wave changes and Q waves are usually absent.<sup>12</sup> Electrocardiogram findings of myocarditis can be similar to those of pericarditis or mimic a STEMI pattern.<sup>12</sup>

ST elevation due to metastatic lesions within the myocardium is characterized by the persistence of ST-segment changes and absence of the typical evolutionary pattern of infarct, such as the development of Q waves in consecutive ECGs. The mechanism of ST elevation is unclear; however, autopsy findings in one study demonstrated that transmural myocardial damage by tumour infiltration is thought to be the cause. Furthermore, tumour cells were noted to invade the myocardium without evidence of myocardial necrosis. This observation might explain the lack of typical evolutionary changes that are seen with acute myocardial infarction. This finding may help differentiate acute injury pattern from ischaemia vs. tumour infiltration.

Hyperkalaemia can occur in cancer patients as a result of chemotherapy-induced tumour lysis syndrome. Several ECG changes can be seen, including narrow-based, peaked T waves,<sup>12</sup> ST elevation in the anterior leads, and ST depression in the inferior leads.<sup>4</sup> The downward sloping of the ST segment can help distinguish between hyperkalaemia-induced ST elevation and that caused by an acute coronary occlusion.<sup>12</sup>

Cancer-associated hypercoagulability can lead to an increased risk of venous thromboembolism.<sup>14</sup> Cancer cell-specific prothrombotic factors, such as tissue factor, coupled with host cell inflammatory response contribute to this procoagulant state.<sup>14</sup> One potential consequence of this procoagulant state is an acute vascular event, such as an acute myocardial infarction as described above. Another consequence is pulmonary embolism. Some chemotherapy agents confer risk of venous thromboembolism. These drugs include thalidomide particularly in combination with dexamethasone or doxorubicin, lenalidomide, bevacizumab, and erythropoiesis-stimulating agents.<sup>15</sup> The ECG changes of pulmonary embolism typically include an right ventricular strain pattern (T-wave inversion in V1 and V2 plus at least one of the following: T wave inversion in lead III, the precordial lead with the deepest T wave inversion is V1 or V2). Less commonly, right ventricular injury pattern may be seen: ST elevation in aVR and ST depression in lead I; ST elevation in V1–V3 and/or ST depression in V4–V6.<sup>12</sup>

Our patient presented with chest pain and new ST elevations on ECG. These ST-segment changes did not evolve in a typical STEMI fashion. Additionally, the lack of traditional cardiovascular risk factors and the atypical nature of chest pain steered us away from the diagnosis of an acute ST elevation myocardial infarction even though

cancer patients are at an increased risk of developing acute thrombotic vascular events. Cardiac imaging with TTE and cardiac MRI revealed the presence of myocardial metastatic lesions. In a cancer patient presenting with new ST elevations on ECG, a broad differential diagnosis must be considered.

## Conclusion

Squamous cell carcinoma of the head and neck is a rare cause of cardiac metastasis. The mechanism by which squamous cell carcinoma spreads to the heart is poorly understood. When it does metastasize to the heart, the following tissues are affected in decreasing order of frequency: pericardium, myocardium, epicardium, and endocardium. ST-segment elevations and troponin leak are thought to be due to tumour extension into the myocardium. Cardiac metastases usually present in patients with advanced widespread malignancy. Treatment is palliative as prognosis is poor. In any cancer patient with cardiac symptoms or ECG changes, it is important to consider the possibility of cardiac metastasis. Multimodality imaging with MRI, positron emission tomography-CT, and echocardiography plays a pivotal role in the diagnostic workup and management.

## Supplementary material

[Supplementary material](#) is available at *European Heart Journal - Case Reports* online.

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** The author/s confirm that written consent for submission and publication of this case report including image(s) and

associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** none declared.

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