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A CAUTIONARY NOTE ON PEMBROLIZUMAB USE IN PATIENTS WITH ASCENDING AORTIC ANEURYSMS

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ABSTRACT

Case description: We describe a case of a patient treated with pembrolizumab (an immune checkpoint inhibitor) for metastatic scalp melanoma. He had a previous history of colorectal cancer, prostatic cancer and chronic polymyalgia rheumatica. The patient was known to have a stable ascending aortic aneurysm of 4.5 cm. However, he developed a rapid expansion of the ascending aortic aneurysm with the size crossing the threshold for surgery. The patient was referred to the cardiothoracic surgery service for intervention and he subsequently underwent surgery. The patient was electively admitted one week later for resection of aortic aneurysm, aortoplasty and external graft fixation. Pathologically, gross evidence of dissection was not identified; however, the histological analysis of the media showed laminar medial necrosis, multifocal in nature, with occasional clusters of histiocytic cells appreciated at their edge reminiscent of that seen in an inflammatory aortitis (granulomatous/giant cell type).

Discussion: Immune checkpoint inhibitor-induced aortitis is becoming increasingly evident, and its presentation can vary. It has been discovered incidentally on surveillance imaging with the use of nivolumab. In other cases, patients have been symptomatic to severely symptomatic. Atezolizumab with carboplatin and etoposide has been reported to cause abdominal aortitis which was responsive to corticosteroids and subsequent discontinuation of atezolizumab. Pembrolizumab has been linked to a case of transverse aortic arch aortitis. In our case, the inflammatory aortitis due to pembrolizumab was the cause of the rapid expansion of the ascending aortic aneurysm.

Conclusion: Patients with known aortic aneurysms should undergo careful surveillance when commencing immune-checkpoint inhibitor therapy.

KEYWORDS

Immune checkpoint inhibitors, pembrolizumab, ascending aortic aneurysm, aortitis, melanoma

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LEARNING POINTS

- Immune checkpoint inhibitors are being increasingly used in the treatment of metastatic malignancy. However, they are a relatively new group of medications, and the side effect profile of each is yet to be fully recognised. Aortitis has occurred with several different immune checkpoint inhibitors.
- Patients with known aortic aneurysms should undergo careful surveillance when commencing immune checkpoint inhibitors.
- All interventional therapeutic options should be considered early in these patients on the development of aneurysmal expansion.

INTRODUCTION

Aortitis is the term used to describe inflammation of the aorta. A wide variety of causes have been documented, the classification of which is divided into infectious and non-infectious causes. The former includes syphilis, tuberculosis and human immunodeficiency virus (HIV)[1].

On the other hand, non-infectious causes may encompass inflammatory conditions such as rheumatoid arthritis, vasculitic conditions and radiotherapy[1,2]. Monoclonal antibodies (MABs) and immune checkpoint inhibitors (ICIs) are implemented in cancer treatment and some are known to have adverse cardiac effects[3]. While MABs are designed to target specific antigens on cancer cells to boost the immune response, ICIs act by slowing the hyperactive immune response with the potential to damage healthy cells in addition to cancer cells that initiated the immune response. ICIs work by preventing T-cells from interacting and hence enhancing an immune response against other cells[4]. Aortitis is a rare condition and rarer still in the setting of MAB therapy[5,6].

CASE DESCRIPTION

A man was diagnosed with scalp melanoma. He had a history of Dukes B colorectal carcinoma requiring anterior resection and adjuvant chemotherapy, prostatic carcinoma requiring radiotherapy and chronic polymyalgia rheumatica. He was also under surveillance for a 4.5 cm ascending aortic aneurysm that had been stable for over two years.

The patient was initially diagnosed with Clark level V scalp melanoma with a Breslow thickness of 8.7 mm. This was treated with radical excision. Time zero surveillance computerised tomography of the thorax, abdomen and pelvis (CT TAP) demonstrated no metastatic disease but revealed a 4.5 cm ascending aortic aneurysm *(Fig. 1A)*. There was no indication of aneurysm surgery at this stage.

Follow-up imaging exhibited stability in aneurysm size as evidenced by the 6-month CT imaging *(Fig. 1B)*. However, CT imaging seven months later showed new right-sided pulmonary metastatic lesions: a 10 × 12 mm nodular thickening in the right pulmonary oblique fissure, and a 5 × 10 mm right lower lobe pulmonary lesion, both consistent with metastatic melanoma *(Fig. 1C, red arrow)*.

The patient was started on pembrolizumab for low-volume metastatic melanoma at 15 months post-initial scan. Three months post-initiation of pembrolizumab, CT TAP demonstrated complete resolution of the metastases *(Fig. 1D, green arrow)*. However, there was also rapid expansion of the ascending aortic aneurysm from 4.5 to 6 cm *(Fig. 1D)*. Therefore, due to the rapid expansion of the aneurysm and the size crossing the threshold for surgery, he was referred to the cardiothoracic surgery service for intervention.

The patient had mild non-obstructed coronary artery disease. Transthoracic (TTE) and transoesophageal echocardiogram (TOE) *(Fig. 3)* revealed good biventricular function, with mild aortic incompetence and trace mitral and tricuspid regurgitation. The left atrium was mildly dilated. Atrial fibrillation was noted during the TOE. The angiogram and echocardiograms again demonstrated dilation of the ascending aorta, ranging between 5.8 and 6.4 cm.

A final pre-operative CT thorax and aortic angiogram was performed at month 22. While the lung fields remained clear, the ascending aorta had rapidly increased in size to 7 cm *(Fig. 1E)*.

The patient was electively admitted one week later for resection of aortic aneurysm, aortoplasty and external graft fixation. A median sternotomy was performed, and the aorta appeared to be further dilated, then approximately 8 cm on direct measurement at the sinotubular junction. Cardiopulmonary bypass was established via the aortic arch and right atrial two-stage cannulation. A left ventricular vent was inserted via the right superior pulmonary vein. The aortic cross-clamp was applied, and diastolic cardiac arrest was achieved using both ante- and retrograde cold-blood cardioplegia. A large portion of the ascending aortic aneurysm was resected anteriorly; the aorta was closed primarily using Prolene™ pledget sutures. A circumferential Dacron graft was used to further reinforce the ascending aorta externally. A maze procedure was concomitantly undertaken due to the history of paroxysmal atrial fibrillation. The patient was weaned easily from cardiopulmonary bypass in sinus rhythm. Standard closure was performed.

The patient's intensive care unit stay lasted two days. His postoperative course was complicated by hypervolemic hyponatraemia, which was treated conservatively; he was otherwise well. The patient was discharged home two weeks post-operation.

Macroscopically, the intima appeared normal with areas of yellow focal atheromatous change. The aortic wall appeared

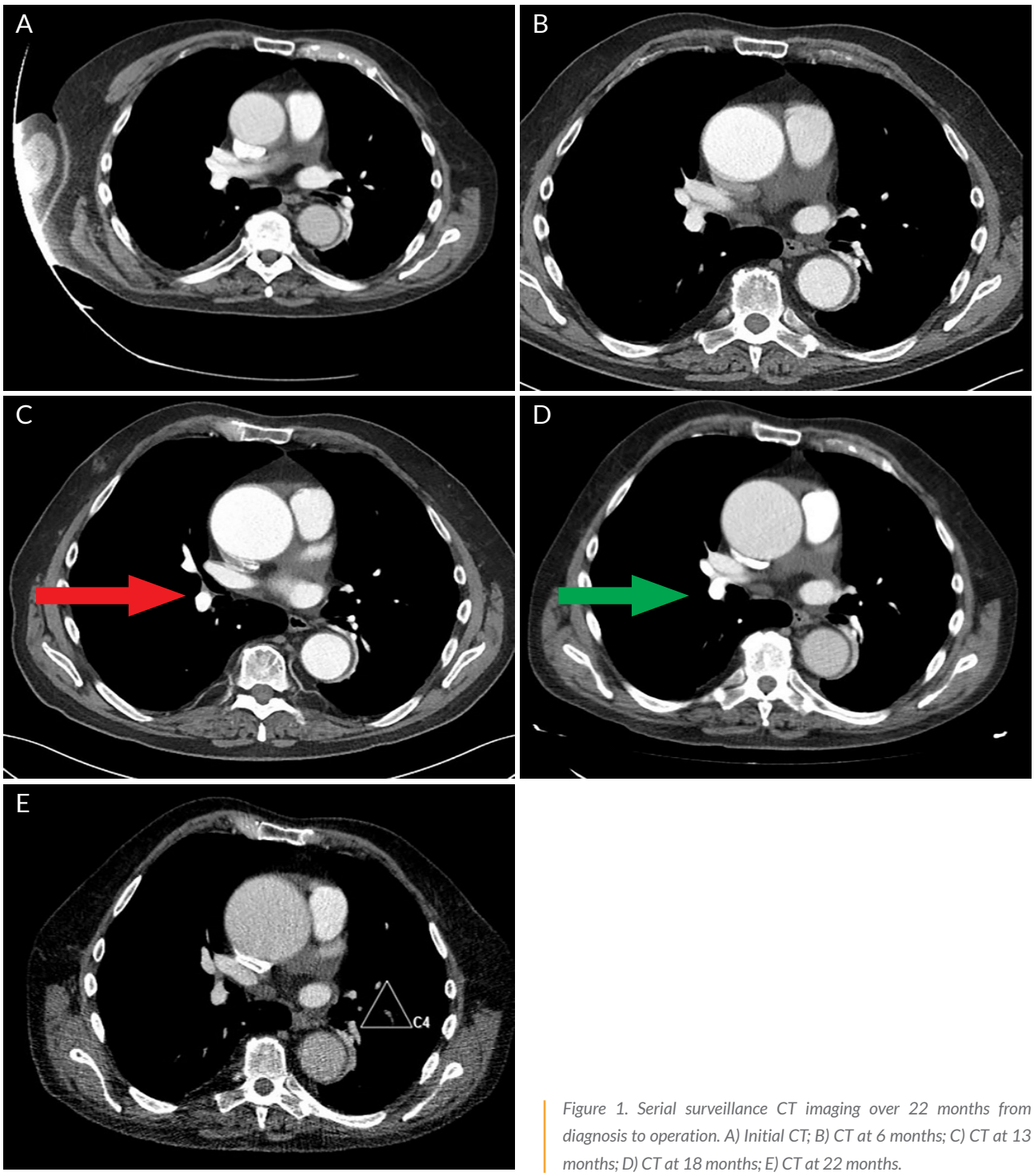

Figure 1. Serial surveillance CT imaging over 22 months from diagnosis to operation. A) Initial CT; B) CT at 6 months; C) CT at 13 months; D) CT at 18 months; E) CT at 22 months.

macroscopically normal. Gross evidence of dissection was not identified, however haematoxylin and eosin (H&E)-stained sections of the media showed laminar medial necrosis, multifocal in nature, with occasional clusters of histiocytic cells appreciated at their edge reminiscent of that seen in an inflammatory aortitis (granulomatous/giant cell type) *(Fig. 4)*.

DISCUSSION

While there have been some reports in the literature, medication-induced aortitis remains an exceedingly rare entity. Webb et al. describe a case of aortitis secondary to cisplatin chemotherapy for stage IVB cervical cancer, while Koyama et al. identify granulocyte colony-stimulating factor as the trigger for aortic arch aortitis in a patient with triple-negative breast cancer[7,8].

Immune checkpoint inhibitor-induced aortitis and/or peraortitis is becoming increasingly evident, and its presentation can vary. It has been discovered incidentally on surveillance imaging with the use of nivolumab[6,9]. In other cases, patients have been symptomatic to severely symptomatic[10,11]. Liguori et al. report a case of a patient developing severe abdominal pain after two cycles of atezolizumab with carboplatin and etoposide during his treatment for metastatic pancreatic cancer[10]. A CT revealed abdominal aortitis, which quickly resolved with

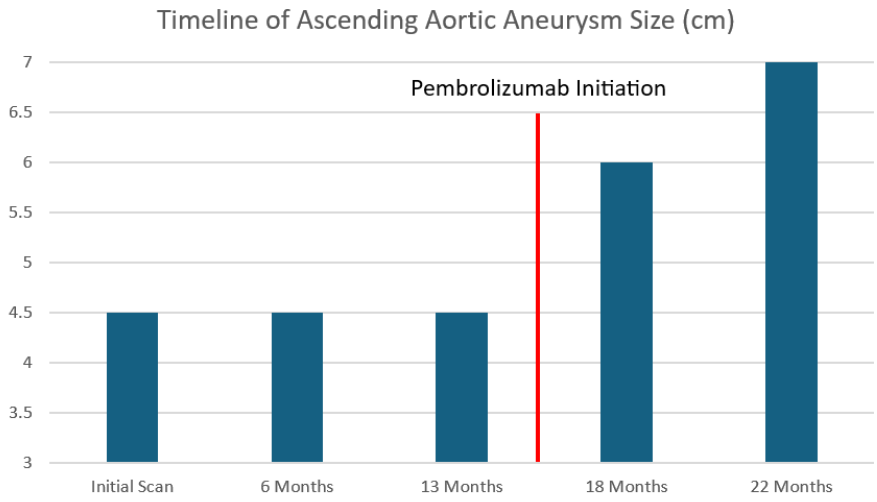

Figure 2. Timeline of ascending aortic aneurysm size as discovered during surveillance computerised tomography scans, showing a rapid increase in aneurysm size post-commencement of pembrolizumab treatment (red line at 15 months).

the institution of steroids and subsequent discontinuation of atezolizumab. However, during a relapse of the patient's malignancy, he was restarted on atezolizumab and developed a recurrence of the aortitis. This, again, was responsive to prednisolone. The patient was subsequently switched to pembrolizumab without further aortic involvement. However, pembrolizumab has recently been linked to a case of transverse aortic arch aortitis[12]. Similar to the case presented here, the patient was undergoing treatment for metastatic melanoma. High-dose steroids was started and pembrolizumab was discontinued. However, high-dose prednisolone cause bothersome weight gain and insomnia leading to a change from prednisolone to tocilizumab as a steroid-sparing agent[12].

In patients with known aortic aneurysms, there have been reports of aortitis/periaortitis developing in these on commencement of immune checkpoint inhibitors[9-11]. Roy et al. described a patient with a known infrarenal aortic and left common iliac artery aneurysm, stable on CT over 3 years, developing acute onset periaortitis secondary to nivolumab during treatment for metastatic squamous cell carcinoma of the lung[11]. CT imaging revealed aortitis in the aneurysmal

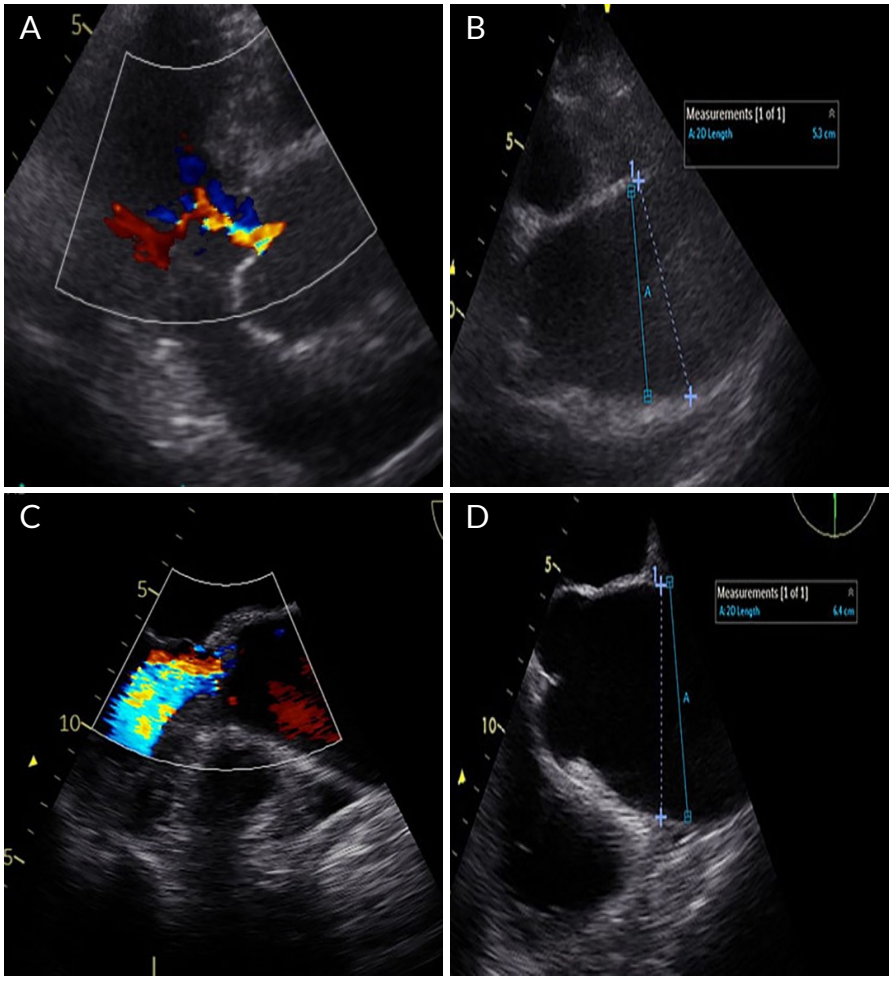

Figure 3. A) Transthoracic parasternal long axis view demonstrating mild central aortic incompetence with dilated aortic root (13 months); B) Transthoracic parasternal long axis view demonstrating significantly dilated aortic root and ascending aorta (13 months); C) Long axis view transoesophageal echo demonstrating worsening aortic root dilation with moderate to severe aortic incompetence (20 months); D) Transoesophageal echo demonstrating rapid progression of ascending aortic aneurysm (20 months).
Credit: Dr. Barry Hennigan

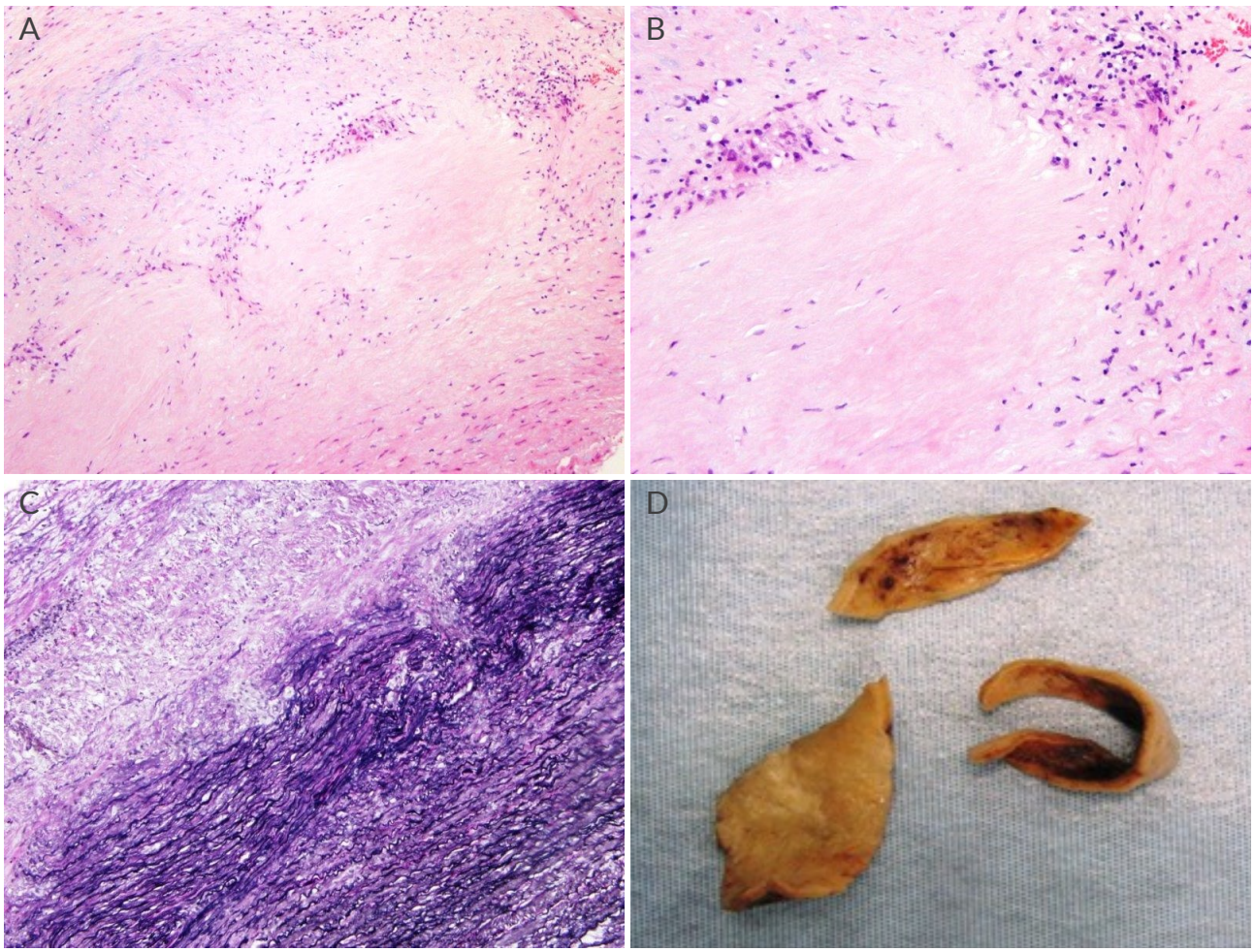

Figure 4. A) and B) Giant cells medium power, giant cells higher power, medium (10×) and higher power (20×) view of H&E stained sections of the media showing laminar medial necrosis, multifocal in nature, with occasional clusters of histiocytic cells appreciated at their edge reminiscent of that seen in an inflammatory aortitis (granulomatous/giant cell type); C) Elastic stain –- Elastic van Gieson's special stain highlights collapse of elastic fibres in the giant cell rich areas; and D) Gross aorta - pieces of aortic wall as received in the histopathology department showing focal yellowing of the intima with no evidence of dissection.

areas that had not been present on prior imaging. This was again resolved with the steroids and cessation of the nivolumab. Nivolumab-induced periaortitis was also observed on a FDG PET/CT scan in a patient with a known abdominal aortic aneurysm[9]. Two studies observed aortitis as a histopathological feature in 6.1% and 4.3% of resected aortic aneurysms, respectively[13,14] It could be possible that there is an increased susceptibility for aortitis in established aneurysms.

In the case presented here, the patient had a known aortic aneurysm, which was stable in size. Surveillance CT imaging revealed a rapidly expanding aorta soon after the commencement of pembrolizumab, and histopathology revealed a diagnosis of aortitis. The temporal relation suggests aneurysmal expansion secondary to pembrolizumab-related aortitis. Most cases of aortitis secondary to immune checkpoint inhibitors are treated with corticosteroids. We believe this is one of the first reported cases of pembrolizumab-induced aortitis requiring surgical repair and highlights the importance of careful surveillance of patients with known aortic aneurysms when they are commencing immune checkpoint inhibitor therapy.

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