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Case Report

# Vasculitic ulcer after programmed death-ligand 1 inhibitor therapy in a patient with metastatic ovarian cancer

# 轉移性卵巢癌患者接受程序性死亡配體 -1 抑製劑治療後的血管炎性潰瘍

E Choi, J Huang, C Tan

Programmed death-ligand 1 (PD-L1) inhibitors are monoclonal antibodies used in the treatment of certain cancers by enhancing a patient's immune system. They are therefore associated with immune-related side effects including cerebral vasculitis. We report a patient who developed a cutaneous vasculitic ulcer likely secondary to PD-L1 inhibitor therapy for metastatic ovarian cancer. She was treated and improved with prednisolone, colchicine and discontinuation of the drug. This case highlights a cutaneous manifesation of PD-L1 therapy, which although not life-threatening, may allow for early detection of PD-L1 treatment toxicity.

細胞程式死亡 - 配體 1（PD-L1）抑製劑是通過增強患者的免疫系統來治療某些癌症的單克隆抗體。因此，它們可引起包括腦血管炎在內的相關免疫副作用。我們報告了一名患者的皮膚血管炎性潰瘍，可能是由醫治轉移性卵巢癌細胞的程式死亡 - 配體 1 抑製劑治療所引起。停止該藥並配以潑尼松龍和秋水仙鹼治療後，她的情況得到改善。此病例展現了細胞程式死亡 - 配體 1 療法的皮膚表現，儘管不危及生命，但可由此及早留意到細胞程式死亡 - 配體 1 療法的毒性。

**Keywords:** Monoclonal antibody, ovarian cancer, programmed death-ligand 1, ulcer, vasculitis

**關鍵詞**：單克隆抗體、卵巢癌、細胞程式死亡 - 配體 1 、潰瘍、血管炎

**Division of Dermatology, Department of Medicine, National University Healthcare System, Singapore**
E Choi, MBBS, MMed(IM), MRCP
C Tan, MBBS, FAMS

**Department of Pathology, Sengkang General Hospital, Singapore**
J Huang, MD, PhD, FRCPath

Correspondence to: Dr. E Choi
National University Hospital, Singapore, 5 Lower Kent Ridge Road, Singapore 119074

## Introduction

Tumour cells evade the immune system by various mechanisms, including the use of immune checkpoints, allowing tumour cells to evade the immune system. Programmed death-ligand 1 (PD-L1) is a receptor found on activated T cells, B cells and myeloid cells, and modulates its activity.[1] Monoclonal antibodies such as pembrolizumab and avelumab inhibits PD-L1 and act as checkpoint inhibitors,

activating T cells and enhancing pre-existing immune response against tumour cells.[2]

Checkpoint inhibitor-based therapies are associated with toxicities, especially immune related adverse events (irAEs) given the activation of the immune system.[3] Cutaneous vasculitis secondary to checkpoint inhibitor has been reported in a patient with metastatic melanoma on pembrolizumab and ipilimumab.[4]

We report a patient treated with avelumab, a PD-L1 inhibitor who developed a vasculitic ulcer.

## Case report

A 51-year-old lady was diagnosed with metastatic serous ovarian cancer when she presented with irregular menstrual cycles and weight loss. A computed tomography scan showed a left ovarian mass with supraclavicular, cervical, mediastinal and abdominal lymphadenopathy. A biopsy of the left supraclavicular lymph node showed poorly differentiated adenocarcinoma with PAX8 and WT1 positivity, consistent with serous carcinoma from the gynaecological tract.

She was started on chemotherapy with carboplatin and paclitaxel from December 2015 to May 2016. There was good response, and she subsequently underwent a laparotomy with hysterectomy, bilateral salpingoophorectomy and omentectomy in May 2016. Histology of the left ovary revealed high grade serous carcinoma.

She was continued post operatively on adjuvant carboplatin for 1 month (paclitaxel was omitted due to G2 peripheral neuropathy), however four months after stopping chemotherapy, a repeat scan showed progressive disease. She was started on avelumab and doxorubicin on 1st March 2017.

She reported a slow-healing right ankle wound after scratching at her skin in December 2016. It was 2 cm x 1 cm and improved with oral antibiotics and regular wound dressings, but subsequently enlarged and became more painful between April and June 2017. On review by dermatology in June 2017, she had a 3 cm x 2 cm ulcer (Figure 1).

A skin biopsy was performed to rule out cutaneous metastasis or vasculitis. Histological examination revealed fibrinoid damage of multiple small blood vessel walls within the reticular dermis. Granular deposits of C3 and fibrin in the blood vessel walls were demonstrated by immunofluorescence. This was consistent with a vasculitic ulcer (Figure 2). An autoimmune screen was positive for ANA at a titer of 1:640, centromere pattern. The rest of the autoimmune screen was unremarkable.

Treatment with avelemumab was discontinued in June 2017 in view of cutaneous vasculitis as a likely side effect. She was started on prednisolone at 0.5 mg/kg and colchicine with a decrease in size

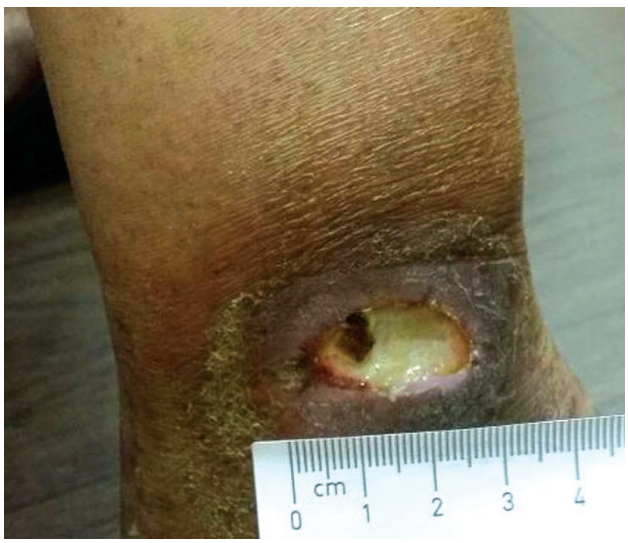


**Figure 1.** 3 cm x 2 cm right ankle ulcer 3 months after starting avelumab

of the ulcer (Figure 3). Colchicine was discontinued and prednisolone successfully tapered off after 1 month of treatment.

## Discussion

Targeting immune checkpoints such as PD-L1, programmed death protein-1 (PD-1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) serve to increase the number and activity of T cells. This upregulates the immune surveillance activity against malignant cells, promoting antitumour immunity. However, there is a risk of T cell and immune overstimulation, increasing the risk of autoimmune disease.[2] Checkpoint inhibitors as a class have been associated with immune-related adverse events (irAEs) affecting the respiratory, musculoskeletal, haematological and nervous systems.[5] In a systematic review, common vasculitic side effects of checkpoint inhibitors include large vessel vasculitis and central nervous system vasculitis.[3] Cutaneous small vessel vasculitis as a complication is rare, and there are few prior reports of cutaneous vasculitis.[4,6] It is postulated that weakening of the checkpoint function by PD-L1 inhibitors in blood vessels may result in an amplification loop leading to immune recognition of self-antigens in the vessels.[7]

Although the patient's ulcer had been present prior to initiation of avelumamb, there was clinical worsening after initiation of PD-L1 therapy, and clinical improvement after cessation of therapy. This, together with vasculitis demonstrated on histology, suggests the contributory role of PD-L1 therapy in the worsening of her ulcer.

Cutaneous vasculitis is infrequently reported as a side effect of monoclonal antibody treatment in cancer,[8,9] however it is likely that similar skin manifestations would be increasingly seen with greater use of monoclonal antibodies in cancer treatment.

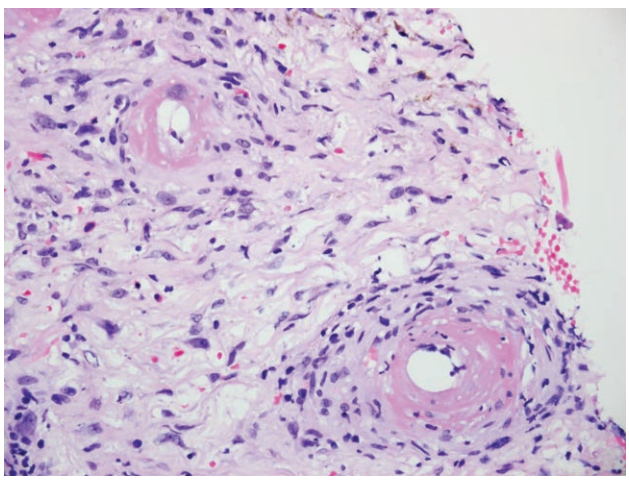

**Figure 2.** Photomicrograph of H&E stained section at 400x magnification showing fibrinoid change in small caliber blood vessel walls within the superficial dermis, associated with inflammatory infiltrate within the walls.

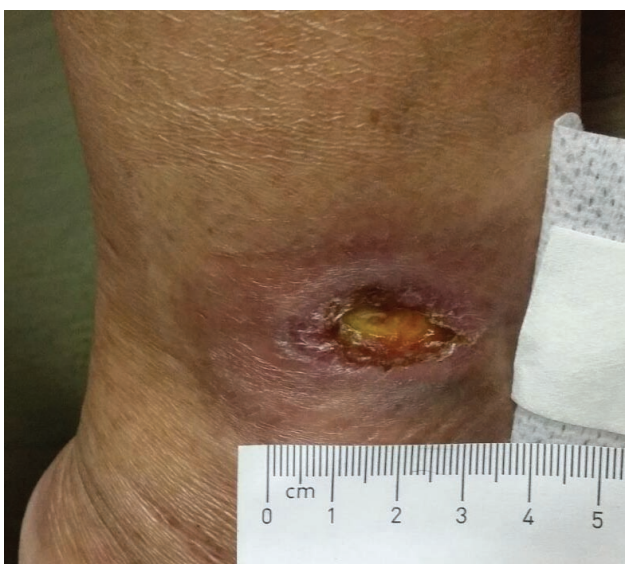


**Figure 3.** Improvement of wound 3 months after cessation of avelumab with reduction in size to 1.8 cm x 0.8 cm.

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