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Letter to the Editor

Cold agglutinin disease as a new immune-related adverse event associated with anti-PD-L1s and its treatment with rituximab

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Dear Editor,

Immune checkpoint inhibitors (ICIs) have been approved or are being developed for the treatment of a growing number of solid and haematological cancers. The ICIs enhance the functionality of cancer-specific T cells by primarily targeting PD-1, PD-L1 and CTLA-4. However, a variety of mainly immune-related adverse events (IrAEs) have been associated with the administration of ICIs [1]. Haematological irAEs are rare [2]. Although cases of autoimmune haemolytic anaemia (AIHA) with warm antibodies have been reported, none involved an anti-PD-L1 agent. The only case of cold agglutinin disease (CAD) reported to date was associated with use of the anti-PD-1 agent, nivolumab [3]. Here, we describe the first case of CAD associated with the anti-PD-L1 agent, atezolizumab.

In 2015, a 26-year-old woman presenting with long episodes of fever and severe chronic inflammatory syndrome (serum C Reactive Protein level: 200 mg/L) was diagnosed with metastatic papillary renal cell carcinoma of the left kidney. She underwent nephrectomy and then first-line treatment with an anti-vascular endothelial growth factor agent (axitinib) as part of a clinical trial.

After a few months, disease progression prompted a switch to treatment with cabozantinib as part of a compassionate use program; this led to a partial response and clinical benefit for 18 months. In March 2018, disease progression prompted the withdrawal of cabozantinib and a switch to the PD-L1 inhibitor atezolizumab as part of a clinical trial. Two weeks after the first infusion, the patient was hospitalised for acute fatigue.

The results of the clinical examination were unremarkable, with the exception of jaundice. The haemoglobin level at admission (90 g/L) had fallen to 50 g/L, with signs of haemolysis (lactate dehydrogenase [LDH] 911 U/L (N<480). No schistocytes were observed, and the patient's white blood cell and platelet counts were normal. A direct antiglobulin test was positive for C3d and negative for IgG. A cold agglutinin test was positive (titre: 1/256). None of the usual aetiologies of CAD (viral infection, mycoplasma infection or haematological malignancy) were observed. There were no signs

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of monoclonal gammopathy. The serum CRP level was 179 mg/L. Treatment with high-dose intravenous methylprednisolone (500 mg per day, for 3 days) and then prednisone (90 mg/day, i.e. 1.5 mg/kg/day) led to normalisation of the LDH level. No red blood cell transfusions were required. The haemoglobin level increased to 70 g/L. However, the improvement was transient; the patient's anaemia worsened; and haemolysis reappeared. Given the mechanism of CAD, two 1 g infusions of rituximab were administered 2 weeks apart. The haemoglobin level stabilised (75 g/L) on discharge, with no signs of haemolysis (Fig. 1).

The patient was monitored closely after discharge. Although the haemoglobin level had not normalised (owing to cancer-related inflammatory syndrome), the CAD regressed because signs of haemolysis were no longer apparent. Eight months after the rituximab infusions, the patient's oncologic status had stabilised with a partial response to a new cytotoxic therapy combined with bevacizumab. At last follow-up, the haemoglobin level was 140 g/L, and the CRP level was between 20 and 35 mg/L. Haemolysis was no longer observed.

The prognosis for metastatic papillary renal cell carcinoma is worse than that of clear cell renal carcinoma [4]. The efficacy of an ipilimumab + nivolumab combination and then nivolumab alone in non-clear cell renal carcinoma is currently being investigated in a phase II clinical trial (NCT03075423).

Although ICI use is associated with irAEs, guidelines on the management of the most frequently described events (mainly skin, endocrine, intestinal and pulmonary disorders) are now available [5]. In contrast, there is no consensus on the treatment of rare irAEs (e.g. haematological irAEs). However, the treatment of severe haematological irAEs will usually involve steroids [5] and the temporary or even definitive withdrawal of the ICI.

There are a few literature reports of AIHA (mainly warm-antibody AIHA) associated with PD-1-inhibitors (especially nivolumab) and CTLA-4 inhibitors but not PD-L1 inhibitors [2,6,7]. The exacerbation of pre-existing AIHA by pembrolizumab [8] has also been reported. Furthermore, a case report has been published on AIHA because of nivolumab-associated CAD [3]. It is important to note that our patient had not been diagnosed with CAD and had not been screened with a direct antiglobulin test prior to the initiation of atezolizumab therapy.

Here, we reported on the first case of CAD associated with the use of an anti-PD-L1. Unlike most other cases of secondary AIHA (but as is expected in CAD), the patient was refractory to oral corticotherapy [9]. Treatment with rituximab led to the remission of CAD, as in the case reported by Hasanov *et al.* [3]. Rituximab is currently the recommended treatment for CAD [9]. However, the patient's persistent, severe inflammation (considered to be a paraneoplastic syndrome) appeared to limit bone marrow regeneration and prevented the

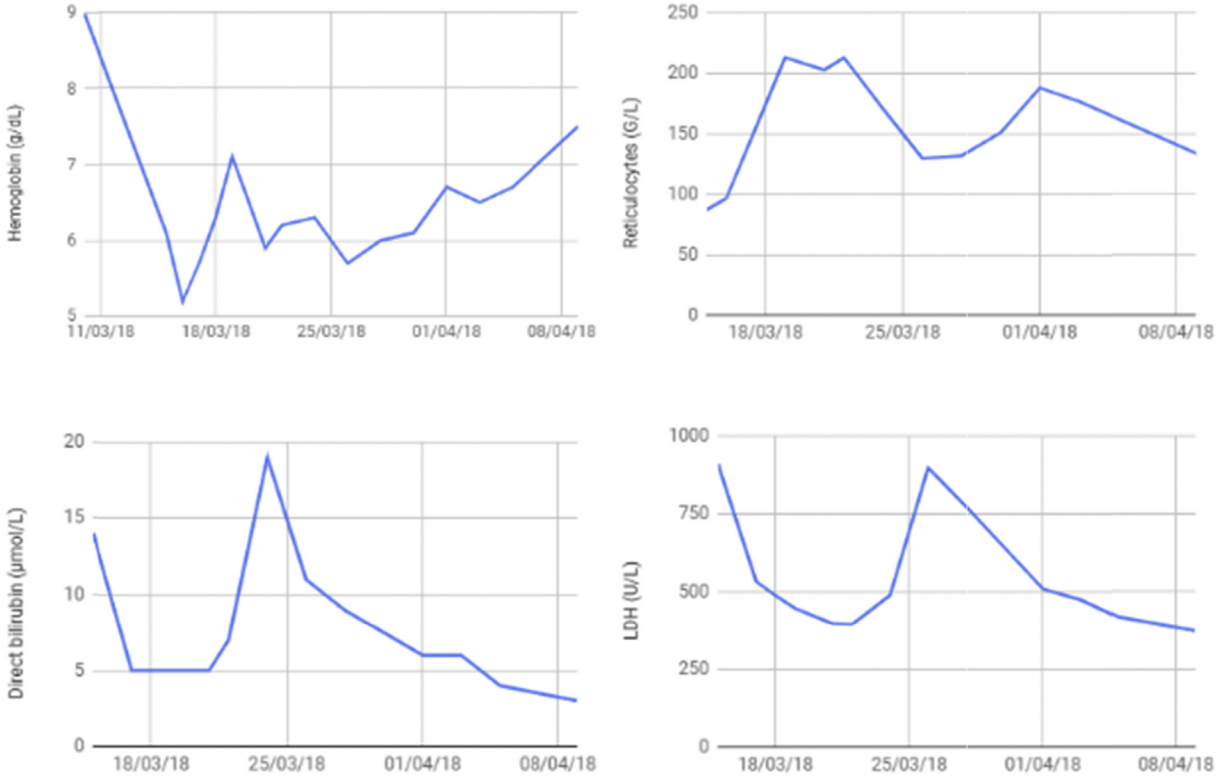

Fig. 1. Changes over time in the haemoglobin level, the reticulocyte count and haemolysis parameters during hospitalisation. LDH, lactate dehydrogenase.

complete resolution of anaemia. This case emphasises that several mechanistic factors may be involved in anaemia in cancer patients treated with an ICI.

In conclusion, we reported on the first case of AIHA caused by atezolizumab-associated CAD. This situation raises the question of whether or not the ICI should be withdrawn following the occurrence of a severe irAE —an increasing frequent situation. We suggest that such cases should be discussed by oncologists and organ specialists in a multidisciplinary team meeting.

Conflict of interest statement

L.A.'s employer has received consultancy fees from Bristol-Myers Squibb, Ipsen, Merck, Novartis, Pfizer, Roche. O.L. has received expert testimony and consultancy fees from BMS France, MSD and AstraZeneca and consultancy fees from Genzyme. All the other authors declare no conflicts of interest.

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