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Letter to the Editor

A case of immune thrombocytopaenia induced by pembrolizumab in a metastatic melanoma patient with a history of immune-mediated pure red cell aplasia

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To The Editor:

Immune checkpoint blocking agents such as the PD1-antagonist pembrolizumab have been approved for the treatment of metastatic melanoma [1]. Owing to its mechanism of action, this drug restores tumour-specific T-cell response and may induce various types of immune-related adverse events (irAEs) [2]. Haematological toxicities are rare, and cytopenia of autoimmune origin remain exceptional. We report, herein, the occurrence of successive haematologic adverse events in a patient treated with pembrolizumab for a metastatic melanoma including an immune-mediated pure red cell aplasia (PRCA) followed by an immune thrombocytopaenia (IT).

A 57-year-old woman was followed up in the dermatology department for a right ankle *BRAF* wild-type melanoma with bone metastases. A first-line treatment with pembrolizumab was initiated at which time blood test values were normal.

Shortly after the seventh injection of treatment, the patient developed acute anaemia (haemoglobin 80 g/L), with normal white cell and platelet counts. Owing to a low reticulocyte count, a bone marrow biopsy was performed finding a marked erythroid hypoplasia (4–8% erythroblasts, with maturation arrest) that was associated with a collapsed haptoglobin. There was no abnormality of lymphoid and megakaryocytic cell lines and no evidence of metastatic invasion. Other laboratory tests were negative or normal, and there was no evidence for thymoma on computed tomography scan (Table 1).

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Table 1
Workup performed to explore patients with anaemia.

Marker or test	Result
Haemoglobin, g/L	80 (N: 13–17)
Mean corpuscular volume, fL	90.5 (N: 82–98)
Reticulocytes, G/L	<10 (N: 20–120)
White blood cells, G/L	4.9 (N: 4–10)
Platelets, G/L	172 (N: 150–400)
Coagulation tests	Normal
Serum protein electrophoresis	Inflammatory syndrome
Indirect bilirubin, µmol/L	4.2 (N: < 17)
Lactate dehydrogenase, UI/L	273 (N: 135–214)
Haptoglobin, g/L	<0.08 (N: 0.3–3)
Direct antiglobulin test	Positive with anti-IgG, negative with anti-C3
Ferritin, ng/mL	741 (N: 15–150)
Antinuclear antibody, rheumatoid factor	Negative
Parvovirus B19, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) DNA testing	Negative
HIV status, hepatitis serologies	Negative
Erythropoietin, UI/L	28.6 (N: 3.22–31.9)
Computed tomography of the chest to rule out thymoma	Absence of mediastinal mass
Bone marrow aspiration	Erythroid hypoplasia (4–8%) with maturation arrest. No lymphoid and megakaryocytic cell lines abnormality. No metastatic or blastic cells invasion.

All the findings were consistent with the diagnosis of PRCA, probably associated with a share of autoimmune haemolytic anaemia (collapsed haptoglobin and positive direct antiglobulin test). The patient received one course of intravenous immunoglobulin (IVIg, 2 g/kg) which was not effective. Cyclophosphamide (50 mg/day) was then initiated, leading to normalisation of the blood cell count within three weeks. Owing to stability of the neoplastic disease, pembrolizumab was withdrawn.

After 16 months, the patient presented with a progressive disease; she had developed lymph node, brain, muscular and peritoneal metastases. Pembrolizumab was resumed under close haematological monitoring.

After four new infusions of pembrolizumab, laboratory tests showed recurrence of aregenerative anaemia associated with a decrease of platelet count (Fig. 1). Ferritin, vitamin B12 and folate levels were normal, and serology tests for antinuclear antibodies, HIV and hepatitis B and C were negative. A bone marrow biopsy was performed demonstrating a marked erythroid hypoplasia, consistent with a recurrence of PRCA, without abnormality of lymphoid and megakaryocytic cell lines, no dysplasia and no metastatic or blastic cell invasion. Quantitative polymerase chain reaction for parvovirus B19 and Epstein–Barr virus performed on medullary blood was negative. The patient was regularly transfused with packed red blood cells. She received two platelet transfusions that were not effective, and thrombocytopaenia continued to worsen until a platelet count <10 G/L (Fig. 1). Based on these composite findings and in the absence of other causes, the diagnosis of IT was retained.

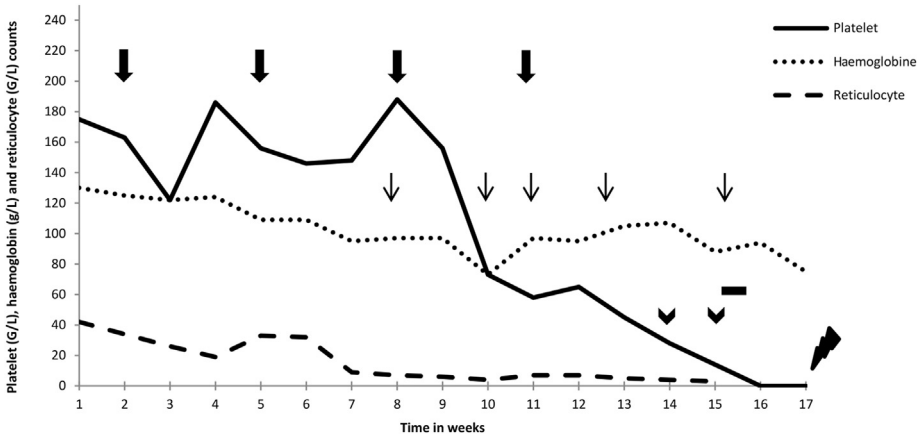

Fig. 1. Changes in platelet, haemoglobin and reticulocyte counts during pembrolizumab resumed. Thick arrows indicate the administration of pembrolizumab (2 mg/kg). Arrowheads indicate platelet transfusions, and thin arrows indicate red blood cell transfusions. The horizontal column represents intravenous immunoglobulin. The lightning symbol corresponds to patient death. X-axis: time in weeks; y-axis: platelet (G/L), haemoglobin (g/L) and reticulocyte (g/L) counts.

Table 2
Characteristics of the six cases of immune thrombocytopaenia induced by anti-PD1.

Characteristics	Case presented herein	Case 1 reported by Le Roy *et al.* [5]	Case 2 reported by Le Roy *et al.* [5]	Case reported by Pföhler *et al.* [6]	Case reported by Kanameishi *et al.* [7]	Case reported by Karakas *et al.* [8]
Age (years), sex	57, F	34, F	51, F	73, M	79, M	78, M
Cancer	Melanoma	Melanoma	Melanoma	Melanoma	Melanoma	Non-small cell lung cancer
PD-1 inhibitor	Pembrolizumab	Pembrolizumab	Pembrolizumab	Pembrolizumab	Nivolumab	Nivolumab
Time to thrombocytopaenia onset	4 courses after resumption of pembrolizumab (11 cycles in total)	1 course of pembrolizumab	9 months	1 month	3 courses of nivolumab	6 courses of nivolumab
Previous immunotherapy	Pembrolizumab, 7 courses	Ipilimumab, stopped for progressive disease	None	Nivolumab, stopped for anaphylactic reaction	None	None
Baseline blood test values	Normal	Normal	Unspecified	Normal except mild thrombocytopaenia (108 G/L)	Normal	Normal
Clinical findings	Epistaxis	Macroscopic haematuria, buccal hemorrhagic bulla, purpura of the limbs	Shaking and chills. No hemorrhagic manifestation	None	Haemorrhage on the oral mucosa, petechial rash on lower limbs	None
Platelet count (G/L)	<10	10	9	About 30	<10	<10
Other laboratory anomalies	Anaemia	Anemia	None	None	None	None
Bone marrow aspiration	Erythroid hypoplasia.	Normal, with high megakaryocyte count.	Normal	Not performed	Not performed	Hypercellularity, increased rate of megakaryocytes
Immune haematology testing	Not performed	Not performed	Not performed	Free and cell-bound platelet-specific IgG autoantibodies (PIFA and MAIPA)	Positivity of antiplatelet antibodies by mixed passive haemagglutination	Not performed
Triggering factor	None	None	Iodinated contrast agent	None	None	None
Treatment	IVIg and intravenous corticoids	IVIg and intravenous corticoids	Corticosteroids	Systemic corticosteroids	Prednisolone, IvIg, romiplostim	Corticosteroids
Outcome	Persistence of deep thrombocytopenia and death from intracranial haemorrhage	Rapidly favourable	Favourable, with normal platelet count at day 4	Normal platelet count by 5 months, but finally death due to disease progression	Favourable, with normal platelet count within 1 month	Improvement without normalisation of platelet count, and death due to disease progression

F, female; M, male; IVIg, intravenous immunoglobulin; PIFA, indirect platelet immunofluorescence assay; MAIPA, monoclonal antibody immobilisation of platelet antigens.

Pembrolizumab was definitively interrupted because of unacceptable toxicities and progressive disease. Given its lack of effectiveness, cyclophosphamide was also discontinued. The patient was treated with high-dose oral corticosteroids (1 then 2 mg/kg/day) associated with one infusion of IVIg (2 g/kg). However, the platelet count did not return to normal, and the patient unfortunately died a few days later because of an intratumor haemorrhage of brain metastases (Fig. 1).

Cytopenia is a rare toxicity reported under anti-PD1 therapy, with an incidence evaluated in clinical trials to be between 5% and 17% [1,3,4]. Furthermore, cytopenia of autoimmune origin seems to be uncommon as only a few cases of IT [5–8] (Table 2) and two cases of PRCA [9,10] induced by PD1-inhibitor have been described in the literature. To the best of our knowledge, the patient presented herein is the only case reported with both IT and immune-mediated PRCA under anti-PD1 therapy. It is, however, of note that, although we did not perform the immune haematology examinations to document the thrombocytopaenia, the bone marrow aspirate confirmed the peripheral origin of thrombocytopaenia, and the ineffectiveness of platelet transfusions was in favour of an immune-mediated mechanism. Otherwise, no other cause of thrombocytopaenia, in particular autoimmune or infectious, was found, and no drug other than pembrolizumab was recently introduced. We implemented a treatment with systemic corticosteroids and IVIg, but we could not determine its effectiveness because of the rapidly fatal evolution.

The therapeutic approach for PRCA typically involves immunosuppression; cyclosporine A or cyclophosphamide seems to be the most effective immunosuppressive agents [11]. In the previous cases of PRCA reported, patients were treated with corticosteroids alone or in combination with IVIg with good effectiveness but at the expense of that of immunotherapy and progression of neoplastic disease [9,10]. In the patient presented herein, cyclophosphamide was effective for the treatment of PRCA, and the patient had stable disease for 16 months without reduction in the antitumour activity of pembrolizumab. Thus, cyclophosphamide could be considered as a treatment of choice for this type of adverse event.

Taken together, immune-mediated cytopenia represents an uncommon irAE occurring with anti-PD1. The mechanism for the development of these immune cytopenia remains unclear, and a greater number of cases are needed to clarify the management of such toxicity. Considering their potentially fatal outcome and the increasing use of immunotherapy, clinicians should be aware of this type of irAE, and meticulous controls of blood count are, therefore, essential during and after any immunotherapy treatment to be able to detect early the occurrence of such adverse events.

Conflict of interest statement

S.D. is the principal investigator in clinical trials promoted by Merck Sharp and Dohme (MSD); he was invited to a meeting by MSD. The other authors declare that they have no relevant conflict of interest.

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