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Severe mesenteric ischemia with multiple organ failure in a patient previously treated with a humanized monoclonal antibody against programmed death receptor-1 (pembrolizumab), a case of pembrolizumab associated catastrophic antiphospholipid syndrome?

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Abstract

Immune checkpoint inhibitors are used in the treatment of different types of tumors including melanoma and non-small cell lung carcinoma. The use of these inhibitors is associated with a broad spectrum of immune-related adverse effects. Here we report a case of a patient admitted to the intensive care unit with multiple organ failure due to catastrophic antiphospholipid syndrome following treatment with pembrolizumab, an immune checkpoint inhibitor, because of metastatic melanoma. The presented patient had multiple organ failure of lung, gastro-intestinal, renal, and the liver. Vascular thrombosis was confirmed by both imaging (pulmonary embolism on computed tomography–thorax) and histopathological examination of the intestines. In combination with the presence of IgA anti-cardiolipin antibodies and initially IgM anti-cardiolipin antibodies, catastrophic antiphospholipid syndrome was suspected. Despite treatment with plasmapheresis and corticosteroids, the patient died due to multiple organ failure. Catastrophic antiphospholipid syndrome is difficult to recognize and has high mortality rates despite supportive treatment. In this case report, discussion is provided regarding the possible immunological mechanism behind catastrophic antiphospholipid syndrome during or after treatment with immune checkpoint inhibitors. It is important to realize that in modern intensive care unit, more patients with immune-related adverse effects of the treatment with immune checkpoint inhibitors will be admitted, because of an increase in the number of patients treated with these checkpoint inhibitors. When these patients are admitted on the intensive care unit, multi-disciplinary consultation is important because of the difficulty of early recognition and optimal treatment of these possible lethal side effects.

Keywords

Checkpoint inhibition, multiple organ failure, catastrophic antiphospholipid syndrome

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Introduction

Immune checkpoint inhibitors are increasingly used in the treatment of different types of malignant tumors including patients with metastatic melanoma and non-small cell lung carcinoma. In contrast to classical cytotoxic chemotherapy, immune checkpoint inhibitors, among which pembrolizumab, enhance activation of immune cells toward cancer cells.

Besides long successful anti-tumor treatment results, the use of immune checkpoint inhibitors is associated with a plethora of immune-related adverse effects (irAEs). These irAEs are mainly described as pulmonary, skin, gastrointestinal, hepatic, and endocrine adverse effects in the literature.[1] The hematologic irAEs can induce cytopenias (neutropenia, thrombopenia, pancytopenia) and autoimmune hemolytic anemia.[2] Although hematologic irAEs are rare, the complications can be life-threatening and therefore they need early recognition and prompt interventions to prevent mortality.[2–4]

Here we report the case of a 74-year-old patient with advanced melanoma and pembrolizumab treatment. He was admitted to the intensive care unit (ICU) with multiple organ failure and the differential diagnosis of catastrophic antiphospholipid syndrome (CAPS) following pembrolizumab treatment of advanced melanoma was made. In this case report, we highlight some important aspects of this case for diagnosis and treatment of this catastrophic disease by multi-disciplinary ICU teams.

Case report

A 74-year-old male patient was diagnosed 3 years ago with a superficial spreading melanoma on his back. The tumor had a Breslow thickness of 4.0 mm and there were two positive sentinel nodes in both axilla. After surgical resection, there was progression of disease 1 year later with increased size of lymph nodes in both axilla and retroperitoneal. There was suspicion of a solitary lung metastasis in the left upper lobe. The patient was referred to our tertiary center for escalation of treatment. Molecular testing showed a NRAS tumor mutation but no BRAF tumor mutation. Immunotherapy with a humanized monoclonal antibody against programmed death receptor-1 (PD-1), that is, pembrolizumab, was started.

A few months later, good clinical response was observed as the lung metastasis and the lymph nodes regressed. After 9 months of treatment with pembrolizumab, the patient developed urticaria and erythema, which were indicated as an adverse effect and successfully treated with hydroxyzine and a topical corticosteroid. The patient was operated on a presumed appendicitis in another hospital. One and a half years later, the patient developed adrenal insufficiency and oral hydrocortisone supplementation was started. A computed tomography (CT) showed stable disease with disappearance of the lung metastasis, therefore pembrolizumab treatment was continued. After a total of 27 treatments, the immune therapy with pembrolizumab was terminated. Shortly thereafter, the patient developed complaints of dyspnea and coughing. Electrocardiography and echocardiography were normal; however, a CT-scan showed bilateral pleural effusion and mesenteric panniculitis. A diagnostic pleural puncture was performed showing exudate with reactive cells; however, no malignant cells were observed. With the work diagnosis of pleural serositis due to immunotherapy, treatment with prednisolone was initiated (60 mg per day). Because of persistent dyspnea, a pleural drainage (1800 mL) was performed 1 week later with good symptom relieving effects. Again, no malignant cells were observed in the pleural fluid.

Two weeks later, the patient presented at the emergency room with dyspnea, fever (38.5°C) and cold shivers. He also had complaints of red and tearing eyes. He was hypoxic and suppletion of oxygen was started. Blood laboratory values are presented in Table 1. Electrocardiography, chest X-ray, and microbiological diagnostics showed no abnormalities. A CT-thorax was performed, showing pulmonary emboli in the right lung and progression of the bilateral pleural fluid. There were no signs of pneumonitis. After another pleural drainage (1600 mL), the patient was admitted to the general ward with therapeutic anticoagulation by means of low-molecular-weight heparin. During his stay in the ward, the fever persisted and the C-reactive protein was rising (102 mg/L), Table 1. Bacterial pneumonia was suspected, for which piperacillin/tazobactam was started and the prednisolone dose was halved (30 mg per day). On the fourth day of hospital admission, clinical deterioration occurred characterized by means of vomiting, severe diarrhea, oliguria, and blue discoloration of the fingers. Despite fluid resuscitation, no improvement was observed and with suspicion on intestinal ischemia or perforation, a CT-abdomen was performed, showing intra-abdominal free fluid, no free air, a slightly distended transverse colon, and no occluded mesenteric arteries.

On the fifth day, the patient was in acute respiratory distress and therefore admitted to the ICU, where respiratory support with nasal positive airway pressure was initiated. Striking findings at physical examination at admittance were a convex, tense, and silent abdomen with diarrhea and poor peripheral circulation with extensive mottling of the legs up to the abdomen; a prolonged capillary refill time of more than 4 s; and severe discoloration (blue-purple) of the fingers on both hands. Laboratory findings are shown in Table 1. Blood and sputum cultures were taken, antibiotics were continued, and a multi-disciplinary consultation was arranged with the intensivist, oncologist, the rheumatology and clinical immunology specialist, and gastroenterologist. This team had a high suspicion of an irAE.

Additional laboratory markers were investigated (including antinuclear, anti-DNA, and antiphospholipid antibodies and complement C3 and C4). Because of abdominal pain, nausea, and vomiting with suspicion on clostridium, colitis

Table 1. Relevant laboratory values.

	Day 1 Emergency room	Day 4 General ward	Day 5 ICU admittance	Day 6 ICU	Day 7 ICU	Day 8 ICU
pH	7.51	7.46	7.52	7.45	7.39	7.38
pCO2 (kPa)	4.4	3.6	2.8	3.5	5.0	5.2
pO2 (kPa)	9.3	8.1	9.8	9.6	8.5	8.9
spO2 (%)	95%	92	96	95	91	92
HCO3 (mmol/L)	27	20	17	18	23	23
Lactate (mmol/L)	1.5	1.9	2.2	2.1	2.1	2.7
Glucose (mmol/L)	5.8	7.7	7.4	7.4	7.4	6.4
Sodium (mmol/L)	137	134	134	136	137	137
Potassium (mmol/L)	4.1	4.1	3.6	3.6	4.1	4.6
Chloride (mmol/L)	105	108	108	108	110	108
Hb (mmol/L)	9.9	10.9	11.0	10.6	8.8	7.5
Leucocytes (10^9/L)	13.9	13.2	19.2	20.0	18.9	18.7
Trombocytes (10^9/L)	235	266	269	254	220	182
CRP (mg/L)	21	102	62	223	84	111
Creatinine (umol/L)	88	123	127	122	127	218
Ureum (mmol/L)	5.7	8.1	7.9	9.4	11.9	18.5
Calcium (mmol/L)	2.25	2.08	2.16	2.04	1.91	2.07
LDH (u/L)	168	211	232	191	175	1376
ASAT (u/L)	18	21	20	18	14	1840
ALAT (u/L)	55	48	35	26	20	1007
AF (u/L)	76	89	77	63	42	42
y-GT (u/L)	123	149	123	96	58	29
Bilirubine (umol/L)	7	–	5	5	3	7
PT (s)	–	–	13.6		–	16.5
APTT (s)	–	–	39	38	–	36
Fribrinogeen (g/L)	–	–	6.7		–	2.9

ICU: intensive care unit.

or intestinal ischemia additional fecal diagnostics were performed. The fecal cultures were negative together with a negative clostridium difficile nucleic acid amplification test. Fecal calprotectin levels were increased (305 mg/kg), whereas fecal elastase levels were decreased (115 ug/g).

The patient underwent a colonoscopy, showing characteristic ischemic colitis in most parts of the colon, whereas the rectum was partly saved. Biopsies were taken and shortly thereafter an explorative laparotomy was performed. Due to extensive intestinal ischemia, 150 cm of ischemic small intestine combined with the sigmoid was resected. Bowel continuity was not restored and a second look laparotomy was scheduled. In the ICU, the patient was sedated, mechanical ventilated, and hemodynamically supported with noradrenaline. Anti-cardiolipin (aCL) antibodies were detected, and together with the clinical picture of progressive multi-organ thrombosis raised the suspicion of CAPS as an irAE.

On the third day of ICU stay, the patient was clinically deteriorating with progressive respiratory failure, oliguria, and impairment of the peripheral circulation. Based on frozen section analysis of the small intestine and sigmoid surgical specimens with macroscopic signs of extensive ischemia (Figure 1(a) and (b)), no clear evidence for a vasculitis could be found. The laboratory diagnostics showed aCL antibodies; aCL IgM: 26 MPL/mL and aCL IgA: 60 APL/mL, raising the suspicion on a CAPS. Lupus anticoagulant (LAC), aCL IgG, and autoantibodies to B2-glycoprotein 1 were negative together with negative previous test results of antinuclear antibodies, antineutrophil cytoplasmic autoantibodies, and antibodies to double-stranded DNA. Complement C3 and C4 levels were normal. All blood and sputum cultures taken during the hospital—and ICU—stay were negative. Due to the rapid disease progression over the past 24 h, plasmapheresis was started and intravenous corticosteroids were continued. Overnight progression of disease was observed with multiple organ failure of the heart, the lungs, the kidney, and the liver and further purple discoloration of the fingers and toes.

Further workup of the resection specimens showed ischemic changes in the mucosa were in the submucosa and more extensive in the subserosa; fibrinoid necrosis was seen in the branches of the small and medium-sized arteries (Figure 1(a) and (b)).

A second look laparotomy was performed where extensive, deep ischemia of the small and large intestine was found. In the light of severe mesenteric ischemia and multiple organ failure, further care for recovery was deemed

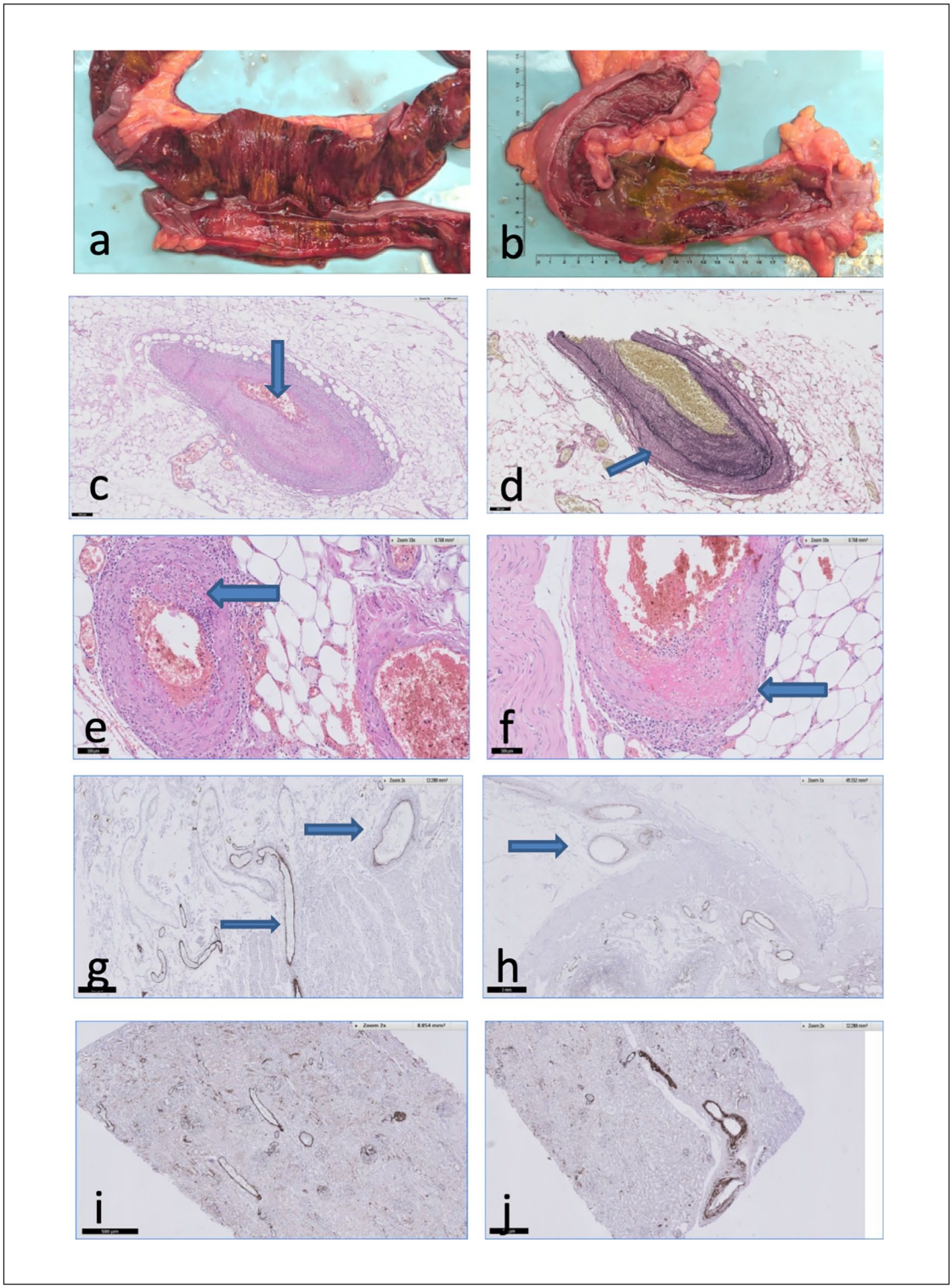

Figure 1. Multiple examples of the pathological examination of the patient. Macroscopic ischemic small intestine (a), and macroscopic ischemic sigmoid (b). Microscopic examination of subserosal artery branch with fibrinoid necrosis and nearly total obliteration of the lumen (arrow) (c), the same artery with the Verhoeff staining showing lamina elastica interna (arrow) (d). Microscopic examination of fibrinoid necrosis of another artery branch with cell dust in the artery wall, neutrophilic granulocyte infiltration, and clear narrowing of the lumen (e), and fibrin deposition (arrow) and damage of the artery wall (f). C5b-9 protein deposition in the wall of blood vessels in the submucosa and muscularis propria (arrows) (g) and subserosa (h) suggestive of an immune mediated etiology. Positive external control of C5b-9 staining in the blood vessels of a transplanted kidney with rejection (i, j).

futile. The patient died shortly after cessation of supportive therapy and maximum palliative care.

During autopsy, there were no signs of malignancy nor enlarged lymph nodes. In the large vessels, there were no thrombi nor emboli. The small and large intestine showed signs of ischemia macroscopically. Microscopic examination of the sectioned intestines and one adrenal gland showed however small blood vessels with thrombi in different phases varying from only fibrinoid deposits on the endothelium (existence in days) to re-endothelization (existence in weeks) (Figure 1(c)–(j)).

In the appendectomy specimen from approximately 1 year earlier, there was chronic active, ulcerative inflammation within the peri-appendiceal fat tissue blood vessels with signs of vasculitis with infiltration of the vessel wall; at that time, this was probably associated with the degree of inflammation. By revision, we consider this finding to be related with the more recent findings.

Blood samples that were taken before this hospital admission were post mortem analyzed for aCL antibodies, showing a raised aCL IgM: 40 MPL/mL and negative aCL IgA antibodies, indicating that the patient was in the process of developing multiple autoantibodies against cardiolipins.

Discussion

(Catastrophic) antiphospholipid syndrome and immune checkpoint inhibitors

In this case report, we present a patient who developed multiple organ failure due to CAPS following treatment with pembrolizumab, a humanized monoclonal antibody against PD-1 for advanced melanoma for a longer period of time. Antiphospholipid syndrome (APS) is characterized by venous and/or arterial thrombosis and/or pregnancy-related morbidity, combined with the presence of antibodies against phospholipid binding proteins and/or LAC, see E-Table 1 in Supplemental Material for revised APS classification criteria.[5] APS is considered as a multifactorial condition that involves both the adaptive and the innate immune system.[6] APS is a primary autoimmune disease but it can also be secondary to other autoimmune diseases such as systemic lupus erythematodes.[7] Besides pregnancy complications, venous, arterial, and/or small vessel thrombosis, other common disease-related features observed in a cohort of 1000 patients with either primary or autoimmune disease-associated APS were thrombocytopenia (22%), livedo reticularis (20%), superficial thrombophlebitis (9%), and stroke (13%) or transient ischemic attack (7%).[7] A small subset of patients with APS develop multiple organ failure due to multiple thromboembolic occlusions with rapid onset, which is called catastrophic APS (CAPS). For the diagnosis of CAPS, the patient must have evidence of involvement of three or more organ systems simultaneously or in less than 1 week, confirmed with imaging or histopathology and antiphospholipid antibodies, E-Table 2 in Supplemental Material.[6] Although CAPS patients represent less than 1% of all patients with APS, it is usually a life-threatening situation that requires treatment in the ICU.[7] Management of a patient with CAPS is challenging because CAPS evolves quickly, is difficult to recognize, and has high mortality rates despite supportive treatment. The development of autoimmunity is prevented by central and peripheral mechanisms. Central tolerance is a process regulated in both the thymus and bone marrow process where self-reactive T or B lymphocytes are removed. This process is not complete. In addition, several peripheral mechanisms act to prevent autoimmunity, including the presence of suppressive regulatory T cells. These cells negatively regulate existing B cell autoimmunity. When new drug therapies like pembrolizumab intervenes with these negative regulators, autoimmunity can develop. Due to the scarcity and complexity of CAPS, it is unclear which immunosuppressive treatment is most beneficial for patients with CAPS in addition to anticoagulation therapy. High-dose steroids, plasma exchange, and/or intravenous immunoglobulin presumably counteract pathogenic autoantibodies. Many experienced clinicians will add cyclophosphamide or rituximab to this regimen depending on the presumed underlying disease.

Pembrolizumab is a humanized monoclonal antibody against PD-1. PD-1 has two main ligands: PD-L1 and PD-L2 and both are expressed by various cells, tissues, and tumors (including melanoma). When tumor antigens bind to PD-1 on T cells, the tumor inhibits T-cell function. Antibodies binding to PD-1 block the interaction with tumor PD-L1 and PD-L2, which result in an active T-cell response and reactivating anti-tumor immunity.[8] The use of checkpoint inhibitors is associated with a wide range of irAEs that can affect every organ.[1] PD-1 inhibitors are known to have a lower incidence of irAEs compared with cytotoxic T-lymphocyte-associated antigen 4 inhibitors (such as ipilimumab especially as monotherapy). The most common irAE in patients treated with pembrolizumab is rash (40%) although diarrhea and/or colitis are also observed in patients treated with checkpoint inhibitors.[1] A grade 3/4 colitis has been described after long-term PDL-1 treatment but is mostly seen with the use of CTLA-4i compared to PD-1 (7% vs 1.8%).[1,9] Other related irAEs are hepatitis, pneumonitis, endocrinopathies, and hematological manifestations such as isolated neutropenia, thrombocytopenia. and autoimmune hemolytic anemia. These side effects are extensively reviewed elsewhere.[2,10,11] In this case, we describe pembrolizumab related irAE characterized by rash, serositis, conjunctivitis, adrenal insufficiency, and CAPS. To our knowledge, all of these side effects are widely known and reported in literature, except for CAPS. This is the first report of CAPS in a patient with checkpoint inhibition treatment. In a literature search, we found three case reports of APS and the use of checkpoint inhibitors.[12–14] However, no cases are reported with catastrophic APS following the use of immune checkpoint inhibitors. This might be explained by the scarcity of CAPS in

general, the relatively recent introduction of monoclonal antibody against PD-1 in larger patient groups, or by the fact that it is very difficult to diagnose (C)APS properly in patients who already developed multiple organ failure.[7] All patients must have evidence of involvement of three or more organ systems which develop in a short period of time, with imaging or histopathological confirmation and laboratory confirmation of antiphospholipid antibodies.[15] The sensitivity of these criteria were reviewed in 220 patients who were included in the website-based international registry of patients with catastrophic APS (CAPS registry) at 1 October 2003. In these 220 patients, that were not critically ill, 89 patients (51%) could be classified as having "definite" and 70 (40%) as having "probable" catastrophic APS.[16]

The differential diagnosis of CAPS is broad and includes many diseases. Clinical manifestations due to sepsis or acute thrombotic microangiopathy, sometimes at unusual sites, can be seen in more (catastrophic) thrombotic syndromes such as hemolytic-uremic syndrome, thrombocytopenic purpura, disseminated intravascular coagulation, heparin-induced thrombocytopenia, Hemolysis Elevated Liver enzymes and Low Platelets syndrome, Trousseau syndrome, and scleroderma renal crisis.[6,17] The diagnostic evaluation of patients presenting with multifocal progressive thrombotic events should include a thorough medical history, physical examination and additive laboratory tests. The initial laboratory findings are important to confirm the suspected diagnosis and to guide treatment. All patients should be evaluated with a complete blood count and blood film, comprehensive metabolic tests, and coagulation tests. Besides that, global testing for antiphospholipid antibodies should be performed.[17] Imaging (e.g. echocardiography or CT) plays another important diagnostic role, identifying the distribution and overall burden of the thrombotic microangiopathy.[17] Consultation of an expert ophthalmologist on retinal changes could be considered to study microangiopathy in this vascular bed.

Treatment options for caps in mods

The treatment of APS must have three aims: treat any precipitating factors (such as infections), prevent and treat ongoing thrombotic events, and probably suppress the cytokine storm.[15] Treatment of CAPS is not standardized because of the lack of literature.[15] The management of CAPS was updated by the recently published European League against Rheumatism Recommendations for the management of APS in adults.[18] The most commonly used treatments are anticoagulation, corticosteroids, plasma exchange, intravenous immunoglobulin, and/or cyclophosphamide. The study of Asherson in the 1990s showed a higher survival rate when a combination of anticoagulation corticosteroids and plasma exchange or intravenous immunoglobulin was used,[19] but this was not confirmed by a second study of the same author.[20] Until now, treatment based upon consensus and is a combination of therapeutic anticoagulation, high-dose steroids, and intravenous immunoglobulin or plasma exchange.[18] In the case of our patient, anticoagulation, high-dose corticosteroids, and plasma exchange were used. Due to the suspicion on a pleural serositis, our patient already used a high dose of prednisolone (30 mg/day) prior to hospital admission, which was switched to hydrocortisone (100 mg/day) during ICU stay. Therapeutic anticoagulation was started by low-molecular-weight heparin ad hospital admission and was continued. During ICU stay, we started with plasma exchange of which our patient only received one session due to the progressive multiple organ failure.

What to do if you admit a patient with complications of checkpoint inhibitors at the ICU?

What we have learned is that diagnosis and treatment of a patient with possible complications due to checkpoint inhibitors is only possible within a multi-disciplinary team. For intensivist, it is important to realize that in the ICU, more patients with irAEs of the treatments with checkpoint inhibitors will be admitted, because of an increase in the number of patients treated with checkpoint inhibitors due to expanded indications and better and longer cancer survival.[3,4]

Conclusion

In summary, we present a patient with multiple organ failure due to CAPS following treatment with a monoclonal antibody against PD-1 (pembrolizumab). In this case report, we highlight some important aspects of this case for diagnosis and treatment of this catastrophic disease by multi-disciplinary ICU teams.

Take home message

Immune-related adverse events are frequently observed in patients using PD-1 inhibitors and these adverse events will be more frequently observed in the ICU as well.

(C)APS can be a new immune-related adverse event in patients who are treated with PD-1 inhibitors; CAPS is hard to diagnose in the critically ill patients with multiple organ failure.

When (C)APS is suspected or diagnosed, care for these critically ill patients should be multi-disciplinary.

Author contributions

E.M., M.V., and M.v.M. drafted the manuscript. G.K.-U., G.H., and A.R. critically reviewed the manuscript and agreed with the final version.

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Informed consent

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Consent for publication

Given by the relatives of the patient.

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Supplemental material

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