Antiphospholipid Syndrome-induced Ischemic Stroke Following Pembrolizumab: case report and systematic review.

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Highlights

- Antiphospholipid syndrome may be induced by immune checkpoint inhibitors.

- Pembrolizumab may cause antiphospholipid syndrome-induced ischemic stroke.

- Immune-related antiphospholipid syndrome outcome may be favorable.

- Pembrolizumab may offer prolonged survival despite early discontinuation.

- Survival benefit of immunotherapy should influence life-saving therapy eligibility.

Abstract

Immune checkpoint inhibitors (ICI) improve the prognosis of patients with advanced non-small cell lung cancer. However, clinicians should be aware of potentially life-threatening immune-related adverse events (irAEs). We report a case of a 67-year-old man with lung adenocarcinoma who developed an acute ischemic stroke (AIS) after the second administration of pembrolizumab. The patient benefited from thrombolysis and mechanical thrombectomy with improved neurological outcome. An anti-phospholipid syndrome (APS) was diagnosed. Simultaneously, he developed a grade IV autoimmune hepatitis. Both manifestations were considered irAEs and the ICI treatment was discontinued. Steroids were initiated resulting in irAEs resolution. Remarkably, the patient achieved a complete oncological response and persistent remission after one year follow-up despite early discontinuation of pembrolizumab. Of note, APS is rarely reported as irAE. To our knowledge, this is the first case reported in the context of lung cancer. A systematic review of the literature is provided.

Keywords

Immune checkpoint inhibitors, non-small cell lung cancer, immune-related adverse event, acute ischemic stroke, antiphospholipid syndrome.

1. Introduction

Immune checkpoint inhibitors (ICI), including anti-PD1 antibodies, improve the prognosis of patients with advanced non-small cell lung cancer (NSCLC) and other systemic malignancies. Immune-related adverse events (irAEs) are unpredictable and may affect any organ. We report a case of a patient treated with pembrolizumab who developed an acute ischemic stroke (AIS) as manifestation of immunotherapy-induced antiphospholipid syndrome (APS) and provide a systematic review of the literature.

2. Case report

A 67-year-old man, recently diagnosed with NSCLC, was admitted to the emergency department with a suspected stroke. His medical history included hypertension, hypercholesterolemia, chronic obstructive pulmonary disease GOLD 3 group D, obstructive sleep apnea treated with continuous positive airway pressure, alcoholic steatohepatitis, alcoholic polyneuropathy and ischemic cardiopathy (myocardial infarction in 2006 requiring percutaneous transluminal coronary angioplasty and stenting of right coronary artery and circumflex artery). A full cardiologic assessment, including a coronarography in addition to a rest and stress echocardiography, had been performed five months earlier and had been reassuring. The patient has no personal or family history of thrombophilia nor

of pregnancy-related morbidity. He was an active heavy smoker (>60 pack-years). His oral medication consisted of acetylsalicylic acid (ASA) 160 mg, rosuvastatin 10 mg, perindopril 2.5 mg and bisoprolol 2.5 mg.

The cancer work-up done six weeks previously including full-body 18F-FDG Positron Emission Tomography (PET) and endobronchial ultrasound biopsy of the primary concluded a T4 (ipsilateral nodule separate lobe) N0 M1a (contralateral nodule) adenocarcinoma. The gadolinium-enhanced brain magnetic resonance imaging (MRI) showed no metastasis but a mild cortical-subcortical atrophy without any parenchymal signal abnormalities. PD-L1 expression profile (DAKO 22c3) showed 75% positivity in tumor cells, while EFGR, ALK and ROS1 were wild type. Next generation sequencing molecular analysis identified a single mutation in KRAS G12C.

He presented to our hospital six days after the second administration of pembrolizumab. In the emergency room, the patient complained of sudden-onset dysarthria and left hemiparesis that had appeared one hour before. His parameters included a regular heart rate at 88 bpm, blood pressure at 125/76 mmHg and room air blood oxygen saturation level at 97%. The neurological examination revealed a right gaze deviation, dysarthria, left hemiparesis, left hemisensory loss and inattention, leading to a National Institute of Health Stroke Scale (NIHSS) of 14. Baseline modified Rankin Scale (mRs) score was 0. Cardiovascular auscultation revealed no heart murmur or carotid bruit. An electrocardiogram (ECG) showed a regular sinus rhythm with a known first-degree atrioventricular block. A routine blood test was performed and revealed a grade III transaminitis (table 1). Brain Computed Tomography (CT) scan followed by CT angiography, showed a complete occlusion of the M1 distal segment of the right middle cerebral artery. Following a rapid interdisciplinary discussion, the decision was taken to offer reperfusion therapy in light of the recent introduction of ICI offering the chance of a reasonable life expectancy. Intravenous tissue plasminogen activator (Alteplase 0.9 mg/kg) was administered with an onset-to-needle time of 105 minutes. This was followed by mechanical thrombectomy (Material used: Sophia, Trevo) with an onset-to-reperfusion time of 270 minutes and a modified Thrombolysis In Cerebral Infarction score of 3 (Fig.1).

The patient's NIHSS score at 24 hrs was 6 with no sign of hemorrhagic transformation on brain CT. ASA 160 mg was therefore resumed. A neurovascular work-up was performed including a carotid and transcranial duplex ultrasonography revealing a non-significant stenosis at the intracranial carotid artery bifurcation causing some flow turbulence, a 24-hours ECG Holter monitoring showing a first-degree atrioventricular block, and a transthoracic echocardiogram demonstrating the presence of a limited aortic sclerosis and minimal mitral insufficiency. At day four, a brain MRI identified a recent ischemic stroke in the right middle cerebral artery territory, in the left cingulate gyrus and bilateral small peripheral punctiform ischemic lesions (Fig.2). Thrombophilia screening revealed the presence of anticardiolipins IgG (16 U/ml, normal < 10) and anti-beta2 GP1 IgG (83 U/ml, normal <10), while lupus anticoagulant results were negative. Antinuclear antibodies were positive at a titer of 1/160 but not identified on BLOT.

Around the same time, the patient developed a psoriasis-like grade 2 skin rash and a transaminitis worsening to grade IV within a few days. Viral serology analysis including HAV, HBV, HCV, CMV and EBV were inconclusive and anti-LKM1 antibody was negative. A liver doppler ultrasound excluded portal vein thrombosis and focal hepatic lesions. A trans-jugular liver biopsy was performed which revealed patterns suggestive of an immune-mediated hepatitis, including non-necrotic granulomas, and portal and peri-portal lymphocyte infiltrate. Moreover, no sign of venous thrombosis was found (Fig.3). In light of the grade IV autoimmune hepatitis and symptomatic APS, both considered to be severe irAEs, Pembrolizumab was discontinued. Intravenous methylprednisolone (2 mg/kg) and therapeutic low-molecular-weight heparin (LMWH) were initiated, whilst ASA was suspended. Rapid and dramatic improvements of the liver tests were observed within one week. The patient was discharged 15 days following his admission with a NIHSS score of 2 and mRS of 2, with complete resolution of his skin rash and a residual grade II transaminitis. LMWH and oral methylprednisolone were maintained at the same dosage.

Close monitoring of his blood tests showed an improvement of the hepatitis leading to a glucocorticoid tapering regimen over 2 months. At three-month follow-up, the patient showed a full neurological recovery (NIHSS 0) but remained unable to carry out all previous activities of daily-living (mRS 2). The lung CT scanner showed a complete radiological response in terms of his NSCLC (Fig.4). Only anti-beta2 GP1 IgG remained detectable at a low titer 12 weeks later. LMWH injections were stopped and ASA 160 mg/d was started at this point. One year after pembrolizumab discontinuation, antiphospholipid antibodies were undetectable with the NSCLC remaining in complete remission.

3. Discussion

During the last decade, the introduction of ICIs including anti-PD1, anti-PDL1 and anti-CTLA4 antibodies prompted a revolution in stage IV NSCLC treatment and prognosis. In a selected population of highly expressing PDL-1 tumors (≥50% PDL1 positive cancer cells), first-line pembrolizumab offers a 31.9% five-year overall survival rate [1]. However, clinicians must be aware of their new side-effect profile, otherwise known as irAEs, which may affect any organ, be unpredictable and potentially life-threatening. Pembrolizumab has been associated with a 10% risk of grade 3 or higher irAEs [2], leading to its discon- tinuation and immunosuppressive treatment.

Compared to the general population, cancer patients have a two-fold increase risk of developing stroke and lung cancer patients have one of the highest stroke-related standardized mortality ratio in the first year after diagnosis. The underlying mechanisms are common to non-cancer patients and atherosclerosis remains the most frequent cause of stroke [3]. However, several cancer's specific pathways involved in the path- ogenesis of arterial thrombosis are noted: some chemotherapies,

radia- tion therapy, cancer-supportive therapies (growth factors, stem cell transplant), invasive procedures, direct tumor effects, and coagulopathy [4]. APS is characterized by the presence of lupus anticoagulant, anti- cardiolipin and/or anti-beta2 glycoprotein 1 antibodies in patients with a history of venous or arterial thrombosis and/or recurrent miscarriages. The diagnosis of APS is based on the revised Sapporo criteria [5]. Despite being often considered an acquired autoimmune disease, APS can also be secondary to infectious or neoplastic diseases.

Our patient suffered from an AIS due to large vessel occlusion and benefited of acute reperfusion therapies. Following the assessment re- ported above, large-artery atherosclerosis and small-vessel occlusion, representing two of the most common stroke etiologies identified by the TOAST stroke subtype classification system, could be reasonably excluded. Although a cardioembolic stroke has not been ruled out at the time of the APS diagnosis, we considered the absence of atrial dilation, of arrhythmias during three days of ECG monitor and on the twenty-four hour Holter monitoring, sufficient arguments set aside this hypothesis. Indeed, neither atrial fibrillation nor other cardiac arrhythmias have not been detected during one year follow-up. Disseminated intravascular coagulation might also occur as thrombotic complication of lung cancer, however, in our case, the clinical suspicion was low and the laboratory tests were not in favour (normal Partial Thromboplastin Time and platelet count, fibrinogen slightly above the upper limit). Thrombotic thrombocytopenic purpura has been observed in patients undergoing ICI [6], nevertheless, in our case, the clinical presentation (large vessel occlusion) and paraclinical findings did not support this hypothesis.

In presence of APAs and after excluding frequent stroke etiologies, we considered an APS-induced AIS. APS diagnosis was based on the association of multiple brain arterial thromboses with the presence of anticardiolipin and anti-beta2 GP1 antibodies (and its sustained posi- tivity at 12 weeks). Although the presence of APAs prior to the reported event cannot be ruled out, symptoms appeared after ICI initiation. The causal link between ICI and APS onset is also supported by the lack of ischemic lesions on baseline brain MRI, the favorable outcome of APS and the disappearance of APAs following corticotherapy. We therefore concluded that the APS-related stroke was most likely induced by Pembrolizumab. Our patient successfully benefited from thrombolysis and thrombectomy. According to the current neurology guidelines on AIS management, extra-axial metastatic cancer is not an absolute contraindication for reperfusion procedures [7]. However, neurologists are often reluctant to aggressively treat AIS in patients with active malignancy because of the perceived increased risk of hemorrhage or poor long-term prognosis. Even if time is crucial in AIS management, reperfusion therapies should be discussed at a multidisciplinary level, on case by case basis, especially considering the potential improved life- expectancy in patients undergoing immunotherapy.

ICI induced APS is not frequently report in the literature. We per- formed a systematic review (methodology in the appendix A) for which four eligible articles were retrieved in Ovid Medline and SciVerse Scopus databases. All four are single case reports associating ICI and APAs [8–11] in the

setting of metastatic melanoma. To our knowledge, we report the first case in the context of NSCLC. The characteristics of each case, including ours, are summarized in Table 2 and discussed hereafter. All patients but one were male with a median of age of 67 years. Four out of five cases reported an APS fulfilling the revised Sapporo criteria, among which two presented a Raynaud phenomenon with distal ischemia, one a multiple organ vessel occlusion (catastrophic APS) and our patient an AIS. In three cases, concomitant irAEs were described, with hepatitis and skin rash each reported twice. Three patients showed positivity for anticardiolipin antibody, either alone or in association with another APA. Any association with a specific antibody and a

clinical manifestation or disease severity could not be found. In any case, the screening for APAs before the APS onset is reported. In three cases, the irAEs resolved after corticotherapy. ICI-induced APS occurred either early (2nd course) or late (27th course) after treatment initiation. At the time of APS diagnosis, all patients were responding partially or completely to the ICI and three of them showed a durable remission despite cessation of the immunotherapy. In all reported cases, patients were treated by at least one anti PD-1 at the time of event. However, given the small number of cases, it is too early to conclude a class effect.

The underlying physiopathological mechanism associating the onset of APS and ICI is not clearly established. So far, within the field of lung cancer, APS has been described as a rare catastrophic paraneoplastic manifestation in adenocarcinomas mostly [12]. A possible explanation of the ICI-induced APS could be that the introduction of the immuno- therapy might sustain and amplify the production of pre-existing auto- antibodies [13]. As described above, even if the clinical manifestations defining the APS appeared after the onset of ICI, in none of the cases reported baseline anti-phospholipid antibody titer is assessed. Although infrequent, a wide variety of autoimmune paraneoplastic syndrome associated to lung cancer and their corresponding auto-antibodies are documented in the literature [14]. Screening of auto-antibodies prior to ICI could help discriminating the underlaying mechanism in case of immunotherapy-induced autoimmune syndrome. However, the rele- vance of testing routinely auto-antibodies at baseline should be evaluated through a prospective translational trial.

A growing number of authors are reporting an association between the occurrence of irAEs and ICI efficacy [15]. Indeed, all patients dis- cussed above were responding to immunotherapy at the time of APS onset. A hypothesis could be that the immunogenic cancerous cell death induced by the ICI and the subsequent exposure of self-antigens may represent the *primum movens* of the autoimmune response in a pro- inflammatory environment. This might be particularly true for anti-cardiolipin antibodies since these phospholipids are widely represented in mitochondria membrane.

APAs, especially anticardiolipin and anti-beta2 GP1, have also been

reported in association with autoimmune liver disease, which might suggest that ICI-induced hepatitis may play a role in APS pathogenesis [16].

We would recommend screening of ICI induced APS in case of arte- rial thrombosis remaining unexplained after classical workup. Immune- related APS or arterial thrombosis management are not specifically discussed in the published scientific societies guidelines. Based on the few reported cases it is difficult to recommend a definitive approach.

Considering the potential catastrophic outcome of an ICI induced APS we would classify this adverse event as grade III or IV, depending on the location of the thrombosis. Beyond anticoagulation specific to APS, we would recommend to follow the published statement on the common attitude for severe irAEs: permanently discontinuation of ICI, and immunosuppression, starting with high dose steroids (prednisone 1 to 2 mg/kg/d or methylprednisolone 1 to 2 mg/kg/d) [17].

If indicated, revascularization procedure should be performed as soon as possible taking in account the risk benefit ratio and a secondary prevention with anticoagulation should be initiated. Apart from cancer population and pregnancy, vitamin K antagonist (VKA) (International Normalized Ratio (INR) 2–3) and low dose aspirin or VKA alone (INR 3–4) remains the first choice [18]. Efficacy and safety data of LMWH in this indication are missing and this treatment is usually considered in case of recurrence on well conducted VKA. Considering that LMWH is more efficient (recurrence of venous thromboembolism event) and safer than VKA (less of clinically relevant non-major or minor bleeding) as secondary prevention of venous thromboembolism in cancer patients [19], we suggest considering LMWH as a front-line option in case of ICI induced APS.

4. Conclusion

Immune checkpoint inhibitors revolutionized the therapeutic approach to NSCLC. Alongside undeniable benefits, clinicians must be aware of unpredictable and potentially severe irAEs, including APS. This syndrome might occur in patients responding to immunotherapy and, if promptly detected and treated, could have a minimal impact on the overall outcome. Potential improvement in the life expectancy of cancer patients undergoing immunotherapy might influence the decision-making process in providing life-saving therapies in this population.

Disclosure statement

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Figures legend

Figure 1. Cerebral arteriography showing occlusion of the M1 distal segment of the right middle cerebral artery (A) and its revascularization after thrombectomy (B).

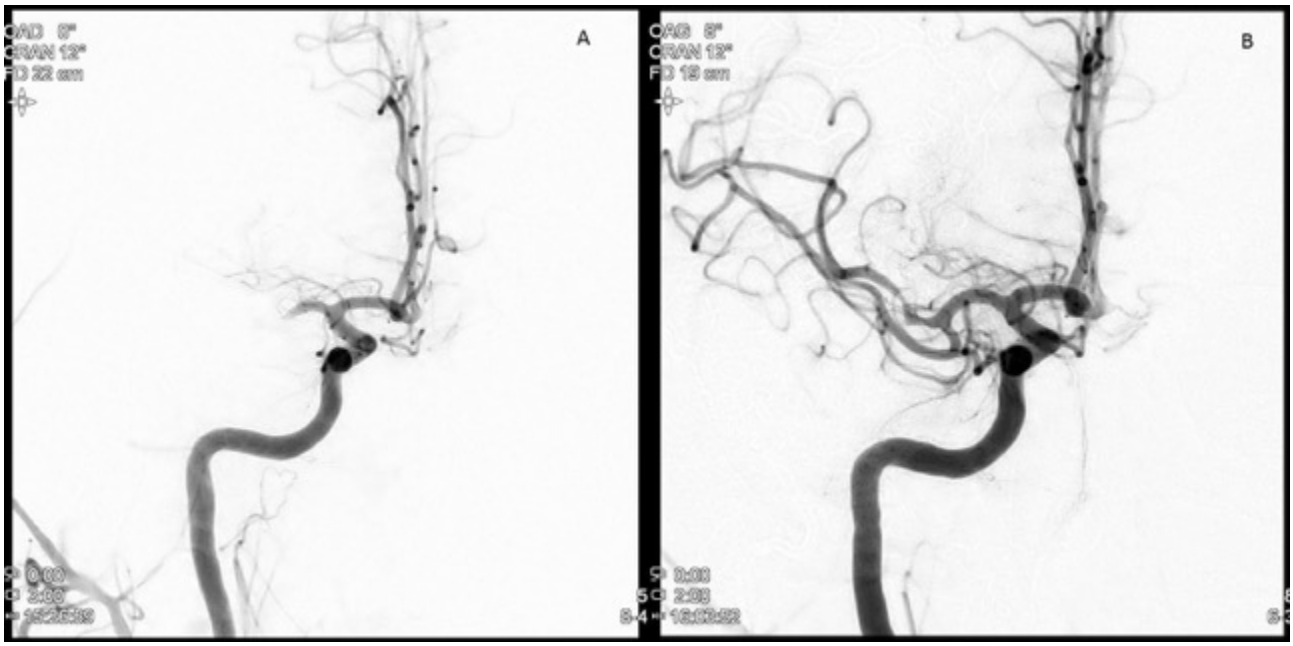

Figure 2. Brain MRI diffusion-weighted sequence imaging done at day 4 showing synchronous bilateral signal abnormalities within the right middle cerebral artery (A) and left anterior cerebral artery (B) territories.

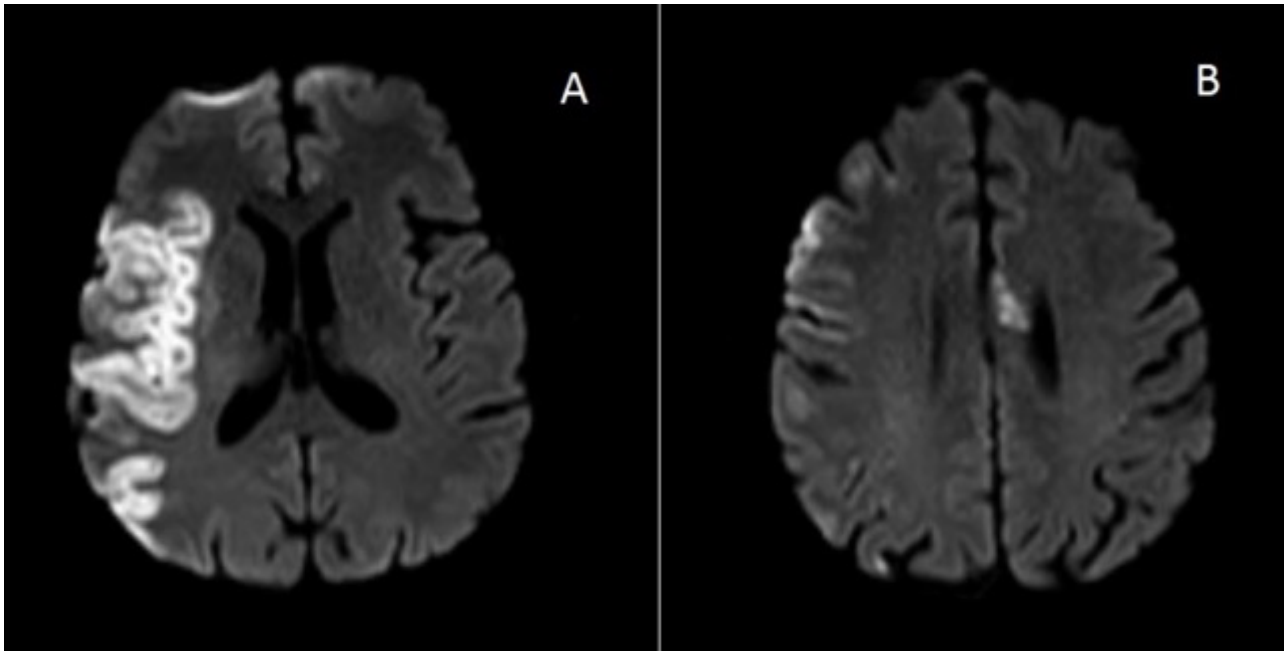

Figure 3. Histopathology of the liver trans-jugular biopsy (hematoxylin and eosin staining * 200). Picture A: The horizontal arrow indicates a non-necrotic granuloma whilst the vertical arrow points towards a peri-portal inflammatory infiltrate. Picture B: The arrow points towards a portal space invaded by lymphocytes. No sign of venous thrombosis was found.

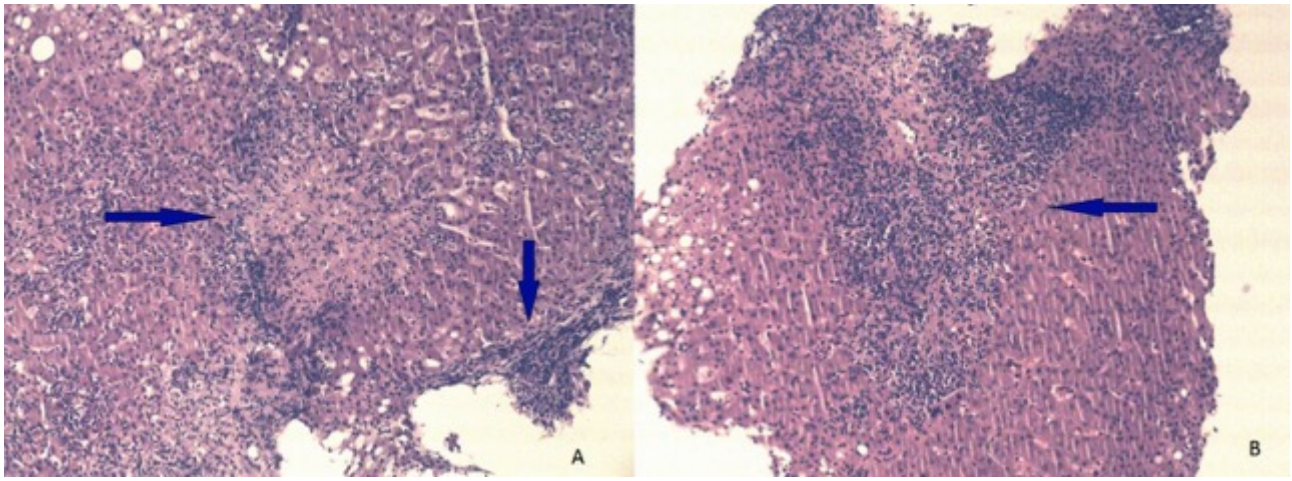

Figure 4. Lung CT performed at diagnosis (left column, A and B) showing two separate lesions in the right upper lobe, with complete resolution 3-months after the first course of Pembrolizumab (right column, C and D).

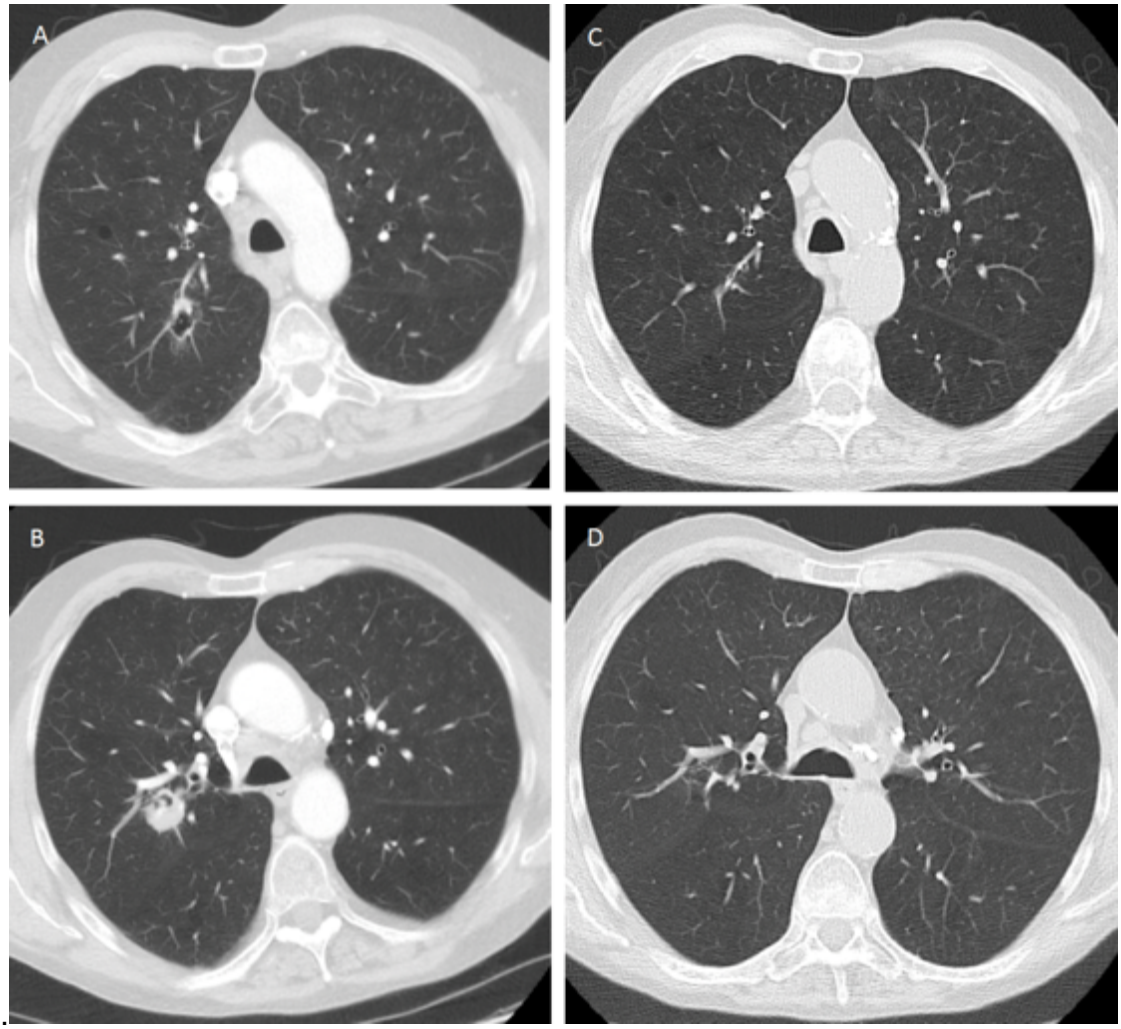

Table 1 – Relevant routine blood test results at admission.

White blood cell count	10,7 thousands/mm³ (NV 4.2 - 11.4)
Hemoglobin	12,2 g/dL (NV 13.5 - 17.6)
Platelets	337 thousands/mm³ (NV 174 - 402)
Partial Thromboplastin Time	80% (NV > 70%)
Activated partial thromboplastin time	26,4 sec (NV 20-36)
Fibrinogen	486 mg/dl (NV 200-400)
Creatinine	0,71 mg/dL (NV 0,2-1,2)
Alanine transaminase (ALT)	212 U/L (NV 7-37)
Aspartate transaminase (AST)	223 U/L (NV 7-40)
Gamma glutamyl transpeptidase (GGT)	71 U/L (NV 10-64)
Alkaline phosphatase (ALP)	97 U/L (NV 40 – 150)
C-reactive protein	28,9 mg/L(NV <5)

NV: Normal values; mm: millimeters; g: grams; mg: milligrams; U: units; dL: deciliter; L: liter

Table 2

Reference (n)	Age	Sex	APS criteria	Other irAEs	Histology and stage	Immunotherapy (cycle at event)	Treatment of the APS	APS Evolution	Response to ICI
2017 Gupta et al (4)	62	M	- Clinical criteria : Raynaud phenomenon with distal ischemia - Laboratory criteria: anti-beta2 glycoprotein 1 IgM	- Hepatitis - Hypothyroidism	Melanoma Stage IV	Ipilimumab-Nivolumab (4)	- UFH first, then LMWH - Prednisone - Definitive ICI discontinuation	Clinical and biological resolution	- At event: PR - Follow-up : CR (timing unknown)
2018 Sanchez et al (5)	60	F	- Clinical criteria: Raynaud phenomenon with distal ischemia - Laboratory criteria: anticardiolipin IgG, Lupus anticoagulant	None	Melanoma Stage IIIb	Pembrolizumab (10)	- Prednisolone 1 mg/kg/d - Definitive ICI discontinuation	Clinical resolution	- At event: PR - Follow-up: PR at 7 months
2018 Aburahma et al (6)	71	M	- Clinical criteria : unfulfilled - Laboratory criteria: Lupus anticoagulant (death before 12-weeks)	Not defined	Melanoma Stage IV	Nivolumab (3)	- Vitamin K - Prednisolone 60 mg - ICI discontinuation	NA (early death)	
2020 Mintjens-Jager et al (7)	74	M	Catastrophic APS - Clinical criteria : multiple vessel occlusion - Laboratory criteria: anticardiolipin IgM and IgA (post-mortem pre-hospitalisation blood sample analysis)	- Skin rash - Serositis - Conjunctivitis - Adrenal insufficiency	Melanoma Stage IV	Pembrolizumab (27)	- LMWH - Prednisolone first, than - Hydrocortisone - Plasma exchange - ICI discontinuation	Resulting in death	- At event: PR - Follow-up : NA
2021 Tota et al (*)	67	M	- Clinical criteria : Acute Ischemic Stroke - Laboratory criteria: anticardiolipin IgG, anti-beta2 glycoprotein 1 IgG	- Hepatitis - Skin rash	Lung Adenocarcinoma Stage IV	Pembrolizumab (2)	- LMWH - Prednisolone 2 mg/Kg/d - Definitive ICI discontinuation	Clinical and biological resolution	- At event: PR - Follow-up : CR at 1 year

ICI: immune-checkpoint inhibitor; IrAE: immune-related adverse events; APS: antiphospholipid syndrome; NSCLC: non-small lung cancer, UFH: unfractioned heparin; LMWH: low-molecular-weight heparin; IgM: immunoglobulin M; IgG: immunoglobulin G; PR: partial response; CR: complete response; NA: not applicable

Appendix A. Methodology of the systematic literature review and search strategy.

A literature search was conducted and updated last on february 2021 using the Ovid Medline and SciVerse Scopus databases. These researches were performed by a scientific librarian experienced in searching for medical and scientific publications.

The ‘‘PICO’’ (population, intervention, comparator, outcome) model for clinical questions was used to identify the concepts included in the questions. The corresponding search criteria of “P” and “I” were translated into MeSH terms, and free-text keywords that were searched for in titles, abstracts and name of substances in Medline and in titles, abstracts and keywords in Scopus.

List of MeSH terms and free-text keywords used to search Ovid Medline database

Database: *Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline® Daily and Ovid Medline® 1946-present*

P criterion	**Searched MeSH terms, free-text keywords and phrases**
Antiphospholipid Syndrome	Antiphospholipid Syndrome/ OR anti phospholipid syndrome*.ti,ab OR anti phospholipid antibody.ti,ab OR antiphospholipid syndrome*.ti,ab OR antiphospholipid antibody.ti,ab OR hughes syndrome*.ti,ab OR soulier syndrome*.ti,ab OR exp Antibodies, Antiphospholipid/ OR cardiolipin*.ti,ab OR anticardiolipin*.ti,ab OR lupic anticoagulant.ti,ab OR lupus anticoagulant.ti,ab OR lupus Coagulation Inhibitor.ti,ab OR Lupus Anticoagulant.ti,ab
I criterion	**Combined with AND**
anti-PD1 immunotherapy	anti-PD1.ti,ab OR anti-PD-L1.ti,ab OR Atezolizumab.ti,ab,nm OR MPDL3280A.ti,ab,nm OR Avelumab.ti,ab,nm OR Durvalumab.ti,ab,nm OR Nivolumab/ OR Nivolumab.ti,ab,nm OR opdivo.ti,ab,nm OR Pembrolizumab.ti,ab,nm OR Cemiplimab.ti,ab,nm OR Ipilimumab/ OR anti-CTLA-4.ti,ab,nm OR yervoy.ti,ab,nm OR tremelimumab.ti,ab,nm OR Keytruda.ti,ab,nm

List of free-text keywords used to search Scopus database

P criterion	**Searched free-text keywords and phrases**
Antiphospholipid Syndrome	TITLE-ABS-KEY("Antiphospholipid Syndrome" OR "Antiphospholipid Syndromes" OR "anti phospholipid syndrome" OR "anti phospholipid syndromes" OR "anti phospholipid antibody" OR "antiphospholipid syndrome" OR "antiphospholipid syndromes" OR "antiphospholipid antibody" OR "hughes syndrome" OR "hughes syndromes" OR "soulier syndrome" OR "soulier syndromes" OR cardiolipin*.ti,ab OR anticardiolipin* OR "lupic anticoagulant" OR "lupus anticoagulant" OR "lupus Coagulation Inhibitor")
I criterion	**Combined with AND**
anti-PD1 immunotherapy	TITLE-ABS-KEY(anti-PD1 OR anti-PD-L1 OR Atezolizumab OR MPDL3280A OR Avelumab OR Durvalumab OR Nivolumab OR opdivo OR Pembrolizumab OR Cemiplimab OR Ipilimumab OR anti-CTLA-4 OR yervoy OR tremelimumab OR Keytruda)

Legend: *term*/ = MeSH term (with all the possible subheading combinations)
.ti,ab,nm = terms are searched in the title, the abstract and the name of substance
TITLE-ABS-KEY() = terms are searched in the title, the abstract and the keywords
* = stands for zero or more characters