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Clinical Manifestations in patients with antiphospholipid antibodies: beyond thrombosis and pregnancy loss.

Cecchi Irene MD^{1*}, Radin Massimo MD^{1*}, Rubini Elena MD¹, Foddai Silvia Grazietta MD^{1,2},
Barinotti Alice MSc^{1,2}, Roccatello Dario MD^{1,3}, Sciascia Savino MD-PhD^{1,3}

1. Center of Research of Immunopathology and Rare Diseases- Coordinating Center of Piemonte and Aosta Valley Network for Rare Diseases, S. Giovanni Bosco Hospital, Department of Clinical and Biological Sciences, University of Turin, Italy.
2. School of Specialization of Clinical Pathology, Department of Clinical and Biological Sciences, University of Turin, Italy.
3. Nephrology and Dialysis, Department of Clinical and Biological Sciences, S. Giovanni Bosco Hospital and University of Turin, Italy.

*These Authors equally contributed to the manuscript

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Corresponding Author: Massimo Radin, MD

Center of Research of Immunopathology and Rare Diseases- Coordinating Center of Piemonte and Valle d'Aosta Network for Rare Diseases, and SCU Nephrology and Dialysis, Department of Clinical and Biological Sciences, S. Giovanni Bosco Hospital and University of Turin, Italy.

Piazza del Donatore di Sangue 3, 10154, Turin, Italy.

Email massimo.radin@unito.it Tel +390112402056 Fax +390112402052

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Abstract

The clinical spectrum of the antiphospholipid syndrome (APS) encompasses additional manifestations other than thrombosis and pregnancy morbidity, which may potentially affect every organ and system. The pathophysiology of APS indeed cannot be explained exclusively by a prothrombotic state and the “extra-criteria” manifestations of the syndrome should be attributed to other mechanisms, such as inflammation, complement and platelet activation. In this case-series, we report patients with uncommon clinical APS presentations, to highlight relevant peculiarities of the syndrome, potentially paving the way for a further update of clinical as well as laboratory manifestations of this complex immunological condition.

Introduction

Since its first description in early 80s, antiphospholipid syndrome (APS) has been considered among the major acquired thrombophilia conditions. At least one clinical event (vascular thrombosis or recurrent pregnancy morbidity) in patients with antiphospholipid antibodies [aPL, namely lupus anticoagulant (LA), anticardiolipin (aCL) and/or anti- β 2-glycoprotein I antibodies (a β 2GPI)] have to be met for the classification of APS [1]. Thrombosis in APS, often recurrent, can potentially occur in any vascular bed (arterial, venous and the microvasculature) and this represents a major peculiarity of this syndrome, potentially explaining the heterogeneity of clinical manifestations described in patients with aPL. Besides, the clinical spectrum of the disease encompasses additional manifestations which may affect every organ and cannot be explained exclusively by a prothrombotic state. In fact, while most of the clinical manifestations can be attributed to underlying thrombosis, other mechanisms (including inflammation, complement and platelet activation) have been shown to play crucial roles in the pathophysiology of the syndrome [2].

In this case-series, we aim to report patients with uncommon clinical APS presentations, to highlight relevant peculiarities of the syndrome, potentially paving the way for a further update of clinical as well as laboratory manifestations of this complex condition.

Cases 1&2: with multi-occlusive arteritis and high-risk APS.

The two patients presented with similar features: at the time of their first clinical manifestation, they were both young males with a silent previous medical history and had no cardiovascular risk factors but active smoking habit in one of the two subjects.

In Patient 1 (24 years old) the first clinical manifestation of the disease was a sudden debilitating claudication at the right limb. After instrumental investigation, made by color Doppler ultrasonography, a critical stenosis of the right posterior tibial artery was documented. The multi-occlusive disease was confirmed at angiography, that showed the presence of multiple stenosis of the right renal artery, celiac artery, right common iliac artery and right posterior tibial artery.

Similarly, Patient 2 (29 years old) had a sudden episode of arterial hypertension, with headache and flushing. At Doppler echocardiography, a critical stenosis of the right renal artery was discovered and at the angiography examination, along with other critical stenosis at the mesenteric superior artery, celiac artery and right colic artery levels.

At the laboratory investigations, both patients were antinuclear antibodies (ANA) positive, whereas extractable nuclear antigens (ENA) and anti-double stranded DNA antibodies (anti-dsDNA) were found to be negative, complement within normal range and highly positive test for aPL, including LA, aCL IgG and a β 2GPI IgG antibodies.

Both patients were treated with stenting of the affected arteries and anticoagulated, firstly with low molecular weight heparin (LMWH) and then switched to vitamin K antagonists (VKAs) with a target international normalized ratio (INR) of 2 to 3, in addition to anti-platelets therapy.

Clinical and laboratory characteristics of the two patients are resumed in Table 1.

Differential diagnosis, in both cases, was considered with Takayasu arteritis (TA), fibromuscular dysplasia and thromboangiitis obliterans. For all these clinical entities there are reported the association of thrombophilic disorders. TA is a rare large-vessel vasculitis variant that affects predominantly young women [3]. TA affects the aorta and its main branches and the pulmonary arteries [4]. TA is commonly seen in Japan, South East Asia, India, and Mexico.

While some cases of patients with TA combined with APS are reported in the current literature [5], these cases are very rare and most of the reported patients had single or double aPL positivity, whether the patients described here had not only a triple aPL positive profile at laboratory investigations, but also other extra-criteria features of APS [1]. In fact, patient 1 had thrombocytopenia (as low as 5000/mm³), retro right malleolus-Achilles ulcers, *livedo reticularis* at lower limbs; after the diagnosis of APS, patient 2 was fully investigated, and white matter lesions at the brain magnetic resonance (MRI) compatible with previous ischemic lesions were found. This is in line with the concept that patients with a higher risk profile (multiple aPL positive, history of arterial thrombosis) should undergo careful routine evaluation and risk assessment. This is particularly important for the risk of developing further arterial events and extra-criteria manifestations of APS.

Case 3: Leukoencephalopathy and lupus anticoagulant

A 49 years old Caucasian woman was admitted in March 2020 to our Centre for immune-rheumatological evaluation after she experienced, two months before, a sudden episode of loss of consciousness, preceded by prodromes including dizziness, muscle weakness, malaise and nausea. At the time of the first event, complete physical examination, along with serological and imaging assessment, including brain and facial bone CT scan, abdominal ultrasonography, chest x-ray and electrocardiogram, were performed at the emergency unit, showing no abnormalities. Therefore, she was discharged without further indications. In the following days, she complained of left temporal headache, associated with nausea, asthenia, malaise and mental confusion. Based on the persistence of these symptoms, an angiographic and MRI study of the brain and the spine were performed, highlighting the presence of

multiple confluent periventricular areas of increased white matter signal on T2 and FLAIR sequences, in the absence of vascular malformations and stenosis (Figure 1).

Her previous medical history was silent (no previous history of diabetes, cardiovascular events, renal disease, obesity, alcohol abuse, smoke habit, oncologic disease, previous thrombotic events, nor pregnancy complications). She also reported no family history of neurological and immune-rheumatic conditions. However, the following comorbidities were present: arterial hypertension treated with anti-hypertensive drugs and migraine associated with phono- and photophobia.

During the admission, she developed mild gait difficulties associated with myalgia particularly involving the upper limbs, and inflammatory arthritis of both hands and wrists responsive to low doses of oral steroids. Physical examination was otherwise unremarkable.

Serological evaluation and laboratory tests demonstrated increased levels of C-reactive protein (CRP) and erythrocyte sedimentation rate, along with elevated platelets count, fibrinogen and d-dimer, with normal complement levels. No remarkable alteration at full blood count (FBC). She underwent a complete diagnostic screening for neurological, genetic, cardiovascular, metabolic and infectious disease, including full body CT scan and positron emission tomography, echocardiography, lumbar puncture and electroencephalogram, among others, showing no significative alteration. Immunological assessment highlighted the presence of LA positivity, whereas ANA, ENA, anti-dsDNA, aCL and a β 2GPI antibodies turned out all negative.

Thereafter, the patient was discharge in good clinical conditions. After strict clinical follow-up patients' conditions remained stable and no further episode of loss of consciousness, movement, articular or muscular symptoms or associated neurological sign were recorded.

Furthermore, LA positivity was confirmed after 12 weeks and anti-platelets therapy was, therefore, started for prophylactic purpose while steroid treatment was stopped.

Ischemic neurological events are life-threatening common features in APS spectrum of manifestations, while non-thrombotic involvement of the peripheral and central nervous system (CNS) is less well documented and their pathogenic link with aPL positivity is still unclear [6]. Nevertheless, several neuro-psychiatric conditions have been observed in association with APS and the presence of aPL, such as migraine, cognitive dysfunction, and seizures [7–9]. Indeed, in addition to their well-proven pro-thrombotic potential, both animal and *in vitro* models demonstrated that aPL are able to induce permeability of the blood–brain barrier and directly bind neurons and glial cells, supporting the idea that an immune-mediated mechanisms of action is also involved in the pathogenesis of these manifestations [10,11].

This patient presented with a peculiar form of leukoencephalopathy, characterized by multiple periventricular white matter lesions, in the persistent presence of LA positivity, progressively developing movement disorders and cognitive impairment, in the absence of other recognized risk factors, except for arterial hypertension and migraine. One should also acknowledge that, while the patient was tested for infectious diseases, a viral etiology should not be fully excluded.

Despite white matter lesions represent the most common imaging abnormality found in aPL positive subjects, proper characterization and classification of these findings are still lacking, leading to diagnostic delay and inadequate management.

Case 4: aPL in a woman with belly dancer's dyskinesia

A 51 years old female patient referred to our attention in February 2020 after the sudden onset of a neurological disorder in aPL positivity setting.

The patient had been complaining of anterior abdominal wall muscles' involuntary movements for about a month (Video 1). She denied any trauma, spinal or abdominal surgeries, at the same time her clinical history reported a chronic pericarditis and the last cardiac MRI showed an abundant circumferential pericardial effusion in the inferolateral site. Previous lab tests showed the presence of aCL [IgM isotype, medium titers (40-60 U/ml)], although she did not report previous arterial and/or vein thrombosis nor positive history of pregnancy morbidity. Upon suspicion of ischemic cerebral event, a brain and spinal MRI was performed along with cerebrospinal fluid analysis. Both investigations resulted negative, potentially ruling out infectious processes and CNS injuries. An electromyography was performed, documenting a typical dystonic involuntary activity affecting the abdominal muscles, while the diaphragmatic activity appeared regular. Those findings were considered in line to Belly dancer's dyskinesia (BDD), which is a rare phenomenon characterized by involuntary and repetitive rhythmic movements of the abdominal wall, often accompanied by abdominal pain. A tendon muscle ultrasound of the abdominal wall was performed, highlighting a dystonic pattern prevalent in the left oblique and rectum muscles, supporting the diagnosis of abdominal focal dystonia such as belly dancer's syndrome.

Many different causes were involved to explain the occurrence of BDD, the most frequent mentioned were disorders of the CNS, in particular encephalitis, peripheral nervous system or organic diseases, spinal malignancies, disc herniations, psychogenic factors, trauma to the spine or head, drugs, metabolic deficiencies or biochemical abnormalities [12]. The occurrence in autoimmune diseases, while documented [13] is extremely rare.

Several treatments have been used in BDD in which, because of the rarity of the syndrome, current therapeutic approaches are based on case reports and small case series. Those include benzodiazepines, anti-cholinergic agents, valproate, and carbamazepine. Physical therapeutic option might be represented by transcutaneous electrical nerve stimulation, deep brain stimulation, and botulinum toxin injection. Based on the current literature, our patient was submitted to botulinum toxin treatment [14] and later to triephenidyl hydrochloride administration, both therapies were completed with only partial benefit.

Since APS first description, different neurological events have been reported even in absence of vascular thrombosis. Movement disorders are known to be part of the clinical spectrum of APS [15], but their aetiology is not clearly understood. Nevertheless, a relationship between chorea and aPL has been established and the neurotoxic effect of aPL might be responsible for basal ganglia cell dysfunction and development of neuroinflammation [10]; furthermore, aPL may also activate endothelial cells and inflammatory vasculopathy resulting in ischemic insult to the basal ganglia.

With reference to our case, a direct correlation between patient's underlying disease, in its idiopathic meaning, and the autoantibody positivity could not be proved. Indeed, the concomitant presence of aPL and movement disorder in this case does not necessarily imply a causality link. However, due to the lack of reliable treatment options, it has been decided to start an *ex juvantibus* therapy with LMWH at prophylactic dose (enoxaparin 4000 IU/daily) for 6 weeks with a significant reduction of involuntary movements. Unfortunately, LMWH was suspended due to occurrence of erythematous skin lesions at lower limbs, which immediately disappear when heparin was stopped. After 6 months of clinical and serological follow-up the

patient remains asymptomatic, without any sign of involuntary dystonic movement or abdominal pain.

Case 5: Aortic thrombosis and high positive anti-phosphatidylserine/prothrombin antibodies

A 55-years old woman presented at the emergency room (ER) with a new onset of purpura at lower limbs. An FBC was performed showing low platelets count (4000/mm³). She was therefore transferred to our Centre and complete medical assessment was made. At the time of the event she was an active smoker, with no family history of immune-rheumatologic disease. She had a previous history of six unexplained early miscarriages (before 9 weeks of gestation) in her 30s. She also presented several episodes of retinal detachment.

During her hospitalization she was found to be negative for both aCL and a β 2GPI antibodies but turned out to be positive for LA (medium-high titre), ANA (high titer with homogeneous pattern), ENA-SSA, hypocomplementemia (C3, C4) and prolonged partial thromboplastin time. The patient was then managed with intravenous immunoglobulin and high dose of steroids (oral prednisone 50 mg/daily), with a gradual resolution of thrombocytopenia.

After three months, she presented again at the ER with diffuse abdominal pain, plegic and marbled lower limb, and femoral hyposphigmia. A CT angiogram showed a massive abdominal aortic thrombosis (Figure 2), that made it necessary an emergency surgical aortic thrombectomy. The patient was also treated with steroids (methylprednisolone 60 mg IV) , in addition to LMWH to prevent the onset of new thromboses and with anti-CD20 monoclonal antibody (Rituximab 375 mg/m² intravenous). During the hospitalization she showed a significant increase in platelet count, but immunological screening turned out all negative

including LA, anti-dsDNA, aCL and a β 2GPI antibodies. Interestingly the patient was found to be highly positive for anti-phosphatidylserine/prothrombin antibodies (aPS/PT) IgM isotype.

The patient was later switched to VKAs with INR target 2-3. Thereafter, maintenance therapy was decided using Rituximab infusions (500 mg IV every 3 months) with tight clinical follow-up. During the following 2 years the patient remains stable, FBC was normal and color doppler ultrasonography was unremarkable. Based on her clinical conditions, the treatment with Rituximab was suspended and maintenance treatment with intravenous immunoglobulins (20 g/monthly) was started in addition to long-term aspirin and VKAs.

In summary, we are dealing with an APS patient with a criteria thrombotic (massive abdominal aortic thrombosis) and extra-criteria haematological (severe thrombocytopenia) manifestations, in addition to several events of early miscarriages. Due to the complexity of her clinical presentation, she suffered for a delay in the clinical diagnosis of APS, as debated elsewhere [16]. Nevertheless, for the purpose of this report, it is interesting to focus on the immunological profile of this patients who did fulfil traditional classification criteria for APS, showing negativity for aCL and a β 2GPI, and inconstant positivity for LA [1]. Nonetheless, we have to consider that classification criteria, in the context of low-prevalence conditions, may fail to encompass all aspects of the disease, including both clinical and laboratory findings, leading to an underdiagnosis of a potentially life-threatening condition. Moreover, in APS setting, the number of antibodies that have been associated with this syndrome is constantly increasing [17]. Among these specificities, aPS/PT antibodies are very promising, and they were found to be strongly positive in our patient. aPS/PT are part of the “extra-criteria” aPL antibodies and have been proposed as an additional tool to be considered in APS diagnosis and risk stratification [18–20]. When looking at those patients such as the one reported here, at high clinical suspicion of APS, but without persistent positivity for traditional aPL, we have

to take into consideration the emerging role of these autoantibodies specificities in order to assure an earlier and correct diagnosis, that is crucial for a better prognosis and the quality of life of the affected subjects.

Case 6: haemorrhagic adrenal infarction and high-risk aPL profile

A 36-year old man referred to the ER of our hospital on June 2019 with acute onset of left flank pain. He had been diagnosed with primary APS at the age of 16, when he suffered from deep vein thrombosis and subsequent pulmonary embolism after being bedridden for an orthopaedic surgical procedure. He resulted positive for LA, aCL at high titers and a β 2GPI IgG antibodies [1]. He was started on VKAs and cilostazol. At age of 34 he suffered a thrombotic recurrence at his left foot distal artery, and therefore therapy was implemented with clopidogrel and hydroxychloroquine (200 mg/daily).

At admission, neurological, cardiological and pulmonary examination were unremarkable. Laboratory analysis showed neutrophilic leukocytosis, INR of 4.15, increased CRP, normal urine analysis. Painkillers were administered, without success. Considering patient's comorbidity, after normal chest and abdominal radiography, an abdomen CT scan was carried out. A 3.6 cm left adrenal mass with not homogeneous high density and periadrenal fat stranding was identified. Post contrast mass resembled hypodense; imagines were concordant with haemorrhagic adrenal infarction (Figure 3). VKAs was switched to LMWH, to better control the haemorrhagic risk, while surgery was not recommended considering patient's clinical history. Mild hyponatremia (132 mEq/L) and asthenia emerged on the third day of hospitalization, but cortisol, ACTH levels and blood pressure always remained in range. As a precautionary measure, steroid supplement was initiated. Left adrenal mass resulted unchanged in a second CT scan examination, conducted after 5 days from the prior. The

patient was dismissed after 10 days and switched back to VKAs plus clopidogrel and hydroxychloroquine (200 mg/daily).

Adrenal haemorrhagic infarction, or adrenal haemorrhage alone, is the most common endocrinological disorder in APS, even if its incidence is really low [21–23]. It's described both as monolateral and bilateral, the latter more frequently reported in catastrophic APS and in high risk aPL profile patients [24,25]. Glandular involvement is portrayed as first manifestation of the syndrome or as recurrence, as appeared in our patient. Infection, surgery, malignancies, anticoagulant withdrawal or switching from oral anticoagulant to heparin are the most frequent precipitating factors. In our case, concurrent out of range INR and high-risk aPL profile might have acted as adding risk elements. Moreover, our patient has a poor adherence to medical care, and he skipped all the follow-up visits since last recurrence episode, and therefore his therapeutic compliance to VKAs was difficult to assess.

Adrenal anatomy determines propensity to vascular accidents. In fact, glands' blood supply is characterized by a rich arterial net that drains into a single vein [26,27]. Adrenal thrombosis appears to be the initial insult to the gland, followed by obstruction of the arterial supply, increased arterial blood pressure and bleeding, particularly in the capillaries within the distal corticomedullary junction.

Adrenal insufficiency, present when more than 90% of the glands are compromised, is a severe and potentially life-threatening condition, that can exert abruptly or in a progressive indolent way, therefore adrenal function should be monitored after any thrombotic or haemorrhagic event in APS patients, as reported in literature [23,28,29]. In our patient, hyponatremia and asthenia were the only two symptoms, abdominal pain aside, probably because the counterpart gland, after the acute phase which might have sustained antidiuretic hormone increase and consequent dilutional hyponatremia, supported the normal

homeostasis. In conclusion, adrenal infarction in APS is relatively rare, but considering the life-threatening risk of a concurrent or consequent adrenal insufficiency, this type of event should be taken into consideration when a patient with APS manifests abdominal pain.

Case 7: Massive microangiopathy

In January 2017, a 16 years old patient was admitted for a sudden onset of hypertensive crisis, associated with intense headache and mental confusion. Complete clinical and family history was collected but no significant data emerged. A careful examination was therefore performed showing the stenosis of the left renal artery with severe renal impairment, along with multiple ischemic areas in the spleen. Laboratory tests documented high positivity for LA, aCL IgG, and a β 2GPI both IgG and IgM isotypes. Based on these findings, APS diagnosis was confirmed, and the patient was started with LMWH at anticoagulant dose (parnaparin sodium 4000 IU and 3000 IU once a day). After a few months, the patient underwent a left nephrectomy, giving the low residual functionality of the left kidney. Kidney's histology showed luminal narrowing of arteriole and glomerulus exhibiting ischemic features (Figure 4).

Thereafter, the patient was switched to VKAs at INR target 2-3 and tightly followed-up with a multidisciplinary approach, both nephrological and immunological, with good outcome.

The case described above represents a dramatic presentation of APS in a young male with no previous history of thrombosis and no traditional cardiovascular risk factor. The association with renal artery occlusion and APS nephropathy (thrombotic microangiopathy) which manifested with a rapid onset of severe arterial hypertension, in the absence of nephrotic syndrome, or haematuria, might be explained based on the high risk aPL profile (triple positivity). The patient tested positive for a β 2GPI domain 1 (β 2GPI-D1) antibodies, which are

now recognised to bind a critical immunogenic epitope in APS setting [30]. This finding was in line with our recent data [31] showing that a β 2GPI-D1 identifies aPL -related injuries in patients with renal manifestations. Indeed, while the presence of anti- β 2GPI-D1 antibodies could not be considered the sole cause of renal involvement in this case, they might represent an important additional tool in order to better profile APS patients and to stratify their thrombotic risk, leading to a more personalized therapeutic strategies and management.

What have we learned from these cases?

Over the last decade since Sydney criteria were detailed, a significant body of basic research and clinical studies on APS has emerged, potentially paving the way for a further update of clinical as well as laboratory manifestations included in the current classification criteria. In fact, a series of clinical features, that are not currently included in the classification criteria, but are recognized to be related to the presence of aPL have been named non-classical or extra-criteria clinical and laboratory manifestations. These clinical features are not exclusively related to thrombosis, and they can occur also when thrombosis is not evident.

Finally, while one should bear in mind that APS is still a rare disease and that the presence of aPL should be weighted taking into account the clinical settings and all the potential differential diagnoses, especially when referring to extra-criteria manifestations.

Addressing the value of clinical extra-criteria presentation beyond thrombosis and pregnancy morbidity is crucial, as they may add prognostic and morbidity correlations, provide a fertile field for research, impact on treatment and improve patient outcome.

Legend of Figures, Tables and Video

Table 1. Clinical and laboratory characteristics of Cases 1 and 2: patients with multi-occlusive arteritis and high-risk APS.

Video 1. Anterior abdominal wall muscles' involuntary movements experienced by the patient of Case 4.

Figure 1. Presence of multiple confluent periventricular areas of increased white matter signal on T2 and FLAIR sequences, in the absence of vascular malformations and stenosis.

Figure 2. Massive aortic thrombosis showed at CT angiogram

Figure 3. Haemorrhagic adrenal infarction at abdominal CT

Figure 4. Histological features of kidney with luminal narrowing of arteriole and glomerulus exhibiting ischemic features: fibrinoid necrosis of pre glomerular arterioles, intimal hyperplasia and *onion skin* lesions with fibrin insudation.

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| | Patient 1 | Patient 2 |
|---|---|---|
| Sex | Male | Male |
| Age at diagnosis (years) | 24 | 29 |
| First clinical manifestation | Claudication, due to the stenosis of the right posterior tibial artery | Episode of arterial hypertension due to the stenosis of right the renal artery |
| Angiography at diagnosis | Multiple stenosis of the right renal artery, celiac artery, right common iliac artery and right posterior tibial artery | Multiple stenosis of the right renal artery, mesenteric superior artery, celiac artery and right colic artery |
| Treatment | Stenting of the celiac and tibial artery and VKA (target therapy 2-3 INR) | Stenting of the renal artery, steroids and VKA (target therapy 2-3 INR) |
| Other relevant clinical manifestations at diagnosis and/or follow-up | Thrombocytopenia, retro right malleolus-achilleus ulcers, <i>livedo reticularis</i> at lower limbs | White matter lesions at the Brain MRI compatible with previous ischemic lesions |
| aPL profile | Triple positive | Triple positive |
| Risk factors and relevant anamnestic information at diagnosis | Smoker | History of epileptic seizures |

Table 1. Clinical and laboratory characteristics of Cases 1 and 2: patients with multi-occlusive arteritis and high-risk APS.

VKA means vitamin K antagonist; INR, international normalized ratio; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome.

Video 1. Anterior abdominal wall muscles' involuntary movements experienced by the patient of Case 4. It is notable the spasm of the diaphragm that withdraws the ribs. With compression of the heart area, the spasm accelerates its rate.

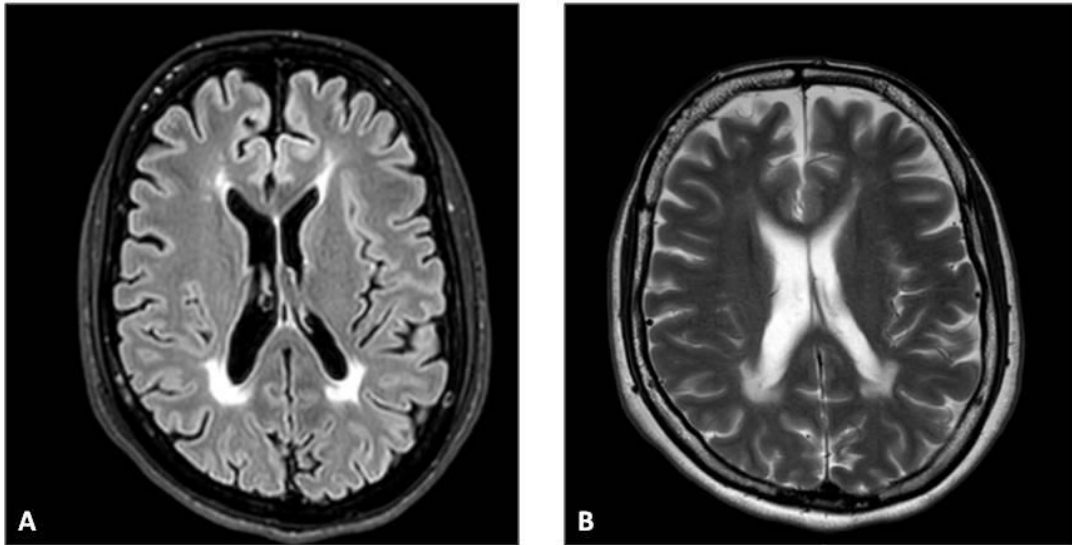


Figure 1. Presence of multiple confluent periventricular areas of increased white matter signal on FLAIR (panel A) and T2 (panel B) sequences, in the absence of vascular malformations and stenosis.

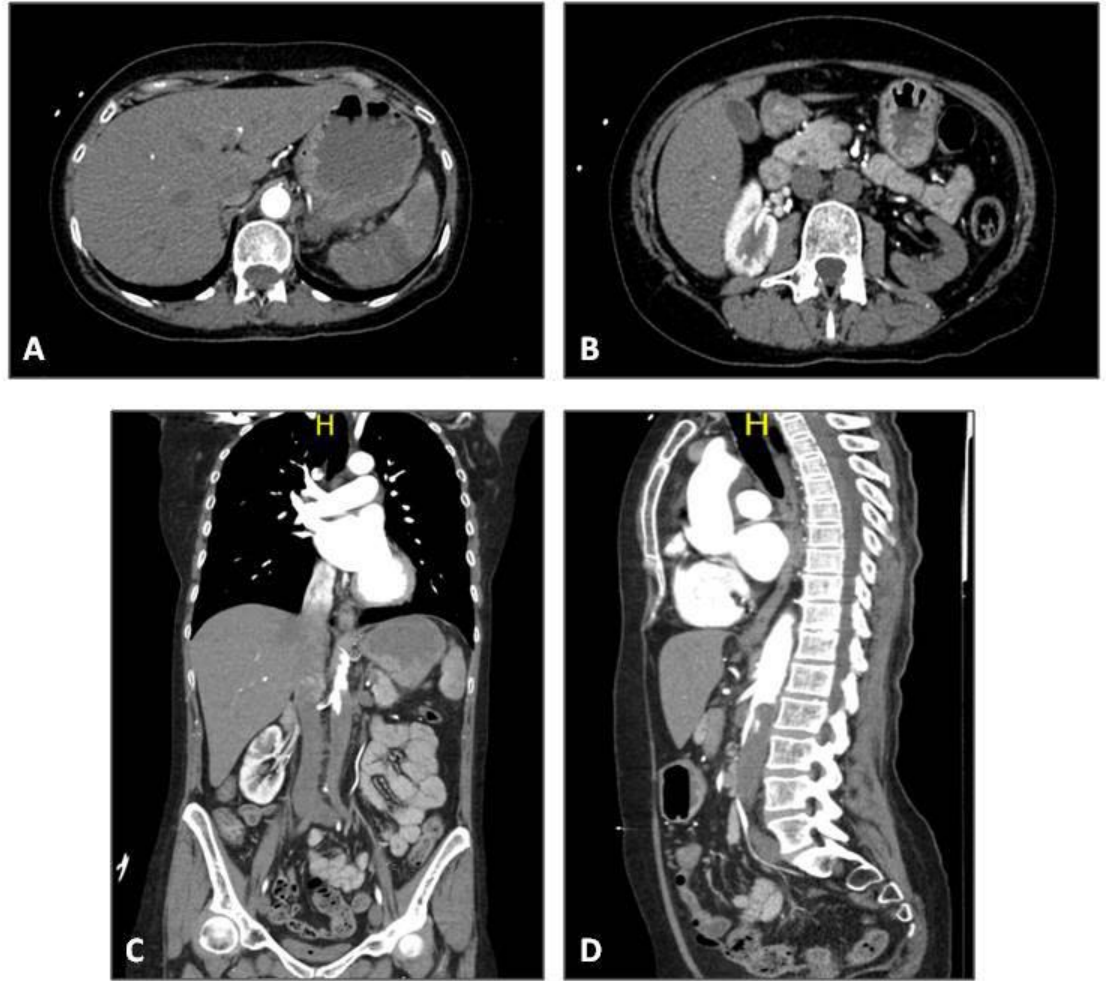


Figure 2. Massive aortic thrombosis showed at CT angiogram

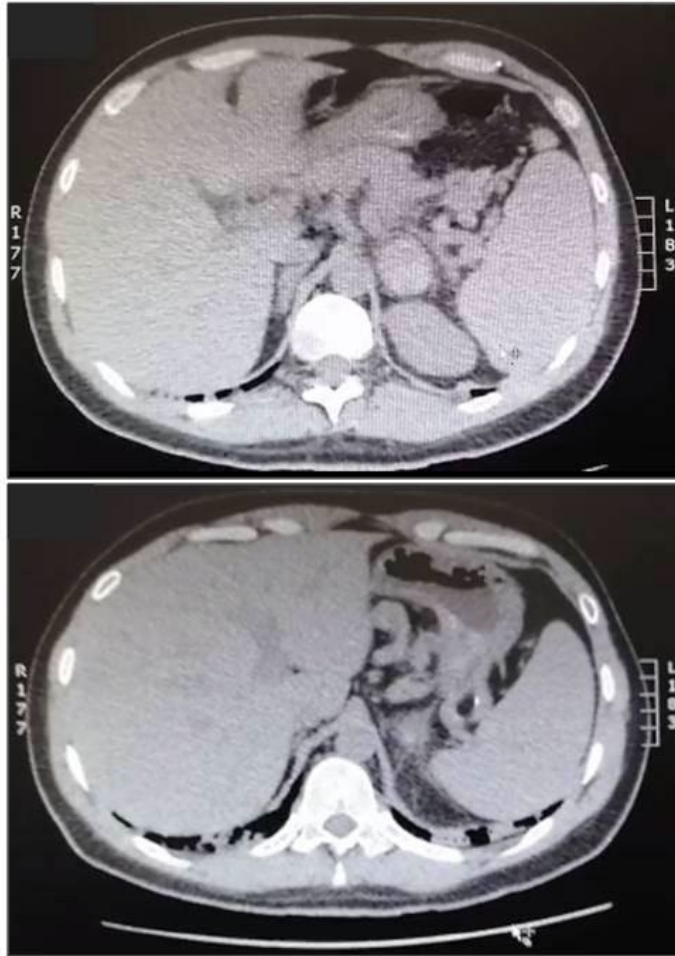


Figure 3. Haemorrhagic adrenal infarction at abdominal CT

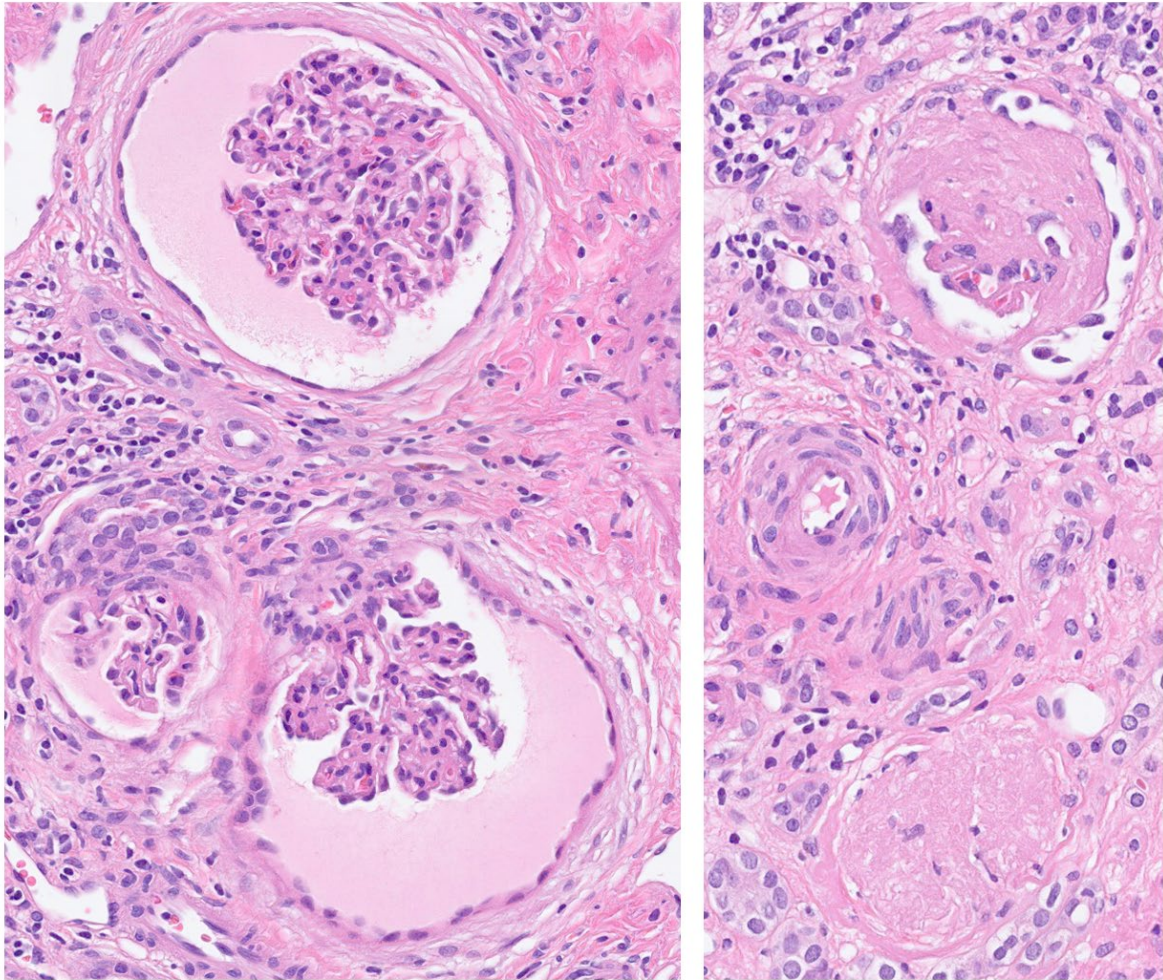


Figure 4. Histological features of kidney with luminal narrowing of arteriole and glomerulus exhibiting ischemic features: fibrinoid necrosis of pre glomerular arterioles, intimal hyperplasia and *onion skin* lesions with fibrin insudation.

