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**Case report,**

# Bilateral Adrenal Hemorrhage and Coagulation Laboratory Abnormalities: A Case Report of a Man with Enigmatic Clinical Features.

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**Abstract:**

**Background:** bilateral adrenal hemorrhage can cause adrenal insufficiency. Antiphospholipid syndrome (APS) is considered a rare etiology of bilateral adrenal hemorrhage with a relatively small number of case reports. APS can be secondary to other autoimmune diseases such as SLE in which cardiac manifestations are common.

**Case presentation:** a fifty-four-year-old male presents with left flank pain as a result of unilateral adrenal hemorrhage, a few days later, bilateral hemorrhage is documented in the presence of abnormal coagulation state and other laboratory clues. APS diagnosis was established.
Coexisting chest pain accompanied by diffused ST elevation, long QT, slightly high troponin with a high pro-BNP, in addition to echo's findings such abnormal regional wall abnormality and the absence of pericardial effusion made the case more interesting, differential diagnosis was proposed in accordance.

**Conclusion:** bilateral hemorrhage in APS considered rare. Requiring a high index of clinical suspicion. Particularly when it is the initial manifestation of APS as in our case. Underlying autoimmune diseases should be screened actively, especially when other unexplained manifestations are presented.

**Key words:** anti phospholipid syndrome, bilateral adrenal hemorrhage, adrenal insufficiency, peri-myocarditis, systemic lupus erythematosus, Prothrombin time, activated partial thromboplastin time.

## Background:

Antiphospholipid syndrome (APS) is characterized by multiple and recurrent venous and arterial thromboses secondary to circulating antibodies.[1-3] APS itself can be either a primary condition or secondary to other autoimmune disorders particularly systemic lupus erythematosus (SLE), malignancies, or even treatments.[4] APS manifestations are variant, including renal, neurological, cardiac, hepatic, hematological, and others. Adrenal manifestations such as spontaneous bilateral adrenal hemorrhage is a very uncommon in APS.[1,5-6] still a serious manifestation that could lead to acute adrenal insufficiency and potentially death.

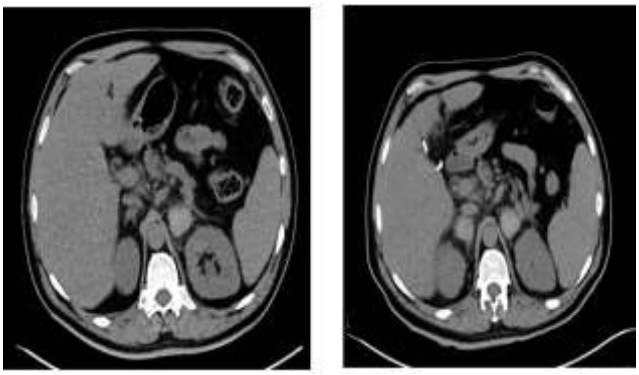
Historically, it was mainly a postmortem diagnosis. In our present time, it became a much easier radiological one established via computed tomography. Obviously, a high index of clinical suspicious need to be present in such cases, nonetheless when it is the first manifestation in undiagnosed APS patients.

APS could be associated with SLE; hence an active screening for underlying SLE is reasonable,

moreover when unexplained presentations occur. Although, Primary APS and APS associated with SLE share some similar manifestations such as thrombocytopenia and leukopenia, as well as certain cardiac manifestations are to be considered specific to SLE.[7-10] various cardiac manifestations were described in SLE. The pericardial disease mainly pericarditis is the most frequent presenting with or without pericardial effusion and may precede the clinical signs of SLE.11 Myocarditis is also common, in which systolic or diastolic dysfunction, Global or patchy hypokinesis is the dominant Echocardiography findings.12-13 Unlike valvular and coronary involvement which can be present in both primary and secondary APS. Pericarditis and myocarditis are not typical in primary APS. In this paper, we are describing a rare case of a patient presented with bilateral adrenal hemorrhage secondary to previously undiagnosed APS and later developed a peri-myocarditis which led to the diagnosis of SLE as well.

## Appendix

**Figure 1- Abdominal and pelvic CT imaging of the patient, Left demonstrating 2.5 cm left adrenal haemorrhage and Right demonstrating bilateral adrenal haemorrhage**

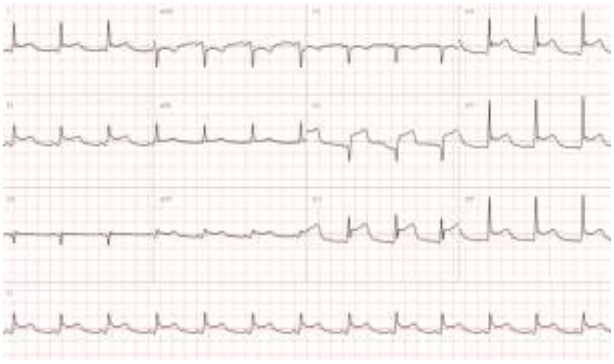


## Case presentation:

A fifty-year-old male patient was admitted to the emergency department with left flank pain. His medical history included nephrolithiasis, NASH cirrhosis, diabetes mellitus, and hypertension. Neither APS nor other autoimmune disease diagnosis was made before his admission Vital signs and physical examination on admission showed no abnormalities. The blood test revealed mild known thrombocytopenia 135 k, and abnormal coagulation profile: Prothrombin time (PT) 18.7 activated partial thromboplastin time (a-PTT) 109 INR1.6 (compared to normal values in the past), which was attributed at that point to either his cirrhosis or to consumption coagulopathy due to bleeding.FFP was given accordingly.

NCCT was performed and revealed left unilateral hemorrhage, whereas the right adrenal gland was normal (Figure 1, A). A few days later, the patient started complaining about chest pain, the initial evaluation including ECG and the cardiac biomarkers were normal, a bedside echo was normal as well. Later that day he was febrile and hypotensive. His chest pain recurred accompanied by extreme fatigue. Another ECG showed mild ST elevation in V2-3 and no reciprocal changes were seen while cardiac enzymes remained normal, a repeated echo was normal with EF of 65%, no regional wall abnormalities were noted. A second CT, conducted the next day, showed a bilateral adrenal hemorrhage (Figure 1, B) accompanied by fever (although only one measurement). A Waterhouse–Friderichsen syndrome was suspected and antibiotics were given. Even though IV steroids were started for his adrenal insufficiency he remained hypotensive (BP around 60/35) and eventually was transferred to the ICU. The ICU re-evaluation revealed: the patient's chest pain had never resolved, he was tachycardic and hypotensive, but no vasopressors were needed to stabilize his blood pressure. The blood test showed that bi-cytopenia (anemia and thrombocytopenia) had developed, abnormal coagulation profile while synthetic liver function remained intact: PT and a-PTT were prolonged up to 30 and 120, mild hyponatremia and hyperkalemia, slightly increased troponin in the presence of high pro-BNP. ECG at this point showed a diffused ST elevation with no reciprocal changes, long corrected QT was documented too (Figure 2).

**Figure 2- ECG of the patient presenting diffused ST elevation**



A third echo was performed, this time demonstrating a new regional wall abnormality, and a relative decline in ejection fraction (55% compared to 65% 2 days earlier), Also no pericardial effusion was demonstrated. A PCI was

performed as well, excluding CAD as an option.

**Table 1: Immunology and Serology laboratory tests results:**

| | |
|---|---|
| **Complement C3** | 55.3 Mg/dl |
| **Complement C4** | 6.5 Mg/dl |
| **ANA**[a] | Positive |
| **ANA titer** | >1:160 |
| **Anti dsDNA**[b] | 129.0 Positive |
| **A.B2 glycoprotein IgG** | >160.0 |
| **A.B2 glycoprotein IgM** | 3.6 Negative |
| **A.B2 glycoprotein IgA** | >160.0 |
| **Anti cardiolipin IgG** | >160.0 |
| **Anti cardiolipin IgM** | 3.5 Negative |
| **Anti cardiolipin IgA** | >160 |
| **LAC SCT**[c] | Increased |
| **LAC RVVT**[d] | Increased |

[a]Antinuclear Antibodies; [b] Anti-double stranded DNA antibody; [c] Lupus anticoagulant Silica clotting time; [d] Lupus anticoagulant Russell's viper venom time.

Differential diagnosis at this point included peri-myocarditis due to either an infectious etiology, possibly meningococcus, but this was less probable since no clinical clues supported the presence of infection: the patient was afebrile, laboratory test with no inflammatory markers and blood cultures were negative. Another option was a pericarditis/myocarditis secondary to an autoimmune disease. APS, although as a rare etiology of BAH, was suggested especially in the presence of abnormal coagulation profile that could not be explained earlier by his cirrhosis. Peri-myocarditis itself could be explained by APS associated with SLE rather than primary APS. Accordingly, a rheumatologic panel including APS and SLE screen was obtained. Lupus Anticoagulant Silica Clotting Time (LAC SCT) and LAC Russell's viper Venom Time (LAC RVVT) were conducted too and showed to be increased; The PTT levels that were around 100 seconds during the hospitalization period were fixed to 32 seconds with Actin FS reagent. Therefore, a diagnosis of APS was made.Later, the blood results came back to show a positive high titer of the three APS antibodies confirming our diagnosis (table1). Moreover, a high titer of ANA and anti dsdna were documented in addition to low c3 and c4 combined with cardiac manifestations SLE was diagnosed. After confirming our diagnosis, CTA was conducted, ruling out pulmonary embolism in the context of APS. Treatment was started as well, including LMWH, which is paradoxically the treatment in adrenal hemorrhage secondary to APS. Nsaids and colchicine were admitted as well.

## Discussion and conclusion:

Bilateral adrenal hemorrhage is not a common cause of adrenal insufficiency. Etiologies of this condition, besides trauma and sepsis, include disseminated bacterial infection such as meningococcus and pseudomonas. It also can be attributed to clotting abnormalities secondary to drugs or even APS. Although adrenal bilateral hemorrhage can easily be diagnosed nowadays via computed CT, it requires a high index of suspicion. Clinical presentation resembles what our patient has demonstrated, involving mainly: pain of varying severity localized to the abdomen, flank, lower chest, or back, cardiovascular, gastrointestinal, and neuropsychiatric symptoms of adrenal insufficiency are less frequent.[14]

The main two features of bilateral adrenal hemorrhage are fall of hemoglobin and hematocrit as a sign of occult bleeding and biochemical evidence of adrenal insufficiency such as hyponatremia and hyperkalemia, both appeared only later in our case.[14] Bilateral adrenal hemorrhage, due to APS, is an exceptionally challenging diagnosis, particularly when it is the first manifestation. A review in which 86 similar cases were scanned throughout 20 years showed a male predominance (55%), an older age (43+/-16), and interestingly up to 36% of which it was the first manifestation.[15] No dominant features in APS patients in general, yet it all applied to our patient. In our case, the diagnosis of the bilateral hemorrhage was relatively rapid since NCCT was performed in the ER setting. The real challenge was to figure the underlying cause that led to this condition in non-diagnosed APS patient. A major clue in solving this enigma was the patient coagulation profile which was misleadingly assumed at First as a consequence of consumption coagulopathy due to bleeding. A markedly prolonged a-PTT as in the case of our patient should be evaluated cautiously. First by reviewing previous a-PTT values as a normal a-PTT as in our patient would rule out a hereditary condition such as factor 12 deficiency. Next, the dominant clinical feature (thrombosis or bleeding) should be

decided. A prolonged a-PTT accompanied by bleeding is suspected in acquired hemophilia which might be secondary to autoimmune disease or malignancy. Whereas a prolonged a- PTT accompanied with thrombosis is suspected in APS. In order to distinguish between the different etiologies mixing study should be conducted.

If the immediate mix corrects, incubated PTT mixing study is performed to determine if a specific inhibitor, usually anti-factor VIII, as present in Acquired hemophilia. A lupus anticoagulant that affects the aptt will not correct in a mixing study with normal plasma, but it will correct with excess phospholipid. If APS is suspected, the dilute Russell's viper venom time (drvvt) can be used to evaluate this possibility. Another challenge that made the case more interesting was the development of peri-myocarditis which is not common in APS which led eventually to a diagnosis of SLE.

We believe the cardiac manifestation the patient developed was indeed peri-myocarditis rather than only pericarditis as the presence of regional wall abnormality and relative systolic dysfunction both to be considered features of myocarditis than pericarditis. A bi-cytopenia that was developed in our patient is also to be considered a specific feature for SLE and not APS. Although anemia could be secondary to the adrenal hemorrhage as the thrombocytopenia could be attributed to APS associated ITP.

**To conclude:** Bilateral adrenal hemorrhage might be present in APS; moreover, it could be the very first presentation as in our case making it difficult to be diagnosed. A high index of suspicion is needed in such cases. Active screening for SLE is recommended, especially if cardiac manifestations such as pericarditis, myocarditis, or other specific SLE manifestations are present.

## References:


[1.] Asherson RA, Khamashta MA, Ordi-Ros J, et al. 1989 the “primary” antiphospholipid syndrome: major clinical and serological features. Medicine.68:366 –374.

[2.] Asherson RA, Hughes GRL. 1989 Recurrent deep vein thrombosis and Addison’s disease in “primary” antiphospholipid syndrome. J Rheumatol.16:378 –380.

[3.] Alarcon-Segovia D, Cabral AR. 1996 the antiphospholipid/cofactors syndromes.J Rheumatol. 23:1319 –1322.

[4.] Asherson RA. 1988 A “primary” antiphospholipid syndrome. J Rheumatol.15:1742–1746.

[5.] Alarcon-Segovia D, Perez-Vasquez ME, Villa AR, et al. 1992 Preliminary classification criteria for the antiphospholipid syndrome within systemic lupus erythematosus. Semin Arthritis Rheum. 21:275–286.

[6.] Mackworth-Young CG, Loizou S, Walport MJ. 1989 Primary antiphospholipid

[7.] Syndrome: features of patients with raised anticardiolipin antibodies and

[8.] No other disorder. Ann Rheum Dis. 48:362–367.

[9.] Vianna JL, Khamashta MA, Ordi-Ros J, et al. Comparison of the primary and secondary antiphospholipid syndrome: a European Multicenter Study of 114 patients. Am J Med 1994; 96:3.

[10.] Cervera R, Boffa MC, Khamashta MA, Hughes GR. The Euro-Phospholipid project: epidemiology of the antiphospholipid syndrome in Europe. Lupus 2009; 18:889.

[11.] Unlu O, Erkan D, Barbhaiya M, et al. The Impact of Systemic Lupus Erythematosus on the Clinical Phenotype of Antiphospholipid Antibody-Positive Patients: Results From the antiphospholipid Syndrome Alliance for Clinical Trials and international Clinical Database and Repository. Arthritis Care Res (Hoboken) 2019; 71:134.

[12.] Danowski A, de Azevedo MN, de Souza Papi JA, Petri M. Determinants of risk for venous and arterial thrombosis in primary antiphospholipid syndrome and in antiphospholipid syndrome with systemic lupus erythematosus. J Rheumatol 2009; 36:1195.

[13.] Doria A, Iaccarino L, Sarzi-Puttini P, et al. Cardiac involvement in systemic lupus erythematosus. Lupus 2005; 14:683.

[14.] Apte M, mcgwin G Jr, Vilá LM, et al. Associated factors and impact of myocarditis in patients with SLE from LUMINA, a multiethnic US cohort (LV). [Corrected]. Rheumatology (Oxford) 2008; 47:362.

[15.] Miner JJ, Kim AH. Cardiac manifestations of systemic lupus erythematosus. Rheum Dis Clin North Am 2014; 40:51.

[16.] P.CARON, M. CHABANNIER et al. Definitive Adrenal Insufficiency Due to Bilateral Adrenal Hemorrhage and Primary Antiphospholipid Syndrome. Journal of Clinical Endocrinology and Metabolism.

[17.] Espinosa G, Santos E, Cervera R, et al. Adrenal involvement in the antiphospholipid syndrome: clinical and immunologic characteristics of 86 patients. Medicine (Baltimore) 2003; 82:106.