Citation: Bakhsh EA, Alkhathami RA, Mukaddam S, Alarfaj O. Bilateral adrenal hemorrhage in APLS (anti-phospholipid syndrome) patient on Novel Anticoagulant: a case report. European Journal of Medical Case Reports. 2017;1(1):47-51.
https://doi.org/10.24911/ejmcr/1/12

European Journal of Medical Case Reports

CASE REPORT

Bilateral adrenal hemorrhage in APLS (anti-phospholipid syndrome) patient on Novel Anticoagulant: a case report

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ABSTRACT

Background: Antiphospholipid syndrome is a prothrombotic state characterized by the existence of persistent antiphospholipid antibodies. The key sequence of events is focal microthrombosis and post-infarction hemorrhage in the adrenal glands. Use of anticoagulant therapy is often used as a prevention and treatment among patients.

Case presentation: We describe a case of 40 year old female who visited Emergency Room with complain of severe right upper quadrant pain for two days associated with nausea and vomiting. Initial laboratory investigations of blood, liver, and renal functions were normal. CT scan of abdomen revealed diffused enlargement of the right adrenal gland and showed relatively less enhancement indicating hemorrhage at the right side which later developed bilateral during admission. A day after admission, platelet count was 60,000 accompanied with worsened abdominal pain lead to diagnosis of catastrophic Anti-phospholipid syndrome (APLS).

Conclusion: APS may lead to a variety of clinical manifestations due to venous and/or arterial thrombosis, so prescribing novel anticoagulants for patients with the APS is selective, and multiple factors are needed to be considered for a successful treatment.

Keywords: Antiphospholipid syndrome, adrenal hemorrhage, case report, anticoagulant therapy, bilateral hemorrhage, adrenal insufficiency.

Background

The term "Antiphospholipid Syndrome" (APLS) is a clinical condition known as acquired autoimmune disease which causes venous, arterial, and small-vessel thrombosis, pregnancy loss, and pre-term delivery for patients with severe pre-eclampsia or placental insufficiency and usually related with significant morbidity and mortality [1]. A severe complication of APLS called Catastrophic Anti-phospholipid Syndrome (CAPS) is characterized by extensive microthrombi in multiple vascular beds, culminating in fulminant multiple organ failure. Renal injury, abnormal liver enzymes, liver as well as respiratory failure and adrenal insufficiency are organ manifestations in CAPS [2].

APS is a prothrombotic state characterized by persistent antiphospholipid (aPL) antibodies in the body fluids. aPL is a heterogeneous class of auto-antibodies against protein-phospholipid complexes [3]. Previous studies have highlighted a relationship between acute adrenal insufficiency and aPL [4, 5]. Through imaging techniques, it is now well understood that the key sequence of events is focal microthrombosis and post-infarction hemorrhage in the adrenal glands. A bunch of nonspecific symptoms

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of adrenal hemorrhage includes abdominal, pelvic, lumbar, or thoracic pain and symptoms of acute adrenal insufficiency, such as fatigue, anorexia, nausea, and vomiting. Other symptoms related to the underlying condition(s) may also be present. In some cases, adrenal hemorrhage can be completely asymptomatic and can be recognized incidentally through imaging techniques and laboratory tests. The incidence of adrenal involvement in APLS is approximately 14% and previous studies reported 4 cases of bilateral adrenal hemorrhage (1.4%) [6].

Various laboratory test was done to identify APS such as Lupus Anti-Coagulant (LAC), immunoglobulin G (IgG) and IgM antibodies to cardiolipin (aCL) and anti-beta2 glycoprotein I (aβ2GPI) [7]. Different treatments are used for APS, such as Rivaroxaban anticoagulant therapy is usually used for prevention and treatment of venous thromboembolism among patients undergoing elective hip or knee replacement surgery. It has also been used to prevent stroke in patients with atrial fibrillation and the treatment of deep vein thrombosis. Using Rivaroxaban anticoagulant therapy usually doesn't need monitoring for coagulation except in certain clinical situations such as life-threatening bleeding or an emergency operation. In this study, we describe a typical case of aPL associated with acute adrenal insufficiency due to of bilateral adrenal hemorrhage.

Case presentation

A 40 year old female was diagnosed with Anti-phospholipid syndrome 8 years back when presented with Bilateral Lower extremity DVT and pulmonary embolism. She was on warfarin 6mg with target INR 2–3. She was switched to Rivaroxaban 20mg daily because of noncompliance with INR follow up. Two weeks later she visited Emergency Room at King Fahad Medical City, Riyadh, Saudi Arabia, complaining of severe right upper quadrant pain for the two days, associated with nausea and vomiting, although she stopped taking Rivaroxaban two days prior visiting the ER.

Laboratory and radiological findings

Initial labs showed CBC: WBC 7.2, HGB 10.9 g/dL, PLT 128, coagulation PT18.4, PTT 176, INR 1.6, LFT ALT 287, AST 197, GGT 88, ALP 128 and renal function test was within the normal limits. CT scan of abdomen with IV and oral contrast was done and revealed diffused enlargement of the right adrenal gland and displayed less enhancement indicating hemorrhage. Additionally, CT angiography of the abdomen showed new moderate bleeding in left adrenal gland with measurement 5.7 × 4.6 cm, blood trickled down to involve perianal space, shown in Figure 1.

Diagnosis and management

The patient was admitted and managed conservatively with IV fluid; analgesics and anticoagulant were withheld. Twenty four hours after admission, thrombocytopenia manifested with platelet count 60,000. Abdominal pain also worsened. A diagnosis of catastrophic APLS was considered. Methyleprednisolone 1.5mg/kg and plasmapheresis were commenced immediately. A total of 3 sessions of plasmapheresis were given. In addition to plasmapheresis, IV immunoglobulin 1mg/kg was given for 2days. platelet dropped to 33,000. Heparin infusion was started setting a target APTT 60-70 Sec. Intravascular methylprednisolone was continued. Abdominal pain dramatically improved, and platelet count increased to 70,000 and liver function remained normal range CT abdomen was repeated and showed no significant interval changes regarding the size, density of the previously seen bilateral adrenal hemorrhage with no evidence of additional bleeding. Warfarin 5mg was resumed, and the patient was discharged with target INR 2–2.5.

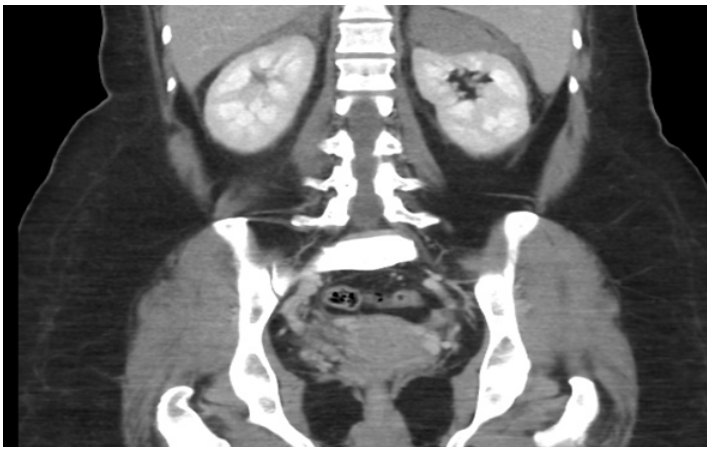

Figure 1: *Adrenal gland enlargement indicating hemorrhage.*

Discussion

Adrenal glands hemorrhage can cause adrenal insufficiency. The presence of aPL-antibodies should be expected mainly in patients who have adrenal hemorrhage and also recurrent thrombosis, both arterial and venous [4]. It is important to consider that APS has an influence on the patients with the history of thrombotic incidence. The discovery of aPL-antibodies in patients with thrombosis is important. Treatment for the APS positive patients is necessary to be done urgently to avoid further complications. APS can be fatal if it attacks different organs in the body. aPL-antibodies have substantial effect on the hemolytic process. Newly, the role of aPT-antibodies in thrombosis in APS patients has been taken into consideration [8]. However, the association between aPT antibodies with thrombosis has been emphasized [9] albeit some studies did not confirm the association [10].

Different mechanisms have been known to show the pathogenesis of thrombosis in APS. For instance, aPL can distract the normal coagulation inhibitory system of protein C and protein S, they can also decrease synthesis of prostacyclin by endothelial cells, and they can facilitate tissue factor activity [11]. At the moment, there is not any clear pathogenic mechanism or direct causal influence to describe the particular and isolated anatomical localization of bilateral adrenal hemorrhage in cases with APS. It is notable that, adrenal glands are supplied with various small arteries on both sides so that it is not possible to generalize arterial embolism.75 percent of the adrenal cortex has been made by the fascicular part of adrenal glands, and its cells contain lots of cholesterol and display a high cholesterol trafficking. They comprise high volumes of late endosomes and LBPA, attracting aPL specifically to that location. aPL could then affect hemostatic mechanisms and lead to local microthrombosis and post-infarction hemorrhage. Moreover, human aPL can activate in vitro cultured endothelial cells to express vascular cell adhesion molecule-1 (VCAM-1) or if they are injected in mice, they can activate E-selectin and they could rise leukocyte bound to endothelial cells [12]. Soluble VCAM-1 has been demonstrated to improve primary APS's patient's conditions than controls [13] suggesting that aPL may contribute to endothelial injury.

It is notable that, the selection of treatment, its dosage and duration needs to be adopted based on the type of the event. For example, it is not necessary to check patients with venous thromboembolism (VTE) for aPL antibodies close to the index event. Use of heparin followed by vitamin K antagonists (VKAs) remained unchanged irrespective of the presence of aPL, and LAC may be false-positive due to the anticoagulant treatment. It is now suggested to use rivaroxaban in thrombotic APS [14] and many studies reported that the efficacy and safety had same benefits with traditional anticoagulation therapy [15]. There is no study reporting that Rivaroxaban is a leading factor of the APS, although no antidotes to reverse Rivaroxaban have been reported as well [16]. To tackle the complications of APLS realizing anticoagulant, its efficacy and safety regarding the disease is a crucial process.

Conclusion

We conclude that APS may lead to a variety of clinical manifestations due to venous and/or arterial thrombosis, so prescribing Novel anticoagulants for patients with the APLS is selective, and multiple factors are needed to be considered for a successful treatment.

Acknowledgements
None

List of Abbreviations

APLS	anti-phospholipid syndrome
CAPS	catastrophic anti-phospholipid syndrome
VCAM-1	vascular cell adhesion molecule-1
VKAs	vitamin k antagonists
VTE	venous thromboembolism

Conflicts of interests
All authors declare that there are no conflicts of interest.

Funding
None

Consent for publication
Informed consent was obtained from the patient to publish this case.

Ethical approval
Ethical approval is not required at our institution for publishing a case report in a medical journal.

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Authors' contributions
EB, was the treating physician who admitted the patient and participated in writing the manuscript. RA was involved in managing the patient and write manuscript SM was the secondary physician, shared in management and reviewed the manuscript. OA was the clinical pharmacist, shared in management of the patient and wrote the discussion part of the manuscript.

Received: 30 September 2016
Accepted: 30 November 2016
Published on line: 10 December 2016

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Summary of the case

Patient (gender, age)	1	Female, 40 year old
Final Diagnosis	2	Catastrophic Anti-Phospholipid Syndrome APLS
Symptoms	3	Severe upper right quadrant pain, nausea, vomiting
Medications (Generic)	4	Methyleprednisolone, Heparin, IV immunoglobulin
Clinical Procedure	5	Methyleprednisolone 1.5mg\kg and plasmapheresis commenced immediately, IV immunoglobulin 1mg\kg given for 2days, heparin infusion started with target APTT 60-70 Sec with close monitoring of blood count.
Specialty	6	Immunology
Objective	7	To describe an uncommon entity
Background	8	CAPS is a severe complication of an autoimmune disease, Anti-phospholipid Syndrome. CAPS is characterized by extensive microthrombi in multiple vascular beds, culminating in fulminant multiple organ failure.
Case Report	9	Authors report a typical case of APLS associated with acute adrenal insufficiency due to bilateral adrenal hemorrhage.
Conclusions	10	APS may lead to a variety of clinical manifestations due to venous and/or arterial thrombosis, so Novel anticoagulants for patients with the APS is selective, successful treatment was found by corticosteroid, anticoagulant and immunoglobulin infusion.
MeSH Keywords	11	Antiphopholipid syndrome, adrenal hemorrhage, case report, anticoagulant therapy, bilateral hemorrhage, adrenal insufficiency