# Spontaneous Perirenal Hemorrhage in Patient with Antiphospholipid Syndrome

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ABSTRACT

**Introduction**: Spontaneous perirenal hemorrhage (SPH), also known as Wunderlich syndrome, is a rare condition that can potentially progress into life-threatening non-traumatic retroperitoneal hemorrhage. Common symptoms include acute flank or abdominal pain, a palpable flank mass, and fulminant hypovolemia, collectively referred to as Lenk's triad, and diagnosis is typically established radiologically using a CT scan. Antiphospholipid syndrome (APS) - a rare, immune-mediated hypercoagulable disorder that occurs in only 5 cases per 100,000 people per year worldwide. It is immune-mediated, characterized by persistent antiphospholipid antibodies (APLA) that cause both arteries and venous thrombosis, and can present as peripheral arterial disease (PAD), acute arterial occlusion, and early atherosclerosis. **Case :** A 33-year-old woman with chronic kidney disease (CKD) presented with SPH and incidentally diagnosed with peripheral arterial disease (PAD) and APS. **Conclusion :** Conservative management was beneficial for SPH without the need for surgical intervention; however, antithrombotic therapy for PAD posed additional challenges before the patient was eventually discharged in improved condition for outpatient follow-up.

**Keywords:** Anticoagulant, antiphospholipid syndrome, spontaneous perirenal hemorrhage, Wunderlich syndrome.

ABSTRAK

**Pendahuluan**: Perdarahan perirenalis spontan (*spontaneous perirenal hemorrhage*/SPH), juga dikenal sebagai sindrom Wunderlich, adalah kondisi langka yang dapat berkembang menjadi perdarahan retroperitoneal non-traumatik yang mengancam jiwa. Gejala yang biasanya muncul seperti nyeri pinggang/perut akut, teraba massa di daerah pinggang dan hipovolemia fulminan yang disebut dengan 'Lenk's triad' dan biasanya akan ditegakkan secara radiologis menggunakan *CT scan.* Sindrom antifosfolipid (APS) adalah gangguan hiperkoagulabilitas langka yang hanya terjadi pada 5 kasus dari 100.000 orang per tahun di dunia dan dimediasi oleh sistem kekebalan tubuh, ditandai dengan keberadaan antibodi antifosfolipid persisten (APLA) yang menyebabkan trombosis arteri dan vena, dapat menyebabkan penyakit arteri perifer (PAD), sumbatan arteri akut, dan aterosklerosis dini. **Kasus:** Wanita berusia 33 tahun dengan penyakit ginjal kronik (CKD) dengan SPH dan didiagnosis memiliki penyakit arteri perifer (PAD) dan APS. **Simpulan**: Penanganan konservatif menguntungkan untuk SPH tanpa perlu intervensi bedah, namun terapi antitrombotik untuk PAD menimbulkan tantangan tambahan sebelum pasien akhirnya rawat jalan dengan kondisi perbaikan. **William Adipurnama, Jacinda Risha Oktaviani, Nicholas Andrian Singgih, Cecilia Noviyanti Salim, Derry Wendians Suhanto, Egi Edward Manuputty, Budiawan Atmadja. Perdarahan Spontan Perirenal pada Penderita Sindrom Antifosfolipid.**

**Kata Kunci:** Antikoagulan, sindrom antifosfolipid, perdarahan perirenalis spontan, sindrom Wunderlich.



## INTRODUCTION

Spontaneous perirenal hemorrhage (SPH) or Wunderlich syndrome is defined by the extravasation of blood into the subcapsular or perinephric space.[1] It is a rare condition and has the potential for fatal non-traumatic retroperitoneal kidney bleeding.[2] Between 2000 and 2016, only 102 cases were reported.[3] The most common etiologies mentioned are renal carcinoma, angiomyolipoma, vasculitis, infection, coagulopathies, and others, with malignancy being the most common pathology leading to spontaneous bleeding.[1] Twenty percent of patients may present with the classic 'Lenk's triad' that consists of acute flank/abdominal pain, palpable flank masses, and ultimately fulminant hypovolemia.[4] Diagnosis is usually established radiologically, with CT as the most preferred since it is sensitive and can provide information on the underlying etiology.[5] In stable patients with no active hemorrhage and stable hematoma, conservative management can be pursued.[1] However, surgical intervention and nephrectomy are sometimes required as it is life-threatening.[6]

Antiphospholipid syndrome (APS) is a rare autoimmune thrombophilia that can cause thrombosis in various organs, both venous and arterial.[7] The global incidence of APS is estimated to be 5 cases per 100.000 persons per year, with an estimated prevalence of 40-

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50 cases per 100.000 persons.[8] APS can occur in association with other autoimmune diseases, mainly systemic lupus erythematosus (SLE), or in its primary form.[9] Definite APS requires at least one clinical and one laboratory criteria according to the updated Sapporo classification (Sydney criteria).[9] The treatment goal is to prevent fatal and disabling complications of APS with antithrombotic and cardiovascular risk prevention strategies.[10] To date, there is only one case study in the literature discussing spontaneous renal rupture as the first presentation of APS.[6] We report a case of a 33-year-old woman with SPH, PAD, and APS. The management of each diagnosis has been a challenge.

## CASE

A 33-year-old woman presented to the nephrology clinic with left flank pain for three days. The pain was continuous and moderate in intensity. No history of trauma or any other complaints. The patient had a history of chronic kidney disease (CKD) with continuous ambulatory peritoneal dialysis (CAPD) and was allergic to levofloxacin.

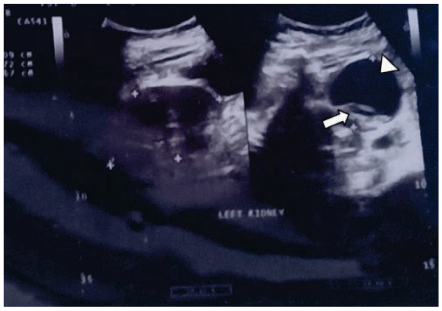

**Figure 1**. Abdominal ultrasound of left kidney. A cyst (arrowhead), intramural nodule (arrow).

On physical examination, the patient was compos mentis, with no tenderness in the abdominal region or the inguinal area. The vital signs: blood pressure 120/90 mmHg, heart rate 88 bpm, respiratory rate 20 rpm, and axillary temperature 37°C. The laboratory examination results were Hb 11.9 g/dL, leucocyte 12.400/µL, thrombocyte 236.000/µL, ureum 95 mg/dL, creatinine 10.75 mg/dL, uric acid 6.3 mg/dL; eGFR 4.202 mL/min/1.73m$^2$. On abdominal ultrasonography, there was a hypoechoic area on the papillae that was difficult to differentiate from the medulla and a 4.67 cm cyst with an intramural nodule on the left kidney **(Figure 1)**. The patient was hospitalized and sent to have a non-contrast abdominal CT scan.

The non-contrast abdominal CT scan showed a contracted right kidney with multiple cysts of 0.77-2.34 cm in diameter. In the left kidney, there was an isodense shadow with a density of 53-87 HU following the contour of the left perirenal space measured 2.67-5.17 cm, and a cystic shadow at the bottom with a diameter of 5.55 cm, suspected to be perirenal bleeding. There was fluid with the same density in the inferior retroperitoneal cavity giving rise to hemorrhage. Bleeding may have been caused by cyst rupture or kidney mass **(Figure 2)**.

Other laboratory tests showed aPTT 39.9s (control 31.4s), prothrombin time 12.2s (control 11.5s), and fibrinogen 248 mg/dL (normal range 180-350 mg/dL). Initial IV drugs given were tramadol 3x100 mg, meropenem 3x500 mg, vitamin K 3x10 mg, and tranexamic acid 3x500 mg. She was also consulted to the urology department with a diagnosis of suspected perirenal hemorrhage *et causa* suspected cyst rupture with a differential diagnosis of kidney mass.

The urologist advised a contrast abdominal CT scan for evaluation, considering there was a mass suspected at the left kidney on the first CT scan. No additional therapy. Contrast abdominal CT scan was done 6 days later. The isodense area in the upper and middle poles of the kidney did not enhance after contrast administration, the isodense area in the cyst at the lower pole decreased, as well as the isodense area in the left peritoneal cavity. It was concluded that the bleeding in the retroperitoneal space had decreased and no new ongoing bleeding **(Figure 3)**. She was diagnosed with perirenal hemorrhage *et causa* suspected cyst rupture with a differential diagnosis of kidney mass and scheduled for nephrectomy.

During hospitalization, the patient complained that her both lower extremities felt cold. Her blood pressure could reach up to 160/100

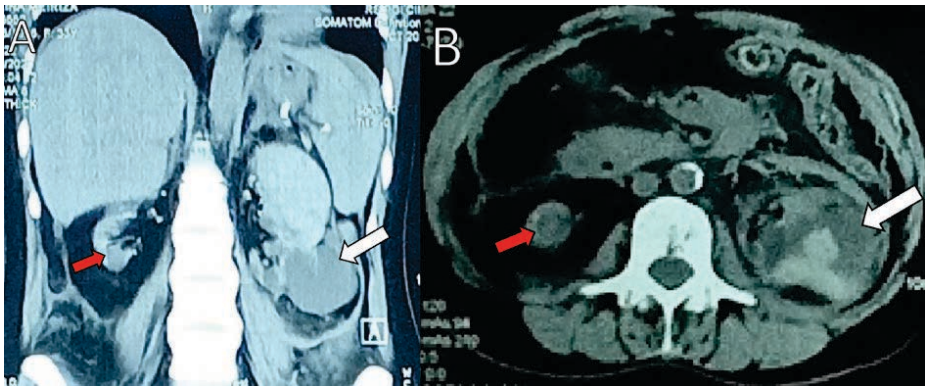


**Figure 2.** Non-contrast abdominal CT scan. (A) Coronal view. (B) Axial view. Isodense area in the cyst at lower pole (white arrow), contracted right kidney (red arrow).

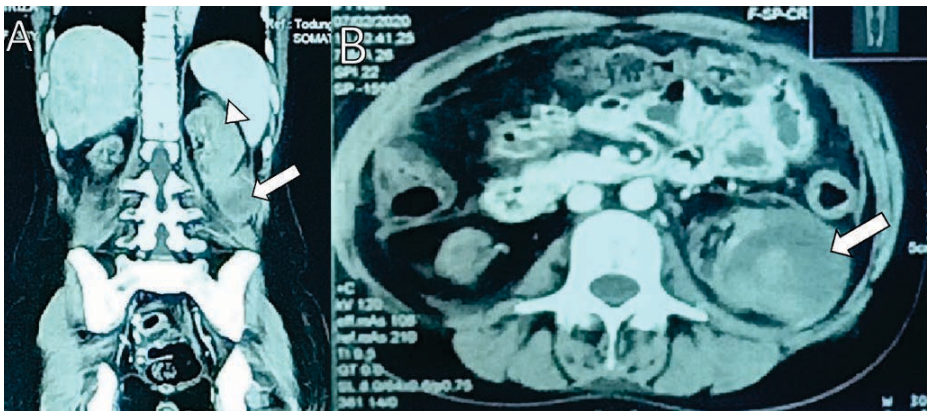


**Figure 3.** Contrast abdominal CT scan. (A) Coronal view (B) Axial view. The isodense area (arrowhead), the isodense area in the cyst at the lower pole (arrow).

mmHg. On physical examination, peripheral cyanosis was found at the tips of the fingers and toes with CRT > 2". She was referred to the cardiologist. D-dimer was 1520µg/L. CT angiography of the lower extremities showed steno occlusion of anterior tibial and bilateral peroneal arteries from mid to distal cruris. Arteriography showed stenosis in the left medial plantar artery, suggestive of peripheral arterial disease (PAD). She was suggested to take triple therapy (TT) but was postponed after considering the perirenal hemorrhage episode. The patient was also consulted to the hemato-oncologist to find the cause of hypercoagulation.

Laboratory findings showed LA 1 54.20s (control 36.7s), LA 2 43.40s (control 37.6s), AT III 139.70% (control 93.1%), ACA IgM 0.96 U/mL (normal value <12 U/mL), ACA IgG 3.39 U/mL (normal value <12 U/mL), Anti β2 GP1 IgM 79.11 RU/mL (normal value <20 RU/mL), Anti β2 GP1 IgG 0.48 RU/mL (normal value <20 RU/mL), protein C 150.00% (control 106.3%), protein S 135.40% (control 66.0%). The patient was diagnosed with antiphospholipid syndrome (APS) and placed on TT consisting of acetylsalicylic acid, clopidogrel, and heparin to treat the PAD.

A day after taking TT, she had a hematoma on some parts of the body. Another non-contrast abdominal CT scan was done to evaluate the perirenal bleeding. The isodense area density in the perirenal and subcapsular left kidney decreased inhomogeneously, suggesting no new left subcapsular and perirenal bleeding (**Figure 4**). Bleeding in the left retroperitoneal space also appeared to have been absorbed, so nephrectomy was canceled. Antiplatelets were stopped, and only heparin was continued.

After receiving heparin for three consecutive days, her condition improved. Pain at the extremities and the left flank was minimal.

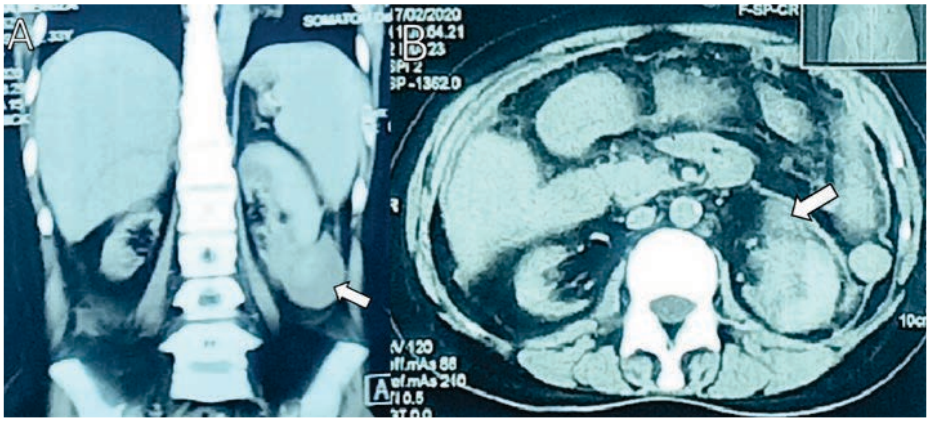

**Figure 4.** Non-contrast abdominal CT scan a day after taking TT. (A) Coronal view. (B) Axial view. Decreasing the density of the isodense area in the perirenal and subcapsular left kidney (arrow).

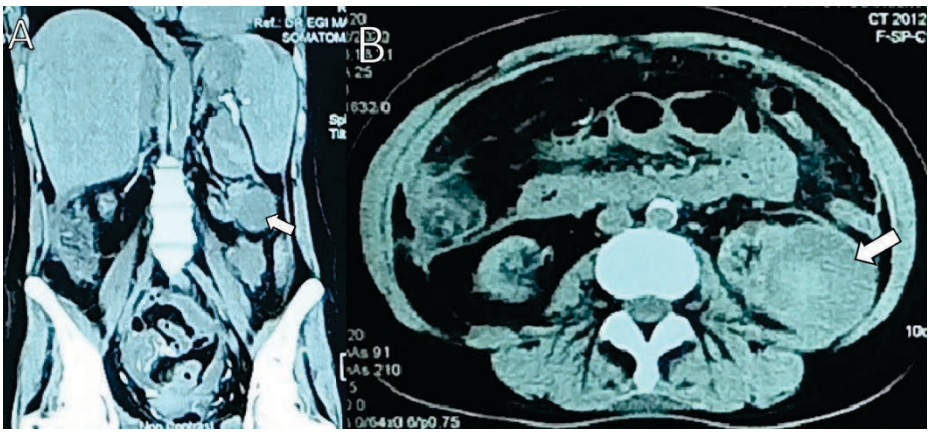

**Figure 5.** Non-contrast abdominal CT scan a week after hospitalization. (A) Coronal view. (B) Axial view. The left subcapsular isodense area (arrow).

The patient was discharged after two weeks of hospitalization. For follow-up, a non-contrast abdominal CT scan was done a week later. The left subcapsular isodense area had decreased in density and was no longer homogeneous, the size of the cysts was about the same, and there was no sign of bleeding in the left retroperitoneal space **(Figure 5).** Twelve weeks later, the patient's Anti β2 GP1 IgG 42.7 RU/mL and IgM 50.2 RU/mL, LA 1 57.20s, LA 2 49.38s, ACA IgM 0.87 U/mL, and ACA IgG 4.25 U/mL. According to the Sapporo criteria, the diagnosis of APS was confirmed. Oral rivaroxaban was prescribed.

## DISCUSSION

Spontaneous perirenal hemorrhage (SPH) is a rare occurrence, almost all cases documented in 3 meta-analyses were before the year 2000. Between 1985 and 1999, a total of 165 cases were published in the English literature. The first meta-analysis, conducted by McDougal, identified 74 published cases before 1975.[11] Cinman's study identified an additional 27 cases between 1974 to 1985.[12] Subsequently, between 2000 and 2016, an additional 102 cases were reported.[3] SPH in the condition of antiphospholipid syndrome (APS) is even more rare. As APS can occur concomitantly with other autoimmune diseases, Castellino, *et al*, (2001)[13] reported pericapsular renal bleeding in systemic lupus erythematosus (SLE) patients with APS.[2]

Zhang, *et al*,[14] in their meta-analysis of 165 patients reported that the most common etiology of SPH is benign (24% to 33%) or malignant (30% to 33%) neoplasm, predominantly angiomyolipoma followed closely by renal cell carcinoma. Vascular disease (18% to 26%) is the second most common cause such as polyarteritis nodosa (PAN), Wegener's disease, and arteriovenous malformation; aneurysms with PAN account for most occurrences.[2] Other possible causes are infection (7% to 10%) and coagulation disorders.[1,15] Zhang, *et al*,[14] also reported that 83% of patients presented with acute flank pain, 19% had hematuria, and 11% had signs of hypovolemic shock. Our patient only presented with acute left flank pain.

Diagnosis of SPH is usually established radiologically. Ultrasound can be done for quick identification, but generally poorly detects and underestimates the extent of




retroperitoneal hemorrhage.[5] As in our case, the ultrasound did not provide significant findings other than a left kidney cyst and suspicion of hydronephrosis. The gold standard is a CT scan since it provides accurate information on the etiology and diagnosis of retroperitoneal masses or hemorrhages with sensitivity ranges from 92% to 100%.[4] The first CT result suggested hemorrhage and another one conducted 6 days after suggested the absence of a new hemorrhagic process or neoplastic pathology. Angiography can be an alternative if CT fails to recognize the underlying cause and surgical exploration becomes another option.[5]

The initial management of SPH is variable. Exploratory surgery and nephrectomy were previously recommended regardless of the patient's status and the severity of the hemorrhage.[2] Such consideration was based on the finding that 43% of patients were diagnosed with renal malignancy after nephrectomy.[16] With the development of imaging tools that consistently result in the correct diagnosis of the underlying predisposing factor, management of SPH has moved toward a more conservative strategy in recent years.[1] In our case, we went through conservative measures with antifibrinolytic and hemorrhage evaluation through serial CT. However, the patient suddenly complained of pain in both distal lower extremities. CT angiography and arteriography showed stenosis suggestive of PAD and triple therapy (TT) was initiated.

The presence of antiphospholipid antibody (APLA) in asymptomatic individuals does not confirm the diagnosis of APS but can be related to an increased risk of thrombosis, depending on APLA characteristics and the coexistence of other risk factors. Our patient met the laboratory criteria which was positive lupus anticoagulant (LA) and anti-β2 glycoprotein-I antibody (anti-β2GPI), consequently defined as a high-risk APLA profile associated with greater risk for thrombotic APS.[9] Even though the thrombotic evidence has not been established, attention needs to be paid to certain symptoms such as those related to atherosclerosis. Over the years, it became clear that APLA relates to subclinical and clinical atherosclerosis in primary APS. APS and PAD have common atherogenic mechanisms such as oxidative/nitrative stress, coagulation activation, and low-grade inflammation.[17] The prevalence of symptomatic PAD is also 7 times higher in patients with APS compared to those without APS.[18] Atherosclerotic disease in patients with APS brings even more attention because they are epidemiologically different from the classic atherosclerotic patient since they are younger, predominantly female, and with a low rate of smoking as seen in this case.[19]

The management of bleeding in patients with positive APLA is challenging. If anticoagulants are temporarily stopped to address acute bleeding, it should be resumed as soon as the bleeding is controlled.[7] In some cases, the decision to continue anticoagulant despite ongoing bleeding may be necessary. This requires careful evaluation and consideration of the patient's clinical condition and the associated risks and benefits of anticoagulation therapy.[16] Heparin is commonly used for thrombotic prevention. Heparin blocks natural homeostasis by forming a complex with antithrombin III and enhancing its effect. However, the administration of heparin still has limitations as it can increase the possibility of vascular and hemorrhagic complications.[1] Similarly, our patient experienced PAD symptoms, but bleeding happened in other areas after TT administration despite APTT monitoring. Eventually, all antiplatelet medications were discontinued, and only heparin drip was maintained to overcome the PAD.

## CONCLUSION

SPH is a rare condition that represents a diagnostic challenge. Patients with sudden onset of flank pain without any history of trauma should raise suspicion to SPH and further examinations are required to define the underlying etiology. Most cases are caused by benign or malignant neoplasm. The management of SPH depends on the hemodynamic condition and in the setting of APS, additional cautions should be considered related to the antithrombotic medications.

## REFERENCES


1. Attri V, Parmar KM, Prateek T, Kumar S. Large spontaneous perirenal haematoma following percutaneous transluminal coronary angioplasty. BMJ Case Rep. 2019;12(11):e232437. DOI: 10.1136/bcr-2019-232437.
2. Zhao Y, Jia X, Tong X, Niu G, Wang R, Liu L, et al. Spontaneous perirenal hemorrhage in systemic lupus erythematosus: a rare case report and literature review. BMC Nephrol. 2021;22(1):217. DOI: 10.1186/s12882-021-02424-9.
3. Parmar N, Langdon J, Kaliannan K, Mathur M, Guo Y, Mahalingam S. Wunderlich syndrome: Wonder what it is. Curr Probl Diagn Radiol. 2022;51(2):270–81. DOI: 10.1067/j.cpradiol.2020.12.002.
4. Ramirez-Limon DA, Gonzaga-Carlos N, Angulo-Lozano JC, Miranda-Symes O, Virgen-Gutierrez F. Wunderlich syndrome associated with angiomyolipomas. Cureus. 2022;14(4):e23861. DOI: 10.7759/cureus.23861.
5. Lee PS, Baikunje S, Teh SP, Chan T. A case of spontaneous perinephric hematoma from rivaroxaban. Cureus. 2022;14(9):e29429. DOI: 10.7759/cureus.29429.
6. Mavridis C, Lagoudaki E, Georgiadis G, Bouchalakis A, Mamoulakis C. Retroperitoneal hemorrhage due to spontaneous renal rupture as the first presentation of antiphospholipid syndrome: A case report. Cureus. 2023;15(3):e36839. DOI: 10.7759/cureus.36839.
7. Chaturvedi S, McCrae KR. Diagnosis and management of the antiphospholipid syndrome. Blood Rev. 2017;31(6):406–17. DOI: 10.1016/j.blre.2017.07.006.
8. Radin M, Foddai SG, Barinotti A, Cecchi I, Rubini E, Sciascia S, et al. Reducing the diagnostic delay in antiphospholipid syndrome over time: A real world observation. Orphanet J Rare Dis. 2021;16(1):280. DOI: 10.1186/s13023-021-01906-1.


9. Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis. 2019;78(10):1296–304. DOI:10.1136/annrheumdis-2019-215213.
10. Tumian NR, Hunt BJ. Clinical management of thrombotic antiphospholipid syndrome. J Clin Med. 2022;11(3):735. DOI: 10.3390/jcm11030735.
11. McDougal WS, Kursh ED, Persky L. Spontaneous rupture of the kidney with perirenal hematoma. J Urol. 1975;114(2):181-4. DOI: 10.1016/s0022-5347(17)66981-7. PMID: 1159905.
12. Cinman AC, Farrer J, Kaufman JJ. Spontaneous perinephric hemorrhage in a 65-year-old man. Journal of Urology. 1985;133(5):829–32. Available from: DOI: 10.1016/S0022-5347(17)49243-3.
13. Castellino G, Cuadrado MJ, Godfrey T, Khamashta MA, Hughes GRV. Characteristics of patients with antiphospholipid syndrome with major bleeding after oral anticoagulant treatment. Ann Rheumatic Dis. 2001;60(5):527-30. DOI: 10.1136/ard.60.5.527.
14. Zhang JQ, Fielding JR, Zou KH. Etiology of spontaneous perirenal hemorrhage: A meta-analysis. J Urol. 2002;167(4):1593-6. DOI: 10.1097/00005392-200204000-00006. PMID: 11912370.
15. Macura KJ, Kawamoto S. Genitourinary imaging: Case review. 3rd ed. Philadelphia: Elsevier; 2015. Case 90. pp.184-85.
16. Pazzola G, Zuily S, Erkan D. The challenge of bleeding in antiphospholipid antibody-positive patients. Curr Rheumatol Rep. 2015;17(2):7. DOI: 10.1007/s11926-014-0481-0.
17. Merashli M, Bucci T, Pastori D, Pignatelli P, Marottoli V, Arcaro A, et al. Antiphospholipid antibodies and lower extremity peripheral artery disease: A systematic review and meta-analysis. Semin Arthritis Rheum. 2020;50(6):1291–8. DOI: 10.1016/j.semarthrit.2020.08.012.
18. Calcaterra I, Tufano A, Lupoli R, Iannuzzo G, Emmi G, Di Minno MND. Cardiovascular disease and antiphospholipid syndrome: How to predict and how to treat? Pol Arch Intern Med. 2021;131(2):161–70. DOI: 10.20452/pamw.15415.
19. Marques MA, von Ristow A, Paschoa AF, Malavazzi AL, de Oliveira JCP, Vivas PM. Arterial manifestations in antiphospholipid antibody syndrome. J Vasc Endovasc Ther. 2018;3(1). DOI: 10.21767/2573-4482.100075.