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SEVERE COMPLICATED SECONDARY ANTIPHOSPHOLIPID SYNDROME CONJOINTLY WITH SYSTEMIC LUPUS ERYTHEMATOSUS – CASE REPORT

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ABSTRACT

Antiphospholipid syndrome (APS), is an autoimmune systemic disorder known to manifest with thrombosis in almost all vessels throughout the body, can also be accompanied by pregnancy morbidity, and is persistent with the presence of antiphospholipid antibodies, including lupus anticoagulant antibodies, or relatively high titers of anticardiolipin, or anti-β2Glycoprotein I antibodies. APS can occur alone or in association with other diseases, more commonly systemic lupus erythematous. In patients with both underlying diseases episodes of arthritis, skin changes in the form of livedo reticularis, thrombocytopenia and leucopenia were more common. Cardiac manifestations have also been reported. Here we present a complicated case of a young female patient with antiphospholipid syndrome and an underlying systemic lupus erythematosus.

Keywords: antibodies, antiphospholipid syndrome, collaterals, systemic lupus erythematosus, thrombosis

INTRODUCTION

Antiphospholipid syndrome is a clinical autoimmune syndrome with a rich pathology in vascular thrombotic events, ranging from large to small vessels, obstetric complications such as fetal death after the 10th week, and persistent antiphospholipid antibodies [1, 2]. It is mostly a standalone syndrome, but when associated with other diseases, most commonly systemic lupus erythematous, it presents with a variety of symptoms including skin changes (livedo reticularis or cutaneous ulcerations), hematologic pathology (thrombocytopenia, hemolytic anemia), cardiac manifestations (valvular heart disease), and kidney disease (nephropathy) [3, 4]. The disease by itself is challenging enough, alongside another autoimmune disease such as lupus makes it difficult for physicians to diagnose and treat before more organs are affected. A low threshold should be maintained in the event of an underlying disease which may further complicate the patient's health and impede his treatment. In a cohort study where out of 1000 patients diagnosed with APS, 36% had SLE [5]. Laboratory testing for SLE should be performed in patients presenting with APS.

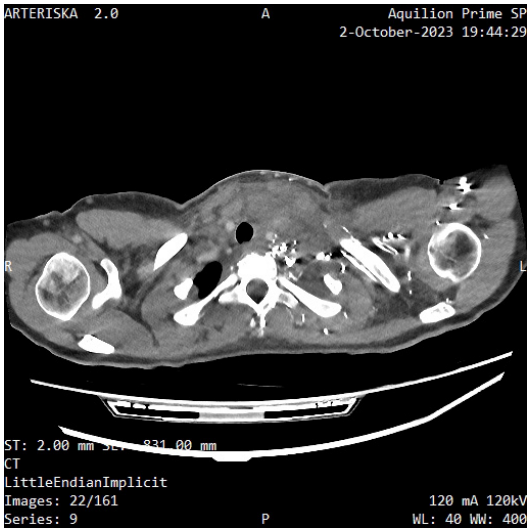
CASE REPORT

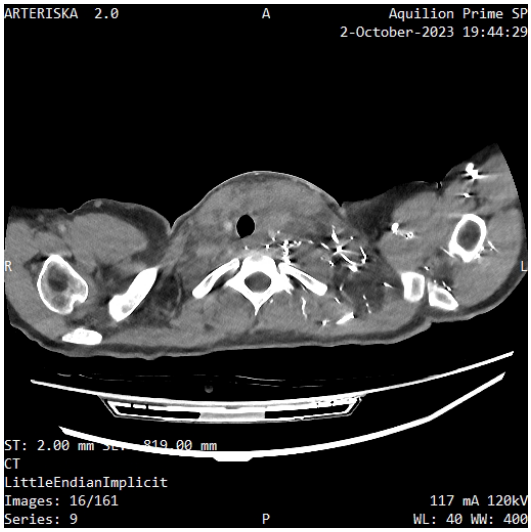
A 23-year-old female patient with a history of pain in both her wrists and knees, dating back to 2020, where after examination, laboratory tests

and further monitoring was recommended. The patient did not heed her physician, but did give information about having no pain or any other symptoms. Two months before admission to our clinic, she had a tooth extraction of the 8th tooth of her right side, after which she reported swelling on the same side that lasted several days with impaired wound healing. Two weeks later she reported chest pains that intensified and subsided during the day, with more intense during inspiration, due to which she was forced to breathe shallowly. In October 2023, three weeks after the tooth extraction, because of swelling on the left side of the neck, difficulty breathing and dysphagia she was referred to a maxillofacial surgeon, who excluded any dental origin of present symptoms. Due to her respiratory difficulties, she was referred to a pulmonologist who ordered a lung CT scan.

On the same day she was admitted to the University Clinic of Cardiology in a moderate

Picture 1 and 2, chest CT scan, Oct. 2023. *Edema is observed in the areas of the neck region of the base, more prominently on the left, where displacement of the thyroid and trachea is observed on the right with peripheral hyperdensity at the level of internal jugular vein on the left, and the edema is with extension and supra, infraclavicular on the left with lymphadenopathy in PCP on the left and axillary and infrasupraclavicular on the left*





to severe condition, with edema on the neck region, difficulty breathing and dysphagia. A cardiac surgeon was consulted to which he advised against surgical procedures and placed her on anticoagulation therapy.

Due to pain in her throat an otorhinolaryngologist was consulted, where a fibroscopy was indicated with results being unremarkable.

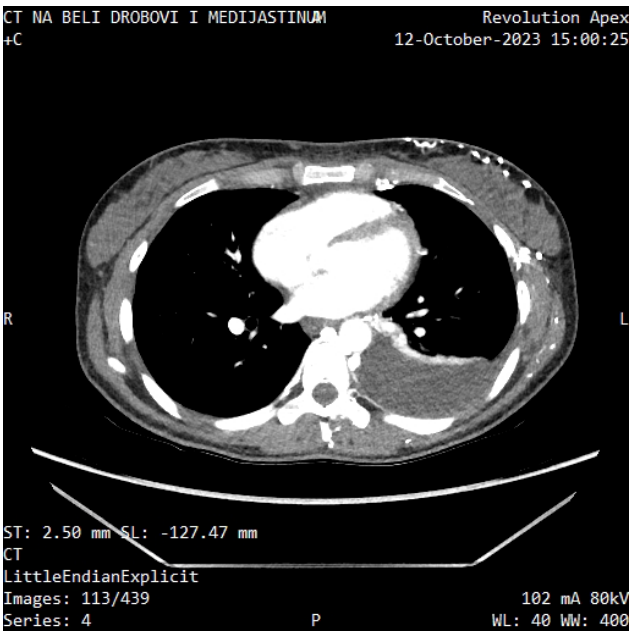
Laboratory tests showed slightly elevated values of inflammatory markers, after which she was treated with parenteral antibiotics. An infectiologist was consulted, where they concluded negative hemocultures from both hands. On recommendation from a Hematologist, the neck gland was punctured for biopsy which resulted in class I cytology. Coombs test was negative.

A lung echotomography revealed pleural effusion on the left side (picture 3) and a puncture was performed during which around 600ml fluid was evacuated, with an appearance of yellow and clear fluid. After consultation with a rheumatologist where laboratory tests (table 1) were ordered and correlating with the clinical picture she was diagnosed with antiphospholipid syndrome and was placed on antimalarials.

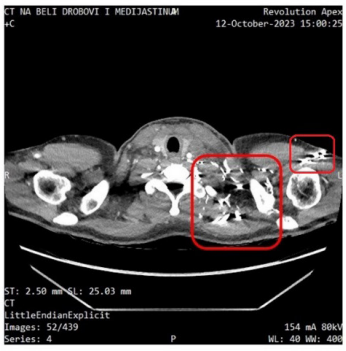
Table 1. *Laboratory test results*

aPTT	47.8s (27.9-37.7)	ANA	1:160+++
Lupus anticoagulant	164.3	Anti-dsDNA	160IU/ml
LA screen	129 (25-42)	ACLA IgM	91.6U/ml
24h proteinuria	0.224g/L	ACLA IgG	23U/ml
Diuresis	3.2L	D-Dimer	1474

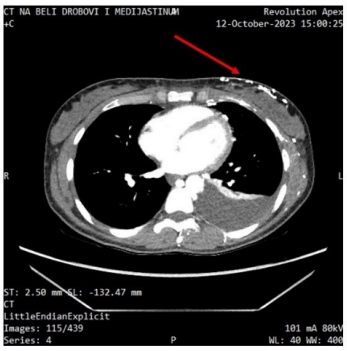
Picture 3. *Chest CT scan, showing pleural effusion on the left lung from apical to posterobasal with denser content with compressive atelectasis basally*



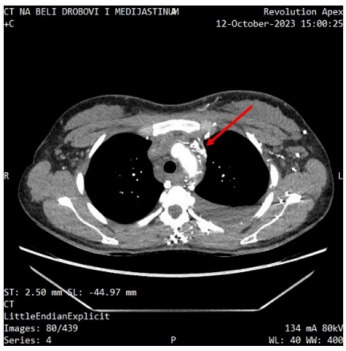
Picture 4-6. *Oct 2023, showing collaterals as a result of thrombosis on the thoracic wall, paratracheal and supraaortal, upper mediastinum which connect to azygos vein*



Picture 4



Picture 5



Picture 6

On admission in our clinic of Rheumatology it was noted that she had scoliosis and suffered from cyanotic fingers when exposed to cold temperatures. Swelling on the left side of the neck was also present. Skin changes in the form of caput medusae between and below the breasts was also noted, which dated back 4 months. On auscultation, in the left basal to midparts of the left lung, weak to silent hearing was noted. Her family history included her father suffers from Gout and mother who died from lung cancer. She reports no past diseases. The patient was a former smoker for 7 years but denies alcohol consumption or taking any drugs. She was allergic to penicillin, ciprofloxacin and vancomycin.

A lung ultrasound was performed where it showed a large left middle pleural effusion. Upon puncture 750ml serohemorrhagic fluid was evacuated.

Classification group 1 hemolyzed erythrocytes were identified along rare mesothelial cells. ADA serum was 23.0, Lysozyme-puncture 14.4, Lysozyme serum 13.8. P/S=1.04, ADA puncture 20.0, P/S=0.87. No presence of bacteria was found.

Table 2. *laboratory results obtained in November 2023*

ESR	28mm/h	IgA	0.9g/L
RBC	3.91x10^12/L	IgG	16.6g/L
HGB	115g/L	IgM	4.80g/L
HCT	0.330rv	C3	1.00g/L
WBC	3.81x10^9/L	C4	0.18g/L
PLT	21610^9/L	CRP	4.81mg/L
MCV	85.2fL	sFe	5.5umol/L

A recommendation for a heart ultrasound was given to rule out any right-hearted pathology.

From immunological tests obtained on the same day, the results showed a positive CRP (6.4mg/l), ANA (++1:160), anti-dsDNA (72.5IU/ml), anti-SM (25.7IU/ml), ACLA IgM (75.2U/ml), ACLA IgG (19.7U/ml), AFA (107.1U/ml), ANCA IFA (++ p-ANCA). Other antibodies were negative.

A consultant pulmonologist concluded a residual pleural effusion. The analysis from the puncture pointed towards exudative fluid. Loop diuretic medication was given for 3 to 5 days.

Heart ultrasound showed pericardial effusion under the lower wall only in systoles with dimensions up to 2mm and pleural effusion on the left up to 63mm.

A follow-up lung ultrasound a month later revealed a small pleural effusion with thickened pleura on the left. Continuation with diuretic therapy was advised and another ultrasound to be performed a month later, which revealed no pleural effusion bilaterally but present A lines on the parenchyma were noted. Dilated hepatic veins persisted with no regression compared to earlier measurements.

24-hour-proteinuria and blood tests were taken mid-November 2023, both being unremarkable. QuantiFERON TB Gold Plus was also negative. By the end of November, the patient had a slightly increased sedimentation rate.

Table 3. *laboratory results from the lung puncture*

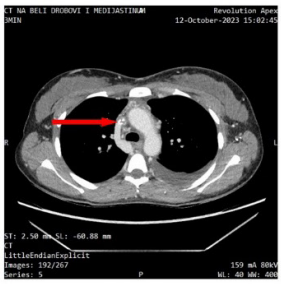
Total proteins	0g/L	Albumins	31g/L
Globulins	19g/L	HDL	0.32mmol/L
Total Cholesterol	2.5mmol/L	Triglycerides	0.29mmol/L
LDL	2.0mmol/L	CRP	2.75mg/L
LDH	207U/L	Alfa-Amylase	37U/L
Indirect bilirubin	0.9umol/L	Direct bilirubin	2.3umol/L
Total bilirubin	3.2umol/L	Glucose	4.9mmol/L

Table 4. *hemostasis performed in the clinic of Transfusion medicine, November 2023, showing secondary activated fibrinolysis. Prolonged aPTT because of inhibitory (LA). Fraxiparine 0.6ml daily was continued.*

Transfusion medicine	20.11.2023	23.11.2023	07.12.2023
aPTT	41.6s	45.8s	40.5s
PT	13.6s	12.4s	24.3s
TT	18.4s	21.9s	21.2s
D-dimer	2025ngr/ml	1756ngr/ml	208.5ngr/ml
INR			2.2 (0.8-1.2)

Lupus anticoagulants were 105 (confirmatory being 38) and screening AFA was 23.

Pictures (7-14). *Oct 2023, showing thrombosis axillary vein, brachiocephalic vein, almost all of left internal jugular vein. Thrombosis extending in the beginning of superior cava vein, with calcification, hinting of its chronic nature*



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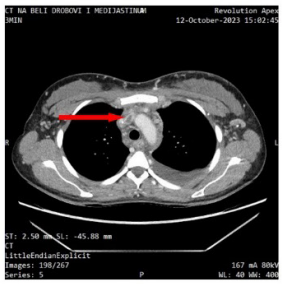

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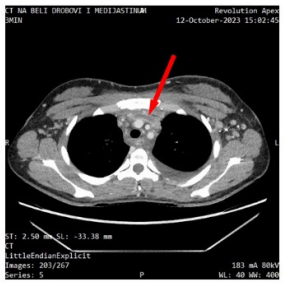

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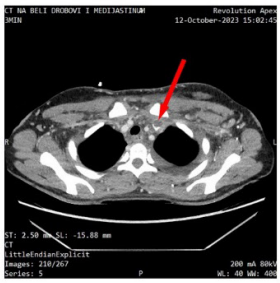

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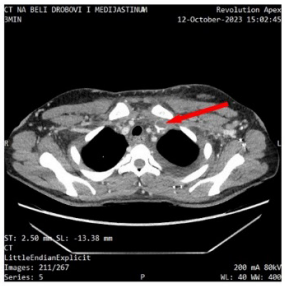
Picture 11



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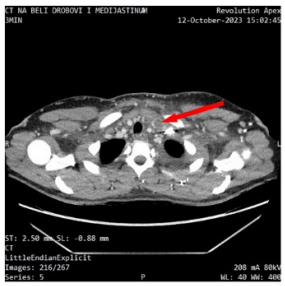

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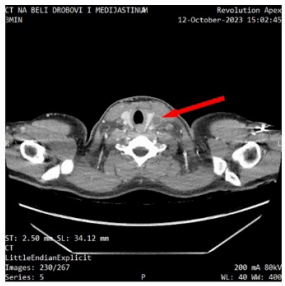
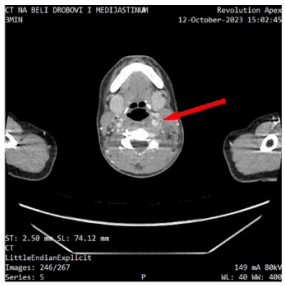


Picture 14



DISCUSSION

The patient was treated with corticosteroids, parenteral anticoagulants which were later switched to oral anticoagulants (vitamin K antagonist), diuretics, antimalarials, proton-pump-inhibitor and placed on immunosuppressive therapy with Mycophenolate mofetil (2mg daily). Studies have further confirmed the efficacy of acetylsalicylic acid (ASA) in primary prevention of thrombosis in patients with APS [6]. Systemic reviews have shown warfarin to be superior to direct oral anticoagulants (DOAC), due to increased risk of thrombotic events in patients with DOAC compared to those treated with warfarin [7, 8, 9]. Recommendations suggest keeping an international normalized ratio of 2.0 to 3.0 for patients on vitamin K antagonist therapy [10], in this patient, on the last checkup it was 2.2. Although the patients' overall condition improved, we continue to closely monitor the patient's health. Treatment courses vary in patients with APS compared to those with unprovoked venous thromboembolism [11]. Screening patients with SLE for aPL antibodies (lupus anticoagulant, antiphospholipid, anticardiolipin and anti-Beta-2-gp1 antibodies) is of utmost importance considering the increased risk of thrombotic events compared to healthy patients [12, 13]. The level of these antibodies also plays a role in the stratification of risk. Due to one of the symptoms in patients with SLE is thrombocytopenia it can further complicate the treatment in these patients [13].

CONCLUSION

Based on the history of the patient, clinical picture and paraclinical examinations, this patient was diagnosed with systemic lupus erythematous presenting with arthritis, leucopenia, anemia and positive ANA, anti-dsDNA, anti-Sm and antiphospholipid antibodies with a dominant clinical picture of antiphospholipid syndrome with thrombosis of the superior vena cava, internal jugular vein, left brachiocephalic vein, subclavian vein which were in the chronic phase with developed bilateral collateral venous drainage of the chest bilaterally. Recurrent unilateral pleural effusion which was in regression. Antiphospholipid syndrome by itself is a challenging disease to diagnose and treat, and presenting as secondary with an overlapping systemic lupus erythematosus further complicates treat-

ment. More than a third of patients with SLE test positive for antiphospholipid antibodies, and a significant number of patients with primary APS have tested positive for ANA/anti-dsDNA antibodies. A high index of suspicion should be maintained in young patients presenting with unprovoked or unusual thromboses or unexplained recurrent early or late pregnancy loss. Standard treatment for APS is mostly preventing thrombotic events with lifelong vitamin K antagonist therapy, some patients may benefit from treatment with low-dose acetylsalicylic acid and warfarin combination. Patients presenting with APS need more than just anticoagulation therapy, potential benefits have been shown from treatment with immunosuppression therapies and statins. Hydroxychloroquine, a drug used in patients with systemic lupus erythematosus is shown to have benefits in patients with APS. It's use in this patient was suitable to treat both SLE and APS. Due to LA-induced effects, partial thromboplastin time (PTT) may be unreliable, using the anti-Xa assay will be more reliable in measuring unfractioned heparin (UFH) efficiency in APS patients. A multidisciplinary approach and close monitoring are paramount in these patients, especially when most vulnerable, in times of pregnancy and perioperative periods, when the risks for thrombotic or bleeding events are high.

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Резиме

ТЕШКО КОМПЛИЦИРАН СЕКУНДАРЕН АНТИФОСФОЛИПИДЕН СИНДРОМ СО СИСТЕМСКИ ЛУПУС ЕРИТЕМАТОЗУС – ПРИКАЗ НА СЛУЧАЈ

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Антифосфолипиден синдром (APS) е автоимуна системска болест позната по тоа што манифестира тромбоза во речиси сите садови низ телото, може да биде придружена со морбидитет при бременост и е упорна со присуство на антифосфолипидни антитела, кои вклучуваат лупус антикоагулантни антитела, или релативно високи титри на антикардиолипин, или анти-β2Гликопротеин I антитела. APS може да се појави сама или да биде поврзана со други болести, најчесто системски лупус еритематозус. Кај пациентите со двете основни болести, епизоди на артритис, кожени промени во форма на livedo reticularis, тромбоцитопенијата и леукопенијата беа почести. Исто така, пријавени се и кардијални манифестации. Овде претставуваме комплициран случај на млада пациентка со антифосфолипиден синдром и основен системски лупус еритематозус.

Клучни зборови: антитела, антифосфолипиден синдром, колатерали, системски лупус еритематозус, тромбоза