Received: 3 March 2023 | Revised: 23 March 2023 | Accepted: 25 May 2023

DOI: 10.1002/ccr3.7519

CASE REPORT

Clinical Case Reports Open Access WILEY

Adrenal insufficiency as a rare manifestation of secondary antiphospholipid syndrome: A pediatric case report and review of articles

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Key Clinical Message

Adrenal insufficiency is a rare, important manifestation of secondary antiphospholipid syndrome (APS) in pediatrics. In the presence of hematologic disorders such as thrombosis, we should consider APS.

Abstract

Adrenal insufficiency can rarely occur in the context of vascular disorders and thrombosis in patients with antiphospholipid syndrome. There are few case reports in pediatrics. Here, we present a pediatric case—the first pediatric case report in Iran—and review articles in this age group.

KEYWORDS

adrenal insufficiency, antiphospholipid syndrome, case report, pediatrics

1 | INTRODUCTION

Antiphospholipid syndrome (APS), which is characterized by thrombotic events and pregnancy morbidity, is a systemic autoimmune disease with constant positive anticardiolipin Antibodies.[1] APS is very rare among pediatric cases; in the largest cohort study, the incidence was 2.8%.[2] Secondary APS occurs in the presence of another disease, mostly systemic lupus erythematosus (SLE).[3] Hematologic and neurologic manifestations are common in pediatric cases.[4]

Adrenal insufficiency (AI) can occur in these patients in the context of vascular disorders including thrombosis and hemorrhage of adrenal glands.[5] AI is either primary, mostly due to autoimmunity, or secondary to hypothalamic–pituitary impairment.[6] Various clinical symptoms are due to impaired secretion of mineralocorticoid and glucocorticoid.[7] Acute AI usually presents with hypotension, abdominal pain, vomiting, fever, and hypovolemic shock, while in chronic cases it presents with fatigue and irritability.[6] Glucocorticoid deficiency also results in hypoglycemia, seizure, weakness, and hyperpigmentation.[8] Acute adrenal crisis is life-threatening and requires special attention and clinical suspicion.[7]

As one of the rare causes of AI in children is secondary APS, it must be considered especially in the presence of

other symptoms. Here, we present a case of AI in secondary APS and review the literature in pediatrics. This is the first pediatric case reported in this concept in Iran.

2 | CASE PRESENTATION

A 15-year-old Iranian girl was referred to the endocrinology clinic, a referral center in southern Iran, with severe fatigue and weakness. She presented with irritability, abdominal pain, vomiting, salt craving, and complaint of right thigh pain. Her problems had started in the last 3 months and had gradually worsened. 3 months later, she was admitted to the hospital due to dyspnea, cough, and fever with the diagnosis of pneumonia and lung hydatid cyst. A chest CT scan showed mild to moderate bilateral pleural effusion, a subpleural cystic structure measuring about 32 × 22 mm in the left lower lobe. ELIZA confirmed a hydatid cyst. Because of a ruptured infected hydatid cyst, surgery was indicated. On preoperational workup, prolonged PT (15.1 s), INR (1.12), PTT (108.2 s), and pancytopenia (WBC 2.1, Hb 6.1, plt 61×10^9) were seen, so the operation was canceled. Thus, Mebendazole was started. The treatment was successful and she was discharged after 24 days with a follow-up of hematologist.

She was ill and had severe fatigue. On physical examination, she had hypotension (blood pressure 80/50 mmHg), tachycardia (heart rate 120/min), fever (temperature 38°C), and generalized abdominal pain without guarding or tenderness. Significant hyperpigmentation was seen especially in the buccal mucosa, mouth, and extremities (Figure 1). She had limping. Edema and swelling on the right lower extremity were also obvious. Her weight was 53 kg (5 kg loss during these 3 months), and her height 159 centimeters.

She was admitted to the hospital for more evaluation and treatment. Color Doppler sonography (CDS) of the lower extremity veins showed thrombosis of the right common femoral vein. With suspicion of secondary APS due to SLE, workups were requested according to pediatric rheumatologic consult, beside laboratory evaluation of AI as shown in Table 1.

The patient was critically ill, and had hypotension and hyponatremia. Due to this emergent condition and no time for delayed treatment of adrenal crisis, the stimulatory test was not done. According to the clinical signs and symptoms and laboratory data (high ACTH 8 AM and low cortisol level), treatment started with the diagnosis of AI. She had a dramatic response to Hydrocortisone (100 mg IV stat and then divided q6h). Enoxaparin (50-unit SQ BID) was also prescribed. She was discharged in good condition with prednisolone (12.5 mg PO TID), fludrocortisone (0.1 mg PO QD), rivaroxaban (20 mg PO daily), and hydroxychloroquine (200 mg QHS).

3 | DISCUSSION AND CONCLUSION

Adrenal involvement is a rare condition in secondary APS, especially in pediatric cases. Here, we presented a case of AI and secondary APS and reviewed the English literature on pediatric cases. Based on a search on google scholar and PubMed with the keywords of antiphospholipid syndrome, APS, Adrenal insufficiency, pediatric, and children eight pediatric cases were reported. Clinical, demographic, and laboratory data are reported in Table 2.

In a cohort study of 1000 patients with APS, 36.2% had APS associated with SLE while 53.2% had primary APS. Thrombocytopenia and leukopenia were more frequent in secondary APS due to SLE.[2] Secondary APS accounts for 50%–60% of pediatric cases.[9] Noticeably, our case, meets the criteria with positive ANA, dsDNA, lupus anticoagulant Ab along with lymphopenia. She had also episode of femoral vein thrombosis. APS secondary to SLE was confirmed for her. Levy et al.[10] also reported a 17-year-old girl presented with bloody sputum and pneumonia. AI was suspected due to confusion and hyponatremia. She

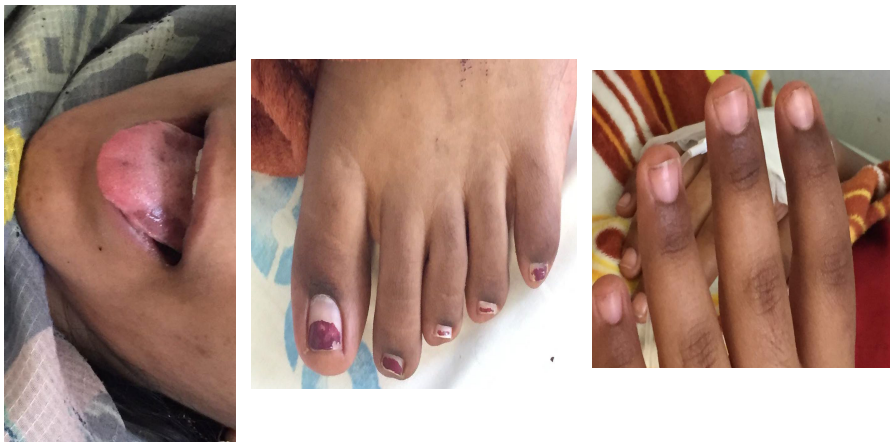

FIGURE 1 Hyperpigmentation.

TABLE 1 Laboratory data.

ANA	Positive	WBC	4.4×10^9/L
Anti-ds DNA	221.6 IU/mL (positive >24)	Neutrophil	71.6%
Lupus anticoagulant	76.3 s (28–43)	Lymphocyte	23.2%
C3	1.049 g/L (0.89–1.87)	Hemoglobin	7 g/dL
C4	0.107 g/L (0.165–0.380)	MCV	90.6 fL
CH50	95.02% (50–150)	Platelet	104×10^9/L
Anti-RO	0.41 (<0.8)	Retic	3.2
Anti-La	0.21 (0.8)	ESR	100 mm/h
Anti-TPO	1.7 IU/mL (<5.61)	CRP	5 mg/L
Anticardiolipin Ab	Positive (> 20)	PT	13.8 s
ACTH 8 AM	1180 pg/mL (7.2–63.6)	PTT	57.6 s
Cortisol 8 AM	4 μg/mL (2.5–12.5)	BUN	13 mg/dL
Renin	>128 pg/mL (2.13–58.78)	Creatinine	0.42 mg/dL
Aldosterone	9.3 pg/mL (up to 160)	Na	129 mmoL/L
TSH	5.43 μIU/mL (0.51–4.30)	K	4.1 mmoL/L
T4	126.5 nmoL/L (76.1–170)	Ca	9.1

had bilateral adrenal enlargement and right-side hemorrhage. During hospital admission she get headache and hemianopia. SLE was documented with clinical and laboratory results. After 4 months, she had admitted with pleuritic chest pain and pulmonary embolism. On further evaluation APS was diagnosed. Many of pediatric cases of primary APS meet the criteria of SLE on follow-ups.[11] Pelkonen et al.[12] reported a boy for whom APS was confirmed at age 12-year-old. 3 years later, on follow-ups, he fulfilled the criteria for SLE.

In the largest cohort study of APS in pediatric cases,[4] 46% of patients were male and 54% female. The rate of Addison disease in APS patients reported 0.4%.[2] Here we reviewed cases of AI and APS in pediatrics. Based on our review and case report, among pediatric cases with AI and APS, 55% are male and 45% female. The mean age is 11.7 ± 3.19 years old.

Vaccination and infections can trigger autoimmune diseases such as APS.[13] Several infectious organisms are known to cause APS in previously well patients.[11] In many of these patients, like our patient, prolonged PTT was the primary factor for APS consideration.[11] In our literature review, pneumonia was the first presentation in 44.4% of the patients (cases 2, 3, 6, and 9). Our patient was also admitted with pneumonia and an infected lung hydatid cyst.

We have limited data about the treatment of APS in pediatrics and most information is from adult or small clinical reports. The treatment is low molecular weight or unfractionated heparin and anticoagulation medication in the acute setting of thrombosis. Long-term anticoagulation therapy is recommended for patients with thrombosis and persistently positive antiphospholipid.[1] We discharged our patient with prednisolone and hydroxychloroquine, as a treatment of lupus, a cause of APS, along with rivaroxaban as an anticoagulant.

Adrenal glands are well vascularized and rich in blood supply as they produce systemic important hormones. The venous drainage consists of the left renal vein for the left adrenal and the inferior vena cava for the right one.[14] The high arterial supply and limited venous drainage may be the cause of thrombosis.[5] The pathogenesis of AI in APS is related to thrombosis and hemorrhage.[15] In Espinosa et al.'s study about APS patients with adrenal involvement, adrenal hemorrhage was observed in 57%, infarction in 14%, enlargement in 10%, and normal imaging was in 7%.[5,15] In Presotto et al., imaging study also revealed 55% adrenal hemorrhage, 15% infarction, and 5% normal cases.[16] In our pediatrics review, 44.4% had adrenal enlargement (cases 1, 3, 5, and 6). 22.2% reported normal (cases 7 and 9), adrenal hemorrhage in 22.2% (cases 3 and 8), and infarction in 11.1% (case 1).

Adrenal crisis is a life-threatening condition and should be considered in patients with hypotension, hypoglycemia, fever, confusion, nausea, vomiting, abdominal pain, or hyperkalemia.[17] Glucocorticoid deficiency is responsible for weight loss, fatigue, and muscle ache. Orthostatic hypotension and salt craving occur in mineralocorticoid deficiency.[17] As the pro-opiomelanocortin (POMC) products (α-melanocyte-stimulating-hormone and adrenocorticotropin hormone) increased significantly in response to decreased cortisol levels, hyperpigmentation could be seen in patients with AI.[18]

Primary AI is confirmed when serum cortisol level is low in the presence of an increased level of ACTH and plasma renin.[19] Stimulatory tests for cortisol deficiency

TABLE 2 Review of literature.

Number	Study	Age (year)	Sex	Manifestation of AI	Manifestation of APS	Laboratory	Imaging	Treatment
1	Inam S et al.1986, Saudi Arabia[21]	10	M	Recurrent abdominal pain, weight loss, vomiting, fever	Loin pain, headache, hypertension	Lupus anticoagulant positive Na 116 Ua: blood 3+ Hb: 10 Plt: 90 PTT 67	Abdominal CT: bilateral enlarged hypodense adrenals, no contrast enhancement consistency with areas of infarction 2nd admission: Adrenal MRI: complete atrophy	Glucocorticoid Mineralocorticoid Warfarin
2	Pelkonen P et al.1988, Finland[12]	10	F	Tiredness, irritability, headache	Swelling leg The dilated vein on the abdomen	Hyponatremia Anemia Thrombocytopenia No cortisol response to ACTH Coombs positive Lupus anticoagulant positive	CXR: pneumonia Phlebography: thrombosis of IVC and both iliac vein	Glucocorticoid Mineralocorticoid Warfarin
3	Levy EN et al.1988, Pennsylvania[10]	17	F	Pneumonia, lethargy, confusion, hypotension	Hemianopia and retinal hemorrhage, pulmonary embolism, left parietooccipital infarction	Anticardiolipin ab IgM positive Cortisol 2.1 μg/dL Aldosterone 1 μg/dL ACTH 388 pg/dL Na 115	Abdominal CT: bilateral adrenal enlargement and hemorrhage on the right side Brain MRI: Left parietooccipital infarction Lung ventilation-perfusion scan: pulmonary embolism	Glucocorticoid Mineralocorticoid Coumadin
4	Rose C et al. 1990, Philadelphia[22,23]	15	F	Hyponatremic dehydration, altered mental status, lethargy	Choreiform movement Headache	Na 131 mmoL/L Morning basal cortisol 0.8 μg/dL ACTH 99 pg/mL ESR 35 ANA 1:1280 PTT 60 s Anticardiolipin Ab positive		Haloperidol Corticosteroid
5	Böber E et al. 2001, Turkey[24]	10	M	Weakness, fatigue, weight loss, rt flank pain, vomiting	Rt inguinal and leg pain due to thrombosis of femoral vein	ESR 75 Na 118 mmoL/L K 6.3 mmoL/L Corticotropin 214 pg/mL Cortisol 2.25 μg/dL Aldosterone 8 pg/mL DHEAS 3 μg/dL Aldosterone 0.2 ng/mL Anticardiolipin Ab positive	Abdominal MRI: unilateral enlargement of Rt adrenal gland CDS: femoral vein thrombosis down to the popliteal region	Mineralocorticoid Glucocorticoid Warfarin

TABLE 2 (Continued)

Number	Study	Age (year)	Sex	Manifestation of AI	Manifestation of APS	Laboratory	Imaging	Treatment
6	Espinosa G et al. 2002, Spain[5]	11	M	Fever, pneumonia (mycoplasma), anorexia, weight loss, hypotension, vomiting	Acute pulmonary emboli	Lupus anticoagulant positive Mycoplasma pneumonia IgM positive ANA weakly positive Plasma cortisol 2.7 μg/dL	Abdominal CT: punctuate calcification in both adrenal glands and enlargement	Glucocorticoid Coumadin
7	Bhakhri B et al. 2011, India[25]	7	M	Intermittent abdominal pain, weakness, gradual pigmentation, weight loss, convulsion	Swelling and gangrene of right forearm	Hypoglycemia Hyponatremia Thrombocytopenia Anemia Randome serum cortisol 115.87 nmoL/L Lupus anticoagulant positive	Abdominal CT: normal CDS: acute thrombosis in Right common femoral vein extending to Right external iliac vein	Mineralocorticoid Glucocorticoid Warfarin
8	Improda N et al. 2012, Italy[26]	11	M	Fever, abdominal pain, and vomiting	Abnormal laboratory data	Hyponatremia ACTH 961 pg/mL Cortisol 31.5 ng/mL Thrombocytopenia Anemia Elevated inflammatory parameters Hypergammaglobulinemia Prolong PTT Antinuclear, antiphospholipid, anticardiolipin, antiplatelet autoantibody-positive Lupus anticoagulant positive Coombs positive	Abdominal CT: nodular lesions in the adrenal glands Abdominal MRI: bilateral adrenal hemorrhage	Mineralocorticoid Glucocorticoid Anticoagulant Cyclosporin
9	Current case Iran	15	F	Abdominal pain, vomiting, weight loss, hypotension, hyperpigmentation	Right thigh pain	Cortisol 4 Renin >128 Aldosterone 9.3 ACTH 1180 Na 129 Lupus anticoagulant	Chest CT: bilateral pleural effusion Subpleural cystic structure in left lower lobe Abdominal CT: normal adrenal glands	Corticosteroid Mineralocorticoid Rivaroxaban

Abbreviations: ACTH, adrenocorticotropic hormone; ANA, antinuclear antibody; CT, computed tomography; CXR, chest radiography; Hb, hemoglobin; MRI, magnetic resonance imaging; Plt, platelet; PT, prothrombin time; PTT, partial thrombin time.

should also be considered[17] which is the gold standard for diagnosis.

In the situation of adrenal crisis, treatment includes sufficient parenteral hydrocortisone, restoring intravascular volume, and normalization of serum sodium and glucose. Maintenance therapy includes glucocorticoid and mineralocorticoid replacement for primary AI and cortisol replacement for secondary AI.[19]

The more prevalent etiologies for primary AI are autoimmune destruction, congenital adrenal hyperplasia, adrenoleukodystrophy, drugs, infections, and hemorrhage.[20] Although it is rare, we should consider APS as an important cause of this fatal disease especially in the presence of hematologic manifestations such as thrombosis. We should also consider AI in patients with SLE or APS in the presence of inexcusable weakness and fatigue, salt craving, hypotension, and specially hyperpigmentation. Adrenal crisis, a fatal condition, would happen if we do not diagnose AI on time. If the patient presents with an adrenal crisis, we should not delay the treatment. As in our patients, with the suspicion of adrenal crisis, we sent laboratory samples and start the treatment emergently and after stabilization we discharged her with the treatment of underlying cause, SLE and secondary APS, as we mentioned above.

AUTHOR CONTRIBUTIONS

Homa Ilkhanipoor: Conceptualization; visualization; writing – original draft; writing – review and editing. **Shabnam Hajiani Ghotbabadi:** Conceptualization; supervision; writing – review and editing. **Hamide Barzegar:** Conceptualization; writing – original draft; writing – review and editing. **Atefeh Sedaghat:** Data curation; writing – original draft; writing – review and editing.

ACKNOWLEDGMENTS

The authors would like to thank Shiraz University of Medical Sciences, Shiraz, Iran and also Center for Development of Clinical Research of Nemazee Hospital and Dr. Nasrin Shokrpour for editorial assistance.

FUNDING INFORMATION

No funding was obtained for this study. All authors have read and approved the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

ETHICS STATEMENT

The study protocol confirmed to the ethical guidelines of the 1975 Helsinki Declaration. The publication of this case was approved by the ethics committee of Shiraz University of Medical Sciences(IR.SUMS.MED.REC.1401.544). We have written informed consent obtained from the parents of the patient for publication of this case report.

CONSENT

We have written informed consent obtained from the parents of the patient for publication of this case report.

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How to cite this article: Ilkhanipoor H, Hajiani Ghotbabadi S, Barzegar H, Sedaghat A. Adrenal insufficiency as a rare manifestation of secondary antiphospholipid syndrome: A pediatric case report and review of articles. *Clin Case Rep*. 2023;11:e7519. doi:10.1002/ccr3.7519