

Case report

CARDIAC TAMPONADE REVEALING AN “APECED SYNDROME” IN A 7-YEAR-OLD MOROCCAN GIRL. WHAT AN UNSUAL MANIFESTATION! A CASE REPORT

Abstract

Background: APECED or multiple endocrine deficiency autoimmune candidiasis syndrome is a rare disease characterized by the manifestation of autoimmune endocrinopathies in a peculiar sequence during infancy. The clinical diagnosis of APECED requires the presence of at least two of these three major components: Chronic mucocutaneous candidiasis, hypoparathyroidism and or primary adrenal insufficiency. Genetic testing is necessary for precise identification in certain instances, particularly those presenting with atypical or subtle symptoms.

Clinical presentation: we report a rare clinical manifestation of APECED syndrome in a 7-year-old girl from a Moroccan origin and 2nd consanguineous marriage, unique child was admitted initially for cardiac tamponade revealing the underlying disease. Patient's assessment after pericardiocentesis confirmed hypoparathyroidism disease and undiagnosed chronic onychomycosis of the nails of her right hand. A genetic test was carried out after multidisciplinary discussion between cardiologists and endocrinologists which tested positive for a mutation in the **AIRE (21q22.3)** gene responsible for **APECED syndrome**. Treatment was based on symptomatic treatment of acute pericarditis according to the guidelines of European Society of Cardiology on the management of pericarditis with a good clinical outcome associated with oral calcium supplementation and levothyroxine.

Conclusion: APECED syndrome is an exceptional disease both in terms of its frequency and its pathophysiological mechanisms and requires a multidisciplinary approach. The management of APECED syndrome involves the management of the various diseases. Patients must be monitored regularly to detect the appearance of other pathological elements of the syndrome.

Keywords : Tamponade, APECED syndrome, onychomycosis, hypoparathyroidism.

Abbreviations : (not mentioned) Abbreviations used in the text to be mentioned.

Introduction

Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), also known as autoimmune polyglandular syndrome type 1 (APS1), is a rare monogenetic autosomal recessive disorder caused by a mutation in the autoimmune regulator (AIRE) gene characterized by complex phenotypic characteristics discovered over years of follow-up [1-3]. The disease frequency is 1: 25,000 in Finns [4]. The clinical spectrum of the disease is characterized by a wide heterogeneity because of the highly variable

pattern of destructive autoimmune reactions toward different endocrine and non-endocrine organs. Chronic mucocutaneous candidiasis, hypoparathyroidism and primary adrenal insufficiency represent the classical triad of the syndrome. The clinical diagnosis of APECED requires the presence of at least two of these three major components [5]. In addition to the typical manifestations, individuals with APECED may also manifest various autoimmune conditions, including but not limited to autoimmune hepatitis, enteropathy, gastritis, pernicious anemia, gonadal failure, and diabetes. Furthermore, the syndrome is linked to ectodermal manifestations such as alopecia and vitiligo, along with inflammatory complications such as intestinal lung disease and nephritis [6-8]. Genetic testing is necessary for precise identification in certain instances, particularly those presenting with atypical or subtle symptoms [9]. Management of this disorder requires collaboration between several specialties due to the multiplicity of organs affected [10]. Here we report a rare clinical manifestation of APECED syndrome in a 7-year-old girl from a Moroccan origin who was admitted initially for cardiac tamponade revealing the underlying disease. Pericardial tamponade has been never reported in the cases of APECED syndrome.

Case Report

A 7-year-old (**child, an – delete it**) only child from a 2nd degree consanguineous marriage, presented to the pediatric emergency room with her mother for exertional dyspnea for a week, **worsened** two days before her admission without an episode of flu. Noted that the child had no particular pathology or history of hospitalization, she **was** in school with good psychomotor development. The clinical examination on admission found a conscious child with a Glasgow score of 15/15, well oriented in time and space with normal colored connective tissue, dyspneic at rest without chest pain. She was tachycardic at 120 beats per minutes, systolic blood pressure (SBP) of 110mmHg and diastolic blood pressure (DBP) of 80mmHg symmetrical in both upper limbs, polypneic at 26 cycles per minute with an ambient air saturation of 96%, afebrile at 37°C with warm extremities of the limbs. The cardiovascular and pleuropulmonary examination revealed muffled heart sounds without added murmurs or pulmonary crackles. The mucocutaneous examination **revealed** mucocutaneous candidiasis affecting the nails of her right hand (Figure 1).



Figure 1 : Patient Right hand photo showing dry skin with ridged nails and brittle place of nail candidiasis (onychomycosis)

A chest x-ray performed showed an enlarge heart without pulmonary parenchyma abnormality for which a cardiologist opinion was requested.

An ECG was carried out which demonstrated a sinus tachycardia with electrical **alteration**. A trans thoracic echocardiography carried out on the patient revealed a large amount of pericardial effusion in tamponade stage (Figure 2).



Figure 2 : Trans thoracic echocardiography : Sub costal 4 chambers view : showing a **floating** heart in a large pericardial effusion ; cardiac tamponade.

Faced with this obvious diagnosis, pericardiocentesis was carried out associated with initial medical treatment based on aspirin (500mg x 3 per day), colchicine (0.5mg per day) and prophylactic antibiotic therapy based on amoxicillin-clavulanic acid

(AUGMENTIN). The biological assessment showed a **normal** blood count, however a spontaneous low prothrombine (PT) level at 42% with a normal factor V; hypocalcemia (70ng/l) and low parathyroid hormone levels (<4pg/nl) suggestive of hypoparathyroidism. A cervico thoraco abdomino pelvic scan done showed no abnormalities apart from bilateral renal nephrocalcinosis confirmed by Reno vesical Doppler ultrasound (Figure 3).



Figure 3 : Abdominal ultrasound showing a bilateral nephrocalcinose of the kidneys

The tumor markers were normal, faced with hypoparathyroidism and mucocutaneous candidiasis, the child was placed on treatment based on Levothyrox, local antimycotic treatment and alfacalcidol (UNALFA Ca²⁺⁺ tablet) after discussion with endocrinologists. Faced with this clinical picture given the endocrine involvement, after exhaustive etiological research, a genetic assessment was carried out after multidispilinary discussion between cardiologists and endocrinologists which **concluded as** in positive for a mutation in the **AIRE (21q22.3)** gene responsible for **APECED syndrome** (Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy). Symptomatic treatment **for** pericarditis was stopped (**after – delete it**) 1 month after discharge and treatment of

hypoparathyroidism was continued **along with topical** antimycotic treatment. The clinical outcome was favorable with no recurrence of pericardial effusion during one year of follow-up.

Discussion

APS type I, also known as autoimmune polyendocrinopathy, candidiasis and ectodermal dystrophy (APECED) or multiple endocrine deficiency autoimmune candidiasis syndrome is a rare disease characterized by the manifestation of autoimmune endocrinopathies in a peculiar sequence during infancy [11, 12]. In most affected children, chronic mucocutaneous candidiasis caused by *Candida albicans* occurs before the age of 5 years affecting up to 5% of the body surface [12].

The female/male ratio of PAS I is 0.8–2.4 showing a slight female predominance. The manifestation peak is in infancy [13]. In contrast, with a prevalence of 1:20,000, the adult form of PAS is far more prevalent with an annual incidence of 1–2:100,000. Further, the prevalence of subclinical incomplete forms is estimated to be 150:100,000 [13-14].

Diagnosis generally relies on three main criteria: chronic mucocutaneous candidiasis (CMC), chronic hypoparathyroidism (CH), and adrenal insufficiency. Nonetheless, genetic testing is necessary for precise identification in certain instances, particularly those presenting with atypical or subtle symptoms [6,15]. Cardiac involvement has never been reported in the literature caused by APECED syndrome as seen in our case. The cause of pericardial effusion can be related to hypoparathyroidism but mechanism of APECED syndrome in direct cardiac involvement is not elucidate.

Since the discovery of the AIRE gene, considerable progress has been made in understanding this disease. AIRE is expressed in thymic medullary cells and encodes a DNA-binding protein, namely an autoimmune regulator. The hypothesis is that this protein helps regulate the thymic expression of various tissue-specific antigens leading to the elimination of autoreactive T cells. In its absence, autoreactive cells escape negative selection and are released into the circulation [16].

Early diagnosis of the rare APS I is difficult because of its clinical variability and inter-individual differences in presentation with sequential occurrence of associated diseases [12]. APS I should be considered in patients with chronic mucocutaneous candidiasis, adrenal insufficiency or hypoparathyroidism in young age combined with at least one minor component such as chronic diarrhea/severe constipation, keratitis/enamel hypoplasia, periodic rash with fever, autoimmune hepatitis, vitiligo or alopecia [17]. In our case, the diagnosis of APECED syndrome was confirmed after 6 months prior hospitalization after an exhaustive work-out to rule out likely causes of pericardial effusion in our context (*Mycobacterium tuberculosis*). Our patient clinical presentation finally associated, pericardial effusion, onychomycosis, hypoparathyroidism and bilateral nephrocalcinoses.

Diagnostic criteria for autoimmune polyglandular syndrome- 1 [17, 18]

Definite diagnosis:

Presence of two of the triad of chronic mucocutaneous candidiasis, hypoparathyroidism, or Addison disease.

- One of the above triad plus a sibling with proven APS-1
- Known disease-causing mutations in the AIRE gene.

Probable diagnosis:

- Presence of one of the triad (before 30 years) along with one of the following components chronic diarrhea, keratitis, periodic rash with fever, severe constipation, autoimmune hepatitis, vitiligo, alopecia, and enamel hypoplasia.
- Any one of the above triad and anti-interferon antibodies
- Any one of the above triad and antibodies against NALP5, aromatic L-amino aciddecarboxylase (AADC), tryptophan hydroxylase (TPH), or tyrosine hydroxylase (TH).

Besides clinical symptoms, serological testing is indispensable for the screening of patients with polyglandular autoimmunity. Concerning PAS I, interferon- ω and - α antibodies show the highest prevalence (95–100%) with early emergence and have been proposed for confirmation of diagnosis [19-20]. These autoantibodies are detectable in *AIRE*-deficient children as early as few months of age, before the appearance of clinical symptoms and/or organ-specific autoantibodies [21-23].

The management of APECED syndrome involves the management of the various diseases. Treatment of CMC is aimed at preventingazole antifungal resistance and squamous cell cancer. Onychomycosis is difficult to eradicate; systemic treatments are often required for six weeks [24]. Whereas in our case, local antimycotic treatment of onychomycosis was opted. The objective of hypoparathyroidism treatment is to maintain normocalcemia. Acute hypocalcemia warrants intravenous supplementation of calcium gluconate or calcium chloride. In nonacute circumstances, oral calcium and vitamin D supplementation may suffice to maintain normocalcemia. The goal is to maintain calcium in the low normal range. Recombinant PTH may be an option in cases where conventional treatment fails to normalize the calcium levels [10]. Oral calcium and levothrox was prescribed in our case. The treatment of pericardial effusion after pericardiocentesis was based on aspirine and colchicine for four weeks according to the management guidelines of the European Society of Cardiology (ESC 2015) [25] with a good clinical outcome without the occurrence of residual pericarditis in a year.

Conclusion

Cardiac Tamponade is a rare manifestation of APECED syndrome and its physiological mechanism is unknown. Exhaustive etiology work-out is important before any cardiac tamponade for better management and improve patient's prognosis. APECED syndrome is an exceptional disease both in terms of its frequency and its pathophysiological mechanisms and requires a multidisciplinary approach. Patients must be monitored regularly to detect the appearance of other pathological elements of the

syndrome.

References

1. Veselin Skrabic, Ivna Skrabic, Roko Skrabic, Blanka Roje and Marko Simunovic. Clinical Characteristics in the Longitudinal Follow-Up of APECED Syndrome in Southern Croatia—Case Series. *Genes* **2022**, 13, 558
2. Capalbo, D.; De Martino, L.; Giardino, G.; Di Mase, R.; Di Donato, I.; Parenti, G.; Vajro, P.; Pignata, C.; Salerno, M. Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy: Insights into Genotype-Phenotype Correlation. *Int. J. Endocrinol.* 2012,2012, 353250
3. Carpino, A.; Buganza, R.; Matarazzo, P.; Tuli, G.; Pinon, M.; Calvo, P.L.; Montin, D.; Licciardi, F.; De Sanctis, L. Autoimmune Polyendocrinopathy–Candidiasis–Ectodermal Dystrophy in Two Siblings: Same Mutations but Very Different Phenotypes. *Genes*.**2021**, 12, 169
4. Kisand K, Peterson P. Autoimmune polyendocrinopathy candidiasisectodermal dystrophy. *J Clin Immunol.* **2015**; 35:463–78
5. Fatih Celmeli, Abdullah Kocabas, Ishak A Isik, Mesut Parlak, Kai Kisand, Serdar Ceylaner and Doga Turkkahraman. Unexplained cyanosis caused by hepatopulmonary syndrome in a girl with APECED syndrome. *J Pediatr Endocrinol Metab.* **2017**: 0276
6. Florica Sandru, Razvan-Cosmin Petca, Mihai Cristian Dumitrascu, Aida Petca, Andreea-Iuliana Ionescu and Livia-Cristiana Baicoianu-Nitescu. Cutaneous Manifestations in Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED): A Comprehensive Review. *Biomedicines.* **2024**; 12: 132.
7. Aytekin, E.S.; Serin, O.; Cagdas, D.; Tan, C.; Aksu, T.; Unsal, Y.; Yeni, S.; Orhan, D.; Ozon, Z.A.; Tezcan, I. A Patient With AIRE Mutation Who Presented With Severe Diarrhea and Lung Abscess. *Pediatr. Infect. Dis. J.* **2021**; 40: 66–69.
8. Perniola, R.; Fierabracchi, A.; Falorni, A. Autoimmune Addison's Disease as Part of the Autoimmune Polyglandular Syndrome Type 1: Historical Overview and Current Evidence. *Front. Immunol.* **2021**; 12: 606860
9. Proust-Lemoine, E.; Saugier-veber, P.; Wémeau, J.-L. Polyglandular autoimmune syndrome type I. *Presse Med.* 2012; 41: e651–e662
10. Manuel O. Bello ; Vishnu V. Garla. Syndrome polyglandulaire auto-immun de type I. <https://www.ncbi.nlm.nih.gov/books/NBK537211/>

11. Taieb Ach, Ben Yamna Hadami, Nadia Ghariani, Randa Saïd ElMabrouk, Asma Ben Abdelkrim, Maha Kacem, Mohamed Denguezliet Koussay Ach. Gastrointestinal manifestations in autoimmune polyendocrinopathy -candidiasis- ectodermal dystrophy (APECED) patient : major effects on treatment and prognosis. **Endocrinology, Diabetes and metabolism case reports: 2023**;2; 22-0352
12. G. J. Kahaly, L. Frommer. Polyglandular autoimmune syndromes. **J Endocrinol Invest 2017**; 41; 91-98
13. Hansen MP, Matheis N, Kahaly GJ Type 1 diabetes and polyglandular autoimmune syndrome: a review. *World J Diabetes*. 2015; 6:67–79.
14. Betterle C, Dal Pra C, Mantero F, Zanchetta R Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. *Endocr Rev*.2002; 23:327–364.
15. Cutolo M Autoimmune polyendocrine syndromes. **Autoimmun Rev (2014)** 13(2):85–89.
16. Anderson MS, Venanzi ES, Klein L, Chen Z, Berzins SP, Turley SJ, von Boehmer H, Bronson R, Dierich A, Benoist C, Mathis D. Projection of an immunological self shadow within the thymus by the aire protein. *Science*. 2002; 298:1395-401
17. Husebye ES, Perheentupa J, Rautemaa R, Kampe O Clinical manifestations and management of patients with autoimmune polyendocrine syndrome type I. *J Intern Med*.2009; 265:514–529
18. Rautemaa R, Hietanen J, Niissalo S, Pirinen S, Perheentupa J. Oral and oesophagealsquamous cell carcinoma--a complication or component of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED, APS-I). *Oral Oncol*. 2007; 43:607-13.
19. Fatma M, Mouna E, Raouf H, Hajer F, Hatem M, Mohammed A Autoimmune polyglandular syndrome type II: epidemiological, clinical and immunological data. **J Endocrinol Metab. 2014**; 4:101–109
20. Kisand K, Peterson P Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy. **J Clin Immunol.2015**; 35:463–478
21. Wolff AS, Sarkadi AK, Marodi L, Karner J, Orlova E, et al. Anti-cytokine autoantibodies preceding onset of autoimmune polyendocrine syndrome type I features in early childhood. *J Clin Immunol*.2013; 33:1341–8.

22. Kisand K, Bøe Wolff AS, Podkrajsek KT, Tserel L, Link M, et al. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. *J Exp Med.* 2010; 207:299–308.

23. Puel A, Döffinger R, Natividad A, Chrabieh M, Barcenas- Morales G, et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. *J Exp Med.* 2010;207:291–7.

24. Leila Rouimi, Sana Abourazzak, Sanae Chaouki Moustapha Hida. APECED SYNDROME (FAMILY OBSERVATION) *Int. J. Adv. Res.* 2023 ;11 : 693-697

Yehuda Adler, Philippe Charron, Massimo Imazio, Luigi Badano, Gonzalo Barón-Esquivias et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). *European Heart Journal.* 2015 ; 42 :2921–2964,