UNUSUAL PRESENTATION OF AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 1 (APS1)

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Autoimmune polyendocrinopathy type 1 (APECED) is an autosomal recessive disease caused by loss of function mutations of autoimmune regulatory (AIRE) gene. Early onset ectodermal dysplasia and mucocutaneus candidiasis is characteristically followed by hypoparathyroidism and primary adrenal insufficiency within the first two decades. Clinical features may be variable, it is suggested that population characteristics and the clinical course of the disease are associated. Herein a case of APECED referred with growth retardation, arthritis, diarrhea and pneumonia, followed by type 1 diabetes and adrenal insufficiency is presented.

CASE

13,5 years-old male, admitted with chronic diarrhea, severe short stature, arthritis, pneumonia

History:
- Chronic diarrea at the age of 9.
- Arthritis of the left knee at the age of 10.

Family history:
- Parents are second degree cousins.
- 16 years old healthy sister
- 15 years old healthy brother

Figure 1. Before and 1 month after HC the treatment.

Physical examination:
- Weight: 17.7 kg (-7.66 SDS), height: 117.6 cm (-5.22 SDS)
- BMI: 12.4 kg/m^2 (-5.08 SDS)
- Immature facial features and high pitched voice
- Dry skin, hyperpigmentation
- Genitourinary system: Tanner stage 1

Hb	9.7 (gr/dl)
MCV	88.7 (fl)
Leucocyte	8000 (mm^3)
Thrombocyte	348000 (mm^3)

Vitamin	(ug/L)
A	61.6 (316-820)
D	16.8 (25-80)
E	2 (6.6-14.3)

CD3	%73 (60-76)
CD4	%52 (31-47)
CD8	%26 (18-35)
CD16+56	%15 (04-17)
CD19	%10 (12-27)
NBT	%100
IgA	349 (62-390)
IgG	2.160 (842-1.943)
IgM	108 (54-392)

Sweat test, quantitative chlorine measurement: 24 mEq/L (0-40 mEq/L)

Intravenous antibiotic and intravenous immunoglobulin therapy were initiated for immune deficiency.

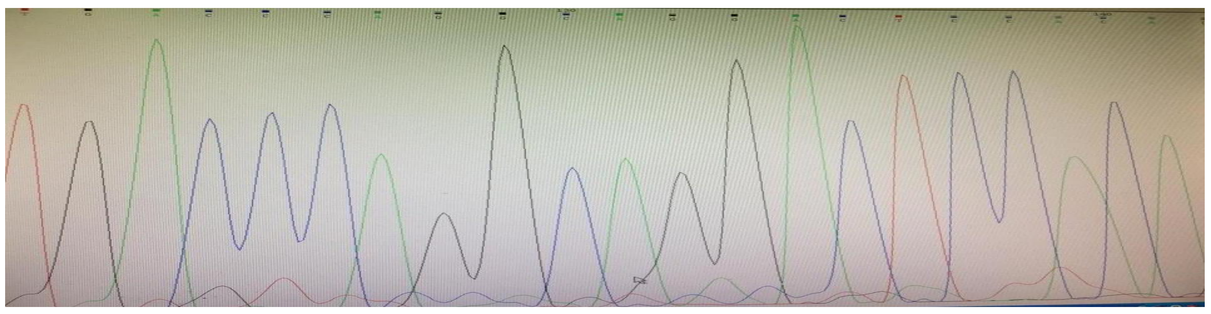
Chronic diarrhea with persistent acidosis required colonoscopy, biopsy revealed eosinophilic ileitis.

Blood analysis	**Result**	**Reference value**
Cortisol	11.21 µg/dl	
ACTH	19.5 pg/ml	0-46
IGF-1	28.28 ng/ml (-2.12 SD)	
IGFBP-3	2102,48 ng/ml (-1.9 SD)	
Anti-TG	<0.9 IU/ml	0-9
Anti-TPO	1.4 IU/ml	0-9
TSH	2.0 uIU/ml	0.38-5.33
sT4	10.1 pmol/L	7.8-13.7
FSH	0.4	
LH	0.02	
Testosteron	<12.98	
Blood glucose	400 mg/dl	
Insulin	3.46 µIU/ml	
C-peptide	1.01 ng/ml	
HbA1c	10%	
Anti GAD	72.37 U/L	<1
Anti-islet	0.03 U/L	<0.02
Standard dose ACTH test, peak cortisol: 14.94 µg/dl		
Urinary analysis		
β-2 microglobulin	10374 mg/g	0-300
Na	176.8 mEq/L	25-301
Tubular P reabsorption	81.78 %	
FeNa	2.0 %	

Chronic diarrrea, type 1 diabetes, primary adrenal insufficiency, tubulopathy was detected. Hypoparathyroidism was exluded.

IPEX syndrome?
FOXP3 gene mutation was not detected.

Next generation sequencing revealed
frameshift mutation in the *AIRE* (*autoimmune regulator*) gene
(c.208_209insCAGG-p.Asp70fs)



Azathioprine as well as supportive therapy were initiated.

CONCLUSION

AIRE gene mutation causes central T cell regulation disorder (thymic tolerance) that has a slower disease course than peripheral T cell disorders. This case is important as it emphasizes the phenotypic variability of APECED. The molecular alteration caused by frameshift mutation may explain the early onset and severity of the phenotypical features of the patient that would be expected in peripheral T cell regulatory disorders.

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