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RESEARCH ARTICLE

AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 1 WITH END STAGE RENAL DISEASE; RARE PRESENTATION WITH NOVEL ALLELIC VARIANT: A CASE REPORT

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ABSTRACT

Autoimmune polyendocrinopathy syndrome type 1 is a rare disease caused by mutations in the autoimmune regulator gene (AIRE) leading to immune injury of multiple organs (mainly endocrine). We describe a case with autoimmune polyendocrinopathy syndrome type 1 presented with features of chronic mucocutaneous candidiasis and hypoparathyroidism. End stage renal disease was found and the renal biopsy confirmed tubulo-interstitial nephritis which is very rarely encountered in these patients. Molecular genetic analysis of AIRE gene showed homozygous variant c.274C>T p.(Arg92Trp) which is classified as pathogenic.

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INTRODUCTION

Autoimmune polyendocrine syndrome type 1 (APS-1), also named autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) is a rare disease with autosomal recessive pattern of inheritance (Eystein , 2018). Mutations in the autoimmune regulator gene (AIRE) lead to this disease. AIRE clearly plays a crucial role in preventing organ-specific autoimmunity. It regulates the expression of ectopic proteins expressed by medullary thymic epithelial cells which contribute significantly to central tolerance; thus preventing autoimmunity and production of autoantibodies (Notarangelo, 2004; Peterson, 2004). Autoimmune polyendocrine syndrome type 1 is characterized by the development of at least two of three cardinal components during childhood; chronic mucocutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency (Addison's disease) (Husebye, 2009).

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Other classic components are less frequent but may include bilateral keratitis, often accompanied by severe photophobia, and periodic fever with rash, as well as autoimmune-induction of hepatitis, pneumonitis, nephritis, exocrine pancreatitis, and functional asplenia (Ahonen, 1990; Bruserud, 2016). Some cases with APS1 develop tubulointerstitial nephritis (TIN) and progress to end-stage renal failure (ESRD) and may recur in the transplanted kidney (Ulinski , 2006; Gwertzman, 2006).

Case Description

A13 years old Saudi child presented to ER with sever carpopedal spasm, discoloration of lips and mucocutaneous candidiasis of oral cavity, fingers and toes. Serum calcium was found to be very low 0.8 mmol/L (2.2 to 2.7 mmol/L) and the patient was euglycemic. Serum parathormone was 0.12pmol/L (1.28 -7.35 pmol/L) and adreno-cortico-trophic hormone (ACTH) was 203.5 pg/ml (4.7-48.8 pg/ml). Serum creatinine was highly elevated at 596.9 umol/L (27-88 umol/L) and blood urea Nitrogen (BUN) 35.5 mmol/L (2.5-7.85 mmol/L). The patient was anemic (hemoglobin 8.7, MCV 96, leukocytic count 6.4 and platelets 367). Vitamin B12 was found to be low at 118 pg/ml (201-1046 pg/ml).

Revision of the recommended autoantibodies revealed parietal cells antibodies titer >1:10(positive), tissue transglutaminase antibodies IgA 307 U/ml (normal < 7), Islet cell antibodies 1:160 (highly positive+++/ normal < 10), Glutamic acid decarboxylase (GAD65) antibodies>2000IU/ml (normal < 10), 21-hydroxylase antibodies 12.9 (normal < 10.0), Thyroid peroxidase (TPO) antibodies 33.24 IU/ml (normal < 5.6). Serum TSH, T3, T4, liver functions testsand hemoglobin A1C were found to be normal. For complete assessment of the kidneys; a renal biopsy through a True-cut left kidney was taken and showed moderate interstitial fibrosis and tubular atrophy. There was tubulo-interstitial nephritis (TIN) of 130 glomeruli (Figure 1).

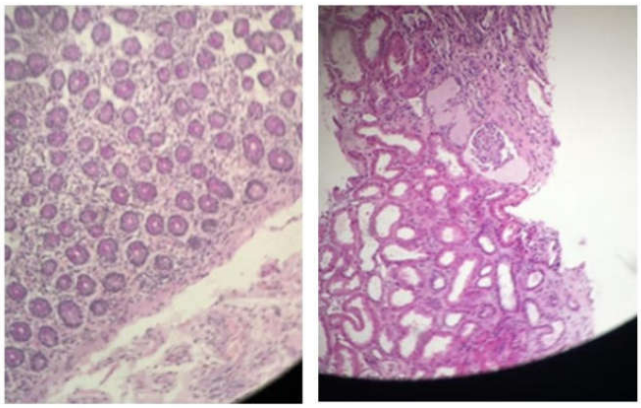

Figure 1. Moderate interstitial fibrosis, tubular atrophy and tubulo-interstitial nephritis (TIN).

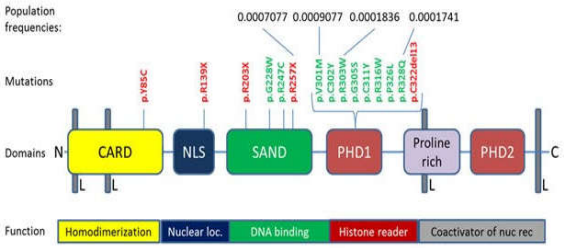

Figure 2. Schematic Structure of the Autoimmune Regulator Gene with Indications of Major Mutations and Functional Domains (1). Founder mutations (red): R257X, Finland; Y85C, Persian Jews; R139X, Sardinia R203X, Sicily. The common 13bp mutation, p.C332del13 (black). Dominant negative mutations (green): p.G228W, p.R247C, p.E298K, p.V301M, p.C302Y, p.R303W, p.G305S, p.C311Y, p.R316W, p.P326L, p.R328Q. Frequencies of mutations in the general population (gray) based on data from the Exome Aggregation Consortium

Molecular genetic analysis of AIRE gene (the coding exons of the AIRE gene were enriched using Roch/NimbleGen sequence capture technology and sequenced on an illumina system (next-generation sequencing, NGS)) which showed homozygous variant c.274C>T p.(Arg92Trp) in the AIRE. The variant has already been described in the literature in a family with APS 1. Allele frequency of this variant in general population has not been documented (gnomAD) and this is the first time we detect it in the database. Considering the available information, the variant is classified as pathogenic.
Patient was treated with elemental calcium and alfacalcidol. At the follow up; eucalcemia was achieved. Dermatology team was involved and the patient is under regular follow up for any complications that may develop any time. Patient was started on haemo-dialysis, and listed for renal transplant.

DISCUSSION

Autoimmune regulator gene (AIRE) mutations are cause of a rare autoimmune disease named autoimmune polyglandularsyndrome type 1. The patients usually present with classic diagnostic dyad/triad of mucocutaneous candidiasis, hypoparathyroidism, and adrenocortical failure (Eystein , 2018). Besides the classical triad, a dozen autoimmune endocrine and other components may be encountered. Other features may include keratoconjunctivitis, hepatitis, chronic diarrhea, periodic rash with fever. Prevalence of most components increases with age, hypothyroidism, diabetes mellitus and testicular failure frequency is higher toward middle age (Perheentupa , 2006). Our case is a Saudi child that presented with clinical features of hypoparathyroidism with hypocalcemia causing carpopedalspasm and mucocutaneous candidiasis. The triad was competed with the elevated serum ACTH level denoting presence of Addison's disease. Some other autoimmune features were discovered as pernicious anemia, thyroid autoantibodies and pancreatic autoantibodies.

Renal functions assessment of our patient revealed features of ESRD. Renal biopsy revealed interstitial fibrosis, tubular atrophy and tubulo-interstitial nephritis TIN. To the best of our knowledge, this is the first report of a Saudi Muslim APS-1 child with TIN leading to ESRD. In the Finnish series of patients, which is the largest internationally; TIN occurred in 8 patients (Perheentupa , 2006). Ulinski et al. (2006) were the first to report an APECED patient with chronic intestinal nephritis leading to ESRD. They found that clinical and biological improvement was observed under post-transplant immunosuppression drugs; tacrolimus and mycophenolate mofetil. Two patients with APS 1 and TIN were described by Gwertzman et al. (9).

TIN was clinically silent in both cases and the diagnosis was confirmed by renal biopsy. In one patient, renal function remained stable with immunosuppressive therapy. A second patient, despite treatment, progressed to ESRD and received a deceased donor allograft. Surprisingly; TIN recurred in the transplanted kidney but was reversed successfully with rituximab. Molecular genetic analysis of AIRE gene in our patient revealed homozygous variant c.274C>T p. (Arg92Trp). Many different mutations have been reported (Figure 2). The most common is the so-called Finnish major mutation, p.R257X located in the SAND-domain (named after a range of proteins in the protein family: Sp100, AIRE-1, NucP41/75, DEAF-1). The Finnish major mutation is especially prevalent in people in Finland, Russia, and Eastern Europe (Bruserud, 2016; Orlova , 2017).

Conclusion

In this patient with this new allele variant with TIN presentation is an important complication of APS 1 that may result in ESRD. It is recommended to keep in mind that TIN may recur in the transplanted kidney based on few past reports. The presentation of TIN may be unapparent clinically with normal urinalysis, so, it is advised to well investigate for its presence.

Statement of Ethics

There are no ethical conflicts to declare. There is no identifying patient information in the manuscript. An informed written consent was taken from the father of the patient. It has been approved by the local ethics committee.

Conflict of Interest Statement: The authors have nothing to disclose.

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