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# Clinical, histological and genetic findings in a donor with a clinical history of type 1 Autoimmune Polyendocrinopathy Syndrome

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ABSTRACT

*Purpose:* Autoimmune Polyendocrinopathy Syndrome (APS) is a rare condition caused by an autoimmune failure of two or more endocrine glands. In this case, we report the ocular findings and correlated histopathology from a human eye donor with a prior clinical history of Type 1 APS.

*Observations:* The 23 year-old patient originally presented with blurred vision at the 20/125 level caused by papilledema of the right eye. Bilateral pigmentary changes in the peripheral retinal were also noted. The patient passed away due to electrolyte abnormalities related to autoimmune illness. Histopathology of the posterior segments documents that these pigmentary changes were caused by pigment deposition around inner retinal vessels with corresponding outer retina atrophy. Postmortem genetic sequence analyses revealed a homozygous R257X (C to T substitution) mutation within exon 6 of the *AIRE* gene.

*Conclusions and importance:* The retinal findings in Type 1 Autoimmune Polyendocrinopathy Syndrome resemble those observed in individuals with retinitis pigmentosa, suggesting that similar pathological processes occur in both.

## 1. Introduction

Autoimmune Polyendocrinopathy Syndrome (APS) is the autoimmune-driven failure of two or more endocrine glands. It is a rare condition that is categorized into two major groups. Type 1 APS, also known as Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal dystrophy (APECED), is an autosomal recessive syndrome caused by mutations in the *AIRE* gene on chromosome 21. This gene encodes for the AIRE protein, a transcription factor involved in the negative selection of autoreactive thymocytes. Loss or absence of functional AIRE protein leads to survival of autoreactive thymocytes that can drive autoimmune disease. Type 1 APS is characterized by hypoparathyroidism, mucocutaneous candidiasis, and/or autoimmune adrenal failure (Addison's disease). The onset of symptoms usually occurs in childhood, and the prevalence is 1:100,000 in the United States.[1,2] The most common ocular manifestations of Type 1 APS are chronic keratitis and dry eye.[3] Other ocular complications include cataract, optic atrophy, hypotrichosis, retinal degeneration, and retinal detachment.[1,4] Type 2 APS is a more heterogeneous group of APS characterized by Type 1 diabetes, Addison's Disease, and/or autoimmune thyroid disease as the main autoimmune diseases present with an age of onset typically between the ages of 40 and 60 years old. Its prevalence in the U.S. is 1:20,000, about five times higher than Type 1. The etiology is believed to be multifactorial.[2] The ocular manifestations in Type 2 APS are related to the specific autoimmune disease present: retinopathy in Type 1 Diabetes, band keratopathy and other ocular calcification in hyperparathyroidism, bilateral cataracts in hypoparathyroidism, and ptosis, ocular surface inflammation, corneal ulcers, cataracts, and papilledema in Addison's Disease.[4]

## 2. Case report

A 23 year-old female with APS (Addison's Disease and hypoparathyroidism) presented with complaints of blurred vision for several

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years. She was diagnosed with APS at age 11 and was on the medications fludrocortisone, calcitriol, sevelamer, and rotation of prednisone, dexamethasone, and hydrocortisone for its treatment. She had decreased vision of 20/125 in her right eye and 20/50 in her left eye and a superonasal visual field defect in her right eye (no prior vision or ocular examinations were available). Slit light examination showed bilateral corneal epithelial erosions and cortical cataracts consistent with patient's reported history of dry eye and cataracts. Fundus examination showed two-plus optic disc edema in the right eye and bilateral peripheral pigment changes.

At initial presentation, the patient was referred to neuro-ophthalmology for the right optic disc edema. She was seen by neuro-ophthalmology two months later, and her right visual field showed partial superior and inferonasal defects consistent with the edema and obscuration of the superior, inferior, and nasal borders of the right optic disc seen on fundus examination. Fundus photographs taken at this appointment show blurring of the right optic disc and some of the peripheral pigment changes (Fig. 1). A brain MRI was also performed at this time to rule out involvement of an intracranial process. It showed optic nerve sheath dilation and mild scleral flattening of the posterior globes consistent with increased intracranial pressure and papilledema, but there were no signs of any masses, hydrocephalus, retinal detachment, or thrombosis.

At her neuro-ophthalmology follow-up four months after her initial presentation, she was started on acetazolamide as the optic disc edema was unchanged and the patient complained of worsening vision and increasing headaches. After two months of acetazolamide treatment, she returned to the neuro-ophthalmology clinic and reported improved vision in both eyes. Of note, one month prior, she had also undergone cataract surgery on her right eye with placement of a hinge-type silicone accommodating posterior chamber intraocular lens (Crystalens AO). There was improvement in the right optic disc edema with only mild inferior edema present on fundus examination.

The patient was lost to follow-up and died 18 months later at age 25 from cardiac arrest due to electrolyte abnormalities. Her globes were donated to the John A. Moran Eye Center Steele Center for Translational Medicine and processed within 4 h of death. Post-mortem photographs of the posterior segments are depicted in Fig. 2. The posterior segment (anterior segment removed) of the left globe was immersion fixed in 4% paraformaldehyde before processing and embedding in paraffin. 5μm thick sections were cut and stained with hematoxylin and eosin. The posterior segment of the right globe was immersion-fixed in one-half strength Karnovsky fixative for 24 hours, washed in 100mM sodium cacodylate buffer, post-fixed in 2% osmiun-tetroxide for 2 h, washed in $DDH_20$, then dehydrated, and embedded in epoxy resin. 1μm sections were cut and stained with Richardson's Stain, 1.0% methylene blue in 1% borax and 1.0% Azure II in water.

As depicted in Fig. 2, the hyperpigmentation that was observed clinically upon funduscopic exam and photography was evident post-mortem. In the right fundus, bone spicule hyperpigmentation was present along a superonasal vessel that corresponds to that observed in the fundus photograph in Fig. 1A. There was also hyperpigmentation along the inferior arcade and in the far periphery of the fundus. Similar bone spicule hyperpigmentation was seen in the left fundus inferotemporal to the macula and in the far periphery nasally.

Histopathology showed focal areas of pigmentation of the inner retina along the vessels (Fig. 3A–D). In addition to the pigment, there is an accumulation of extracellular material inside of the layer of pigment around two vessels of the inner plexiform layer in Fig. 3F. Fig. 3A shows atrophy of the outer retina in the area surrounding the pigment deposition as indicated by the blue arrows. The photoreceptor layer is especially atrophic, as seen in Fig. 3B, and there is also attenuation of the inner nuclear, outer plexiform, and outer nuclear layers. There is loss of pigment and atrophy in the retinal pigmented epithelium (RPE) underlying these areas of pigment deposition (Fig. 3C and F).

DNA sequencing was performed to determine whether the patient had a mutation in the *AIRE* gene, as Type 1 APS was a suspected diagnosis given the onset of disease at age 11. Total genomic DNA was extracted from whole blood received at the time of donation, using a QIAamp DNA Blood Maxi Kit (Qiagen, Valencia, CA, USA). Primers were designed for all 14 *AIRE* (ENST00000291582.6) exons using Primer3 (v.0.4.0). Primer sequences are shown in Table 1. All exons were amplified individually using the Qiagen Multiplex PCR Kit under the manufacturer's recommended conditions. Reaction conditions consisted of an initial denaturation for 15 min at 95° followed by 30 cycles of 94° for 30s, 63° for 30s, 72°for 30s. PCR reactions were run on a 1% agarose gel and gel extracted using the QIAquick Gel Extraction Kit (Qiagen). Samples were sent to the University of Utah DNA Sequencing Core facility for Sanger sequencing. Resulting sequences were analyzed using Sequencher software (Gene Codes Corporation, Ann Arbor, MI, USA). Sequence analyses revealed a homozygous C to T substitution (R257X) in exon 6 of the *AIRE* gene (Fig. 4). This nonsense mutation has been shown previously to be associated with Autoimmune Polyendocrinopathy Syndrome 1 in both heterozygous and homozygous situations and was thus determined to be the causal variant in this individual.[1–3,5,6]

## 3. Discussion

Descriptions of retinal hyperpigmentation in patients with either APS or Addison's Disease have been reported, but this case connects the clinical examination findings with retinal histopathology. Brown (1926) described bilateral dark grey pigmentation around the macula in a patient who presented in adrenal crisis and was diagnosed with Addison's Disease.[7] Wood et al. described retinal bone spicule pigmentation as well as optic nerve pallor and attenuated arterioles in a patient with Type 1 APS who presented for progressive vision loss.[8] Bourgault and co-authors reported fives cases of retinal pigmentary changes in patients

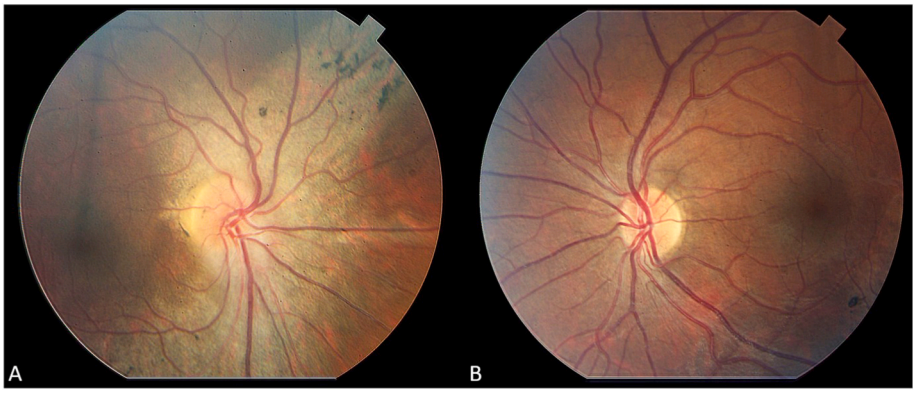


**Fig. 1.** Fundus photographs taken at age 23 during the initial neuro-ophthalmology visit. A: Photograph of right optic nerve and central retina. There is blurring of the superior, inferior, and nasal borders of the optic disc consistent with optic edema. In the superonasal segment, irregularly-shaped areas of hyperpigmentation are observed from one to two o'clock. In addition, there are atrophic pigmentary changes surrounding the superonasal, supertemporal, and inferotemporal vessels of the optic nerve head. B: Photograph of left optic nerve and central retina. There is one circular area of hyperpigmentation inferior to the macula at approximately four o'clock.

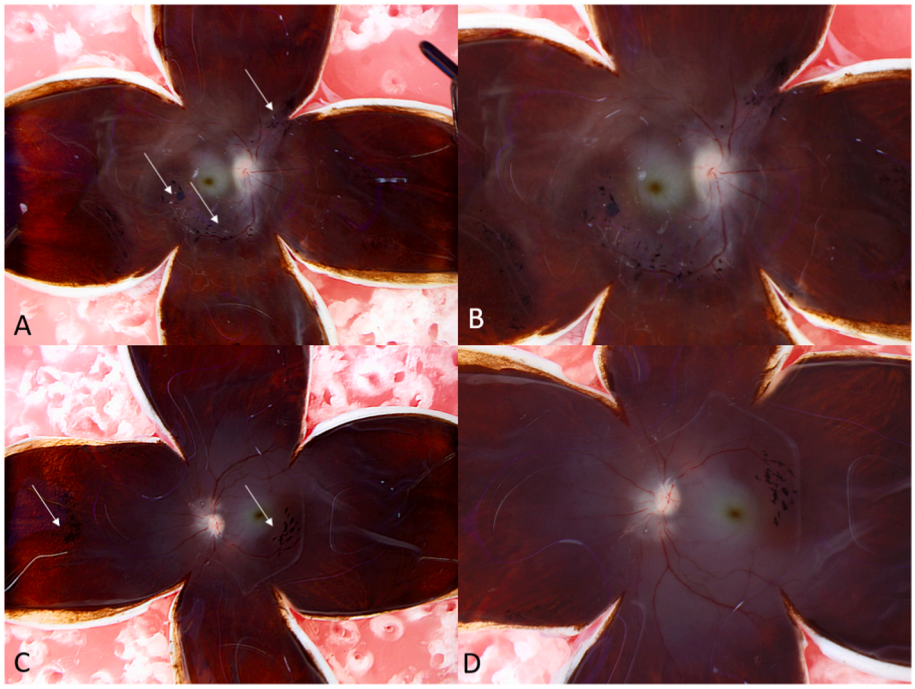


**Fig. 2.** Post-mortem globe photographs at approximately 4 h. A. Right globe with bone spicule hyperpigmentation (white arrows). The hyperpigmentation is present along a vessel at one to two o'clock corresponding to that seen in the fundus photograph in Fig. 1A. There are also bone spicules along the inferior arcade and in the far periphery at seven to eight o'clock. B. Higher magnification photograph of right globe showing the nerve head. C. Left globe with bone spicule hyperpigmentation near the macula at three to four o'clock and in the far periphery from eight to ten o'clock (white arrows). D. Higher magnification photograph of right globe showing the nerve head.

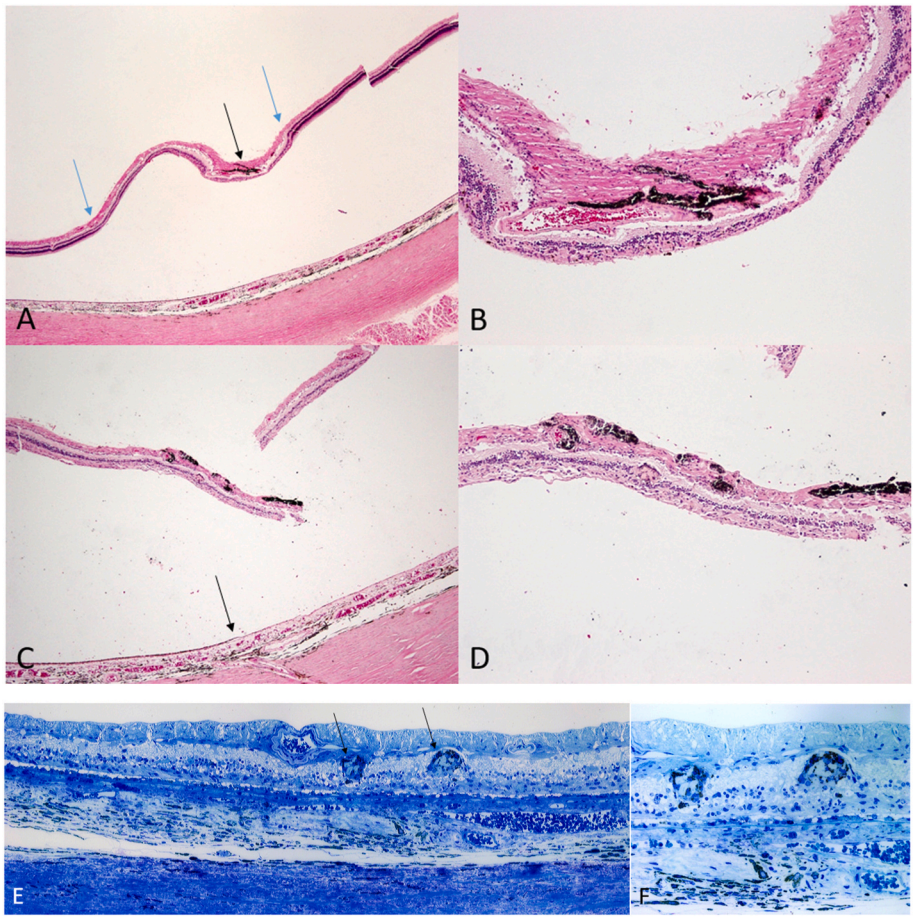


**Fig. 3.** Histopathology Photomicrographs. A. Photomicrograph of the hematoxylin and eosin stained posterior segment of left globe showing atrophy of the outer retina between the blue arrows and deposition of pigment in inner retina at the black arrow. The retinal detachment is an artifact from tissue processing (original magnification x20). B. Higher magnification view of area of pigmentation in the inner retina around a vessel. There is also profound atrophy of the outer retina (original magnification x100). C. Photomicrograph of the hematoxylin and eosin stained posterior segment showing multiple areas of pigment in the inner retina and loss of the pigment in the underlying RPE (black arrow showing transition from pigmented to non-pigmented RPE) (original magnification x40). The retinal detachment is a processing artifact (original magnification x100). D. Higher magnification view of areas of pigmentation in the inner retina. E. Photomicrograph from the Richardson's stained posterior segment of right globe showing pigment deposition in the inner retina (black arrows) (original magnification x200). F. Higher magnification view of areas of pigment deposition. There is also atrophy and depigmentation of the RPE (original magnification x400). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

with Type 1 APS. Some of the patients were also noted to have macular atrophy and attenuated vessels, and four of the patients were found to have anti-retinal antibodies.[9]

The ocular histopathology from the individual with Autoimmune Polyendocrinopathy Syndrome reported here is remarkably similar to the histopathology observed in retinitis pigmentosa. Both show

**Table 1**
Primer sequences employed for screening the 12 AIRE exons.

| | |
|---|---|
| AIRE-1a | CCTCCATCACAGGGAAGTGT |
| AIRE-1b | TCCTCCTGGAACTTCCCC |
| AIRE-2a | CTACACCACCACCTGACTCC |
| AIRE-3b | CTGGTCCAGTGTGTGGGTC |
| AIRE-4a | GGGACTACCCAGCACTGGAC |
| AIRE-4b | ACAGGGTCTCAGAGGGCAG |
| AIRE-5a | GGCATAGAGTATGTGCTTGGG |
| AIRE-5b | GTGGTCCTCCTTCCATCTTG |
| AIRE-6a | ACTGCCAAGGCAGGTCC |
| AIRE-7b | AGGTAAAGGCAGAGGCAGC |
| AIRE-8a | GGAAGGAGGTGGCTCTCAG |
| AIRE-8b | CAGGGTCAGTGGGTGGAG |
| AIRE-9a | GTTTGGGGATCTGTCACCC |
| AIRE-9b | GTGGCCCAGCCTAGGAG |
| AIRE-10a | CACTGACTCCTGGGTGGTG |
| AIRE-10b | CCGTAGGTCCTGGGCTC |

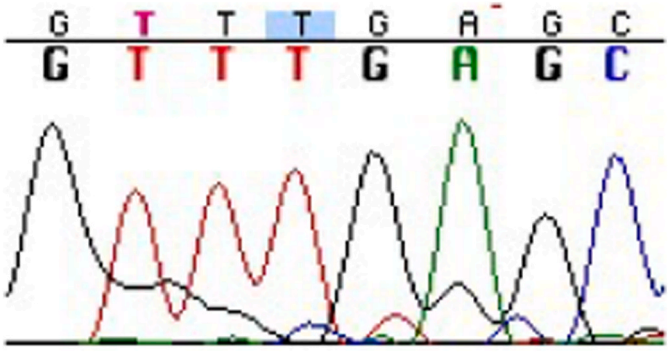


**Fig. 4.** Homozygous C to T substitution (R257X) in exon 6 of the *AIRE* gene confirming a diagnosis of Type 1 APS.

pigmentation and extracellular material around retinal blood vessels, atrophy of the outer retina, and loss of the pigmentation of the RPE. Thus, it is probable that RPE cells migrated to the inner retinal vessels following photoreceptor cell death in this patient, as occurs in retinitis pigmentosa.[10] Clinically, the patient did not report classic symptoms of retinitis pigmentosa, such as night blindness and bilateral peripheral vision loss. Additionally, there is no known family history of retinitis pigmentosa or retinal disease. The mechanism of the photoreceptor cell death is unknown but most likely involves the development of autoantibodies to retinal antigens and failure of thymic negative selection given the function of the AIRE gene that is mutated in APS. The possibility that the retinal findings could be secondary to either hypoparathyroidism or Addison's disease cannot be excluded since the patient had both hypoparathyroidism and Addison's disease. It is noted that all of the patients reported by Bourgault had hypoparathyroidism with 2 of the 5 patients also diagnosed with Addison's Disease.[9]

Finally, the patient's papilledema is consistent with previous cases of papilledema in patients with Addison's disease.[11] She exhibited signs of increased intracranial pressure such as headaches that improved with treatment, but no signs of an intracranial mass or thrombosis. It is uncertain how much the acetazolamide treatment contributed to her improvement in vision since she also underwent cataract surgery on her right eye during the treatment course. The mechanism causing increased intracranial pressure and papilledema in patients with Addison's Disease remains unknown.[11]

## 4. Conclusion

This case report correlates retinal pigmentary changes observed on clinical examination with the histological changes in a patient with Autoimmune Polyendocrinopathy Syndrome 1. The individual's fundus examinations showed bone spicule pigmentation, and light microscopy revealed that the pigmentary changes and outer retinal atrophy in APS is pathologically similar to that seen in retinitis pigmentosa.

## Patient consent

Consent for use in research was obtained as part of the John A. Moran Eye Center Steele Center for Translational Medicine eye donation process.

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## Commercial relationships

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## Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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