

Hydroxychloroquine Reverses Alopecia in Autoimmune Polyendocrinopathy- Candidiasis-Éctodermal Dystrophy (APECED): A Case Report

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Abstract

Background: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare, autosomal recessive disease characterized by the onset of mucocutaneous candidiasis in childhood, followed by hypoparathyroidism, and in a subset of patients, alopecia and other endocrinopathies and autoimmune diseases. There is no known treatment to mitigate the course of the disease.

Goal: To describe the outcomes in a woman with APECED who presented later in her life with Sjogren's disease and alopecia totalis, and was treated with hydroxychloroquine (HCQ). HCQ was in addition to treatment regimens for mucocutaneous candidiasis with esophageal stricture, hypoparathyroidism, insulin-dependent diabetes, hypothyroidism, B12 deficiency, and autoimmune hepatitis.

Methods: Office visits, laboratory studies, including genetic characterization of her disease; and review of available medical records.

Findings: HCQ gradually reversed her hair loss, eased her oral sicca symptoms, and ameliorated other manifestations of this disease.

Conclusion: HCQ may prove effective in patients with APECED in easing the burden of their disease, and improving quality of life.

Keywords: Autoimmune polyglandular syndrome type I; Hydroxychloroquine; Alopecia

Manuscript

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare, autosomal recessive disease classically characterized by the onset of mucocutaneous candidiasis in childhood, followed by hypoparathyroidism, and in a subset of patients, adrenal insufficiency. Dental complications such as enamel hypoplasia are well recognized, and other autoimmune diseases frequently mark the lives of these patients including alopecia, pernicious anemia, malabsorption syndromes, autoimmune hepatitis and keratoconjunctivitis. What is striking about the autoimmunity in APECED is its predilection to cause sequential dysfunction of endocrine glands, such that an individual may suffer from insulin-dependent diabetes, hypothyroidism and hypogonadism in addition to the hypoparathyroidism and adrenal insufficiency that herald this disorder. What is also striking is the relentless progression of disease that may burden an individual life [1,2]. Particularly disheartening in this illness may be the occurrence of alopecia.

This case study reports the reversal of alopecia in a woman with APECED using hydroxychloroquine (HCQ), and describes the impact HCQ has in diminishing some other features of this disease. Started on HCQ in late 2007, she had gradual re-growth of her hair, easing of the sicca symptoms in her mouth, and improvement in other parameters of APECED. This is the first report of HCQ being used in this disorder, and of its efficacy.

Case Report

E.L. is a 58-year-old white female, born in Boston in 1955 to parents with no evidence of consanguinity, or clear Finnish or European ancestry. One of 5 children, E.L. shares this genetic imprint with two other siblings, although their manifestations are remarkably

different and neither sibling has alopecia. E.L. remembers the onset of oral candidiasis in primary or middle school. Dental abnormalities (presumed incongruities in the enamel) are mentioned later in her records, when it is reported that she presented with tetany age 14 years (1970), and was diagnosed with hypoparathyroidism at that time. Her older brother had been identified with hypocalcemia (calcium 5.2 mg/dL) when he was 8 years old; his presentation was with seizures. E.L. was treated with calcium supplements and Vitamin D 50,000 IU, but the exact details of her treatment regimen as an adolescent are unclear. She remembers taking the calcium supplements 4x a day. She grew to normal height and weight, maintaining a low to low-normal serum calcium level by her report. Gravida 3, para 2 with one miscarriage, she delivered her children by caesarian section. She remembers no complications of these deliveries. E.L. had the onset of menarche age 15, and menopause age 42. The course of her disease is outlined in Table 1.

She was referred to me in 2007, entering the office with a baseball cap covering her head. Afebrile, her vital signs were as follows: BP 122/76, P 92, RR 17. She reported no pain. Her oxygen saturation was 100% on room air. She was an abrupt woman, difficult to engage and depressed by affect. She had complete baldness. There was a rash

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Year	Disease	Findings	Rx (current)
Childhood	Mucocutaneous candidiasis		
1970	Dental abnormalities	Unknown	
1970	Hypoparathyroidism	Tetany Currently serum calcium ranges 6.5 – 8.2 mg/dl (NI 8.5 – 10.5 mg/dl)	Calcitriol 0.5 mcg (9x a week). Calcium carbonate 500 mg QID with meals
1984	Keratoconjunctivitis	Anti-nuclear antibody (ANA) +	Non-prescription eye drops
1992	Dysphagia	Esophageal stricture Candidiasis Barium swallow demonstrated “Esophageal contour abnormality at the level of the thoracic inlet which is stable in appearance since 1992.”	Dilatation Nystatin
1994	Hypothyroidism	Thyroid peroxidase (TPO) + TPO 212.7 IU/L/ml in 2005 (Positive >2.0 IU/L/ml)	Levothyroxine
1997	Menopause	Age 42	
1998	Pernicious anemia	B12 deficiency B12 <100 pcg/ml (NI >250 pcg/ml)	Cyanocobalamin 1000 pcg by injection every 2 weeks
2000	Type I diabetes	Glucose 518 (NI 70-110 mg/dl)	Insulin
2002	Sicca symptoms	ANA +, Ro+, Raynaud’s	Punctual plugs
2002	Retinopathy	Not considered typical of diabetic retinopathy by ophthalmology	None
2002	Dyslipidemia	Cholesterol 275 mg/dl (NI <200)	Atorvastatin 40 mg QHS
2004	Alopecia totalis		
2005	Bone Mineral Density (BMD)	BMD Lumbar Spine: 1.28 gms/cm ² T score 2.20, Z score 2.80 BMD Femoral neck: 1.16 gms/cm ² T score 2.80, Z score 3.50	
2005	Autoimmune hepatitis	Anti-smooth muscle antibody negative, and antimitochondrial antibody negative. Biopsy: Chronic hepatitis with bridging fibrosis	Azathioprine 50 mg QD
2007	Sjogren’s	ANA 1:5120 homogenous, Ro+ and anti-mitotic spindle apparatus antibodies positive 1:5120	Hydroxychloroquine 200 mg BID
2007	Iron deficiency	Fe 18 ug/dl (NI 30-160) TIBC 438 (NI 275-425) Ferritin 5 ng/ml (NI 11-307)	Intra-muscular iron , then ferrous gluconate 325 mg TID
2007	Esophageal stricture, choking episodes	Persistent thoracic inlet level stricture and monilial esophagitis	Dilatation, omeprazole and fluconazole
2008	Perioral dermatitis	Working diagnosis rosacea	Erythromycin

Table 1: Sequence of disease manifestations.

around her nose, face and chin which was erythematous and palpable. The membranes of her mouth were dry (Figure 1).

Her dentition seemed poor with teeth soft and brown at some edges. Narrow oral aperture and narrow oropharynx were noted. There was no evident adenopathy. The heart and lung examination were unremarkable, and the total joint examination normal. There was no synovitis. There were dystrophic nail changes on her feet only. At the base of one nail in her right hand, there was a suggestion of a nailed infarct. She had very dry skin, with skin flaking off on her back and limbs. Distal pulses were intact, and there were no distal purpura, ulcers nor edema. Except to note she was de-conditioned, her neuromuscular examination was intact, and her reflexes symmetrical.

Review of the medical records was remarkable for a comment by her internist that a neurologist saw E.L. in her youth, and a weakness of the oral/buccal muscles was postulated to account for the poor oral opening. These notes are no longer available for review. There is no evidence of scleroderma now (Scl-70 antibody negative). E.L. has been left with a narrow oral aperture, and an esophageal stricture at the level of the thoracic inlet (1992); these have persisted throughout her adult life. Dilatations were not successful and the mucocutaneous candidiasis involving her mouth and esophagus could not be eradicated. She felt in this regard, nothing could be done for her.

After confirming the diagnosis of Sjogren’s, a trial of HCQ was initiated. Three months after beginning HCQ 200 mg BID (1/2008), E.L. returned in follow up. Although there was no change in her

symptoms – she still complained of dry mouth - she had more saliva/moisture visible in her mouth. Six months into treatment (4/2008), she had early hair growth visible in patches on her scalp. The perioral rash remained, but lessened in intensity. Her hair continued to grow in over the ensuing years, and topical minoxidil was added to her regimen (2009). The symptoms of dry mouth and oral candidiasis lessened. With careful oral hygiene regimens, her dentition improved (Figure 2).

Although the photographs are difficult to compare, there is a clear improvement in her facial features, and her hair has grown in.

E.L. was treated with B12 injections, and intramuscular iron when she failed to respond to oral iron supplements. Noted to have low zinc and borderline magnesium levels, trace mineral supplements were added to her diet, and creams were prescribed for her skin to enhance moisture (Amlactin 12%, CeraVe®). The flaking of her skin over her torso and limbs stopped. Her calcium remained difficult to control without QID calcium carbonate. The calcitriol was titrated to her serum calcium and to her symptoms.

A liver biopsy in 2005 was performed because of abnormal liver functions studies. This confirmed a diagnosis of autoimmune hepatitis. The pathology report is as follows: “Portal tracts show interface hepatitis with occasional plasma cells and eosinophils. Bile duct injury is noted in some portal areas. Scattered lobular activity is also seen. A trichrome stain reveals portal fibrosis with marked portal to portal bridging and some nodule formation (at least stage 4 of 6). No iron or intrahepatocytic d-PAS globules are seen. ... the findings present



Figure 1: Photograph of patient prior to treatment with hydroxychloroquine.



Figure 2: Photograph of patient after treatment with hydroxychloroquine.

in this biopsy favor autoimmune hepatitis.” She was treated with high dose prednisone initially, and azathioprine (AZA) 150 mg daily. The prednisone was tapered and discontinued in 2006, and the AZA tapered to 50 mg daily in 2007. A repeat liver biopsy later in 2007 (on AZA 50 mg and HCQ 400 mg daily) showed: “very mild chronic hepatitis with no significant activity ... histological findings represent a mild and non-specific chronic portal inflammation with no significant activity and minimal portal fibrosis.” In 6/2009, the AZA was discontinued, but then resumed after 3 months when liver function tests (LFTs) became abnormal. She remains on 50 mg AZA daily, with HCQ with normal LFTs. A colonoscopy in 2010 was normal.

In 2010 as well, a repeat barium swallow was undertaken, and this showed persistence of the focal stricture, but normal swallowing and normal motility with minimal delay in gastric emptying appreciated on follow through studies. In 2011, the pathology report from endoscopy showed normal duodenal mucosa, with no *Candida* organisms seen on routine stain. Cultures would eventually grow out *Candida*, but the mucocutaneous lesions had diminished in severity. E.L. reported transient easing in swallowing, but the presence of stricture would remain a serious clinical problem.

By 1/2009, her internist reported that E.L.’s diabetes seemed easier to manage, and the Hemoglobin A1c levels improved. She remained on an insulin pump. Outside labs confirmed a HgbA1c level in the range of 6.5.

DATE	11/2005	6/2007	8/2008	8/2009	8/2010	8/2011
HgbA1cNormal: 3.80-6.40	8.70	7.10	7.20	6.70	6.7	6.10

HCQ seemed to work well in combination with other directed therapies; however, break-through in glucose control continued (hypoglycemia).

E.L. still struggles with dry eyes, but her ophthalmological examination at the Massachusetts Eye & Ear Infirmary (2010) showed no evidence of the retinal lesion that was reported in 2002. Early cataracts were noted. Warm packs to her eyes and moisturizing eye drops were recommended. She recently required two more dilatations for choking in 4/2013, and 6/2013; the stricture neither improved nor worsened with easing of the candidiasis. HCQ in combination with other therapy resulted in significant improvements in her health, although the medical response remains partial except in terms of hair growth. For the first time since I met E.L. in 2007, she is coming into the office without a baseball cap covering her head. Her spirits have improved, and her humor and moments of eye contact are more present.

Discussion

Autoimmune polyendocrinopathy with mucocutaneous candidiasis and ectodermal dystrophy is a rare disorder of immune dysregulation, in which genetic mutations in *AIRE* affect the autoimmune response of T cells leaving the thymus and, secondarily, the peripheral lymph nodes. The spectrum of autoimmunity varies in the individual, but classically the disorder is heralded by mucocutaneous candidiasis in early childhood, followed by hypoparathyroidism in the later years of childhood, and often Addison’s disease thereafter [3]. In the initial case series published in the *NEJM* in 1990, Ahonen and colleagues captured a Finnish cohort of patients who were diagnosed with APECED between 1910-1988, and followed for up to 31 years [1]. These investigators emphasized the clinical variation in this disease, and described the only cited case of esophageal stricture prior to E.L.

In 1997, the gene responsible for APECED (or autoimmune polyendocrinopathy syndrome type I) was defined by positional cloning [4,5] and identified as *AIRE*, an autoimmune regulator gene on chromosome 21q22.3 (OMIM 240300). Over 60 mutations have been localized to *AIRE*, [6] the R257X mutation accounting for 83% of alleles in the Finnish population affected by APECED and in other pockets of APECED identified in Europe. The 967-979del13 mutation is more prevalent in North America [7]. Genetic testing in E.L. (GeneDx, Gaithersburg, MD) confirmed she was heterozygous for R257X and c.967_979del13 mutations. Dr. Mark S. Anderson’s laboratory – where she is now enrolled in a research protocol - confirmed the presence of antibodies to Type I interferon in her blood (unpublished data). Her mother age 87 carries the c.967_979del13 mutation, and her father age 88 carries the R257X mutation; both have had healthy lives. Of their five children, three are affected by APECED, one sister with mucocutaneous candidiasis (mild), hypoparathyroidism and Cushing’s disease as an adolescent; and one brother with a single dystrophic nail, hypoparathyroidism and retinopathy, with subsequent cardiac disease in his middle age. The eldest sister harbors the R257X mutation only; she was diagnosed with hyperparathyroidism as a young woman. One brother died of unrelated causes.

The deficiency or impairment in the *AIRE* protein expression in the thymus and to some extent in peripheral lymphoid tissue seems to result in profound autoimmunity over time. Whereas medullary epithelial cells in the thymus anticipate auto-reactive T cells, and have devised mechanisms using this autoimmune regulator gene to express tissue-specific antigens to eliminate these, the mutations in *AIRE* impair this process [8]. Since the initial identification of the *AIRE* mutations as fundamental to the pathogenesis of APECED, 3 different mouse models

have been developed [7], and advances have been made in understanding the correlates of the genetic mutations with the subcellular localization of the aberrant protein produced. While phenotype:genotype correlations remain imperfect, and the role of T cells and peripheral lymphoid tissue are still being defined, it is clear that the impairment in centrally-mediated immunity in the thymus results in sequential injury to tissue, caused often by autoantibodies. The hallmark of this disease is antibody to Type I interferons, but many autoantibodies are generated over the course of a life-time – including those to cytokines IL-17 and IL 22 [9]. Many of these autoantibodies target endocrine glands, and many play a role in mediating subsequent organ dysfunction and/or failure. Examples of this are autoantibodies that target cellular antigens in specific tissues, such as steroid 21-hydroxylase antibodies in patients who will eventually express adrenal insufficiency (66%); and glutamic acid decarboxylase antibodies in those who will develop diabetes (37%) [10]. Acquired defects in AIRE protein expression in thymoma [11] and lymphocytic infiltration of the salivary glands and retinas in mouse models have also been described [12].

There is no effective treatment for this disorder, and patients' lives are often marked by sequential tissue failure and disabling disease manifestations as demonstrated in this case [1]. The manifestations are variable even within families, both in terms of the target organs affected, and the temporal dispersion of disease expression. Neither E.L.'s brother nor sister has suffered from alopecia, nor from such diverse organ involvement.

Hydroxychloroquine (HCQ) is sometimes prescribed to patients with Sjogren's syndrome. The drug is reported to improve salivary gland function and oral moisture in some studies [13-15] to decrease dry eyes, [16] and to have no effect on disease manifestations in others [17]. A recent case report describes the efficacy of HCQ in two patients with alopecia totalis [18]. E.L. had a subtle response to HCQ in the first few months, with evidence of increased oral moisture. It was over the next months to years that the drug seemed to play a role in other manifestations of her disease, by reversing the alopecia, mitigating the brittle pattern of her diabetes, improving her dentition, and healing her skin. Why might this drug have contributed to improve the quality of her life?

The mechanism of action of HCQ is postulated to be impairment of the acidification of lysosomes within cells, which results in disrupted protein degradation required for both native and foreign antigen presentation by Class I and II MHC molecules. Glycosylation of proteins, their stabilization and transport may all be affected by this rise in lysosomal and/or endosomal pH [19]. In addition, HCQ has been shown to modulate the innate immune system with inhibition of TLR-9 signaling. This mechanism is important in the inflammatory pathways of systemic lupus and rheumatoid arthritis, where a decrease in inflammatory cytokines have been demonstrated in response to this drug [20]. HCQ is purported to decrease IL-17 cytokine pathways in these disorders as well [21].

A recent study describes a novel effect of HCQ on T cells; the drug inhibits autophagy, leading to pathways of enhanced apoptosis. The authors note that the inhibition is highest in CD45RO positive T cells characteristic of autoimmune diseases, and postulate that HCQ might be effective in diminishing this population of autoreactive T cells through apoptosis [22]. In discussions with my colleague Donald Bloch M.D. about the possible mechanism of action of HCQ in APECED, he noted that in his studies of a rare veno-occlusive disease, drugs like HCQ stabilized the abnormal protein permitting some functional protein to be expressed (personal discussion) [23]. While this mechanism of

action is unlikely to affect the truncated protein R257X on chromosome 21, perhaps it plays a role in stabilizing the product of the base pair deletion c.967_979del13.

Alopecia has had a profound effect on E.L.'s self-esteem and her quality of life, and the resolution of baldness with HCQ was startling and gratifying. She is presented here as a woman whose quality of life was improved by the initiation of HCQ for Sjogren's, a drug that seemed to lessen her sicca symptoms, reverse the alopecia totalis, mitigate the mucocutaneous candidiasis, and ease the course of her diabetes and autoimmune hepatitis. There are limitations in this case report in that her childhood medical history is poorly detailed in our medical records, and the management of her pregnancies unknown. Unless clinically indicated, many antibodies were not measured.

This case report was written to highlight E.L.'s remarkable response to HCQ, demonstrating re-growth of her hair and muting of the other manifestations of APECED. Perhaps others suffering from this rare disorder might benefit. A better understanding of the role of HCQ in APECED may lead to insights into normal immunity and the pathogenesis of APECED. This will be the work of investigators around the world who study autoimmunity as it touches the lives of our patients.

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