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Pili Annulati Coincident with Alopecia Areata, Autoimmune Thyroid Disease, and Primary IgA Deficiency: Case Report and Considerations on the Literature

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Key Words

Pili annulati · Alopecia areata · Molecular changes · Autoimmune disease

Abstract

Pili annulati is a rare autosomal dominant hair disorder clinically characterized by a pattern of alternating bright and dark bands of the hair, the bright bands appearing dark if observed by transmitted light. This pattern is due to the periodic occurrence of air-filled cavities along the hair cortex which scatter and reflect the light while precluding its transmission. A susceptibility region, including a possibly responsible Frizzled gene, has been mapped to the telomeric region of chromosome 12q, although a specific mutation has not been identified. The condition has sometimes been observed in concurrence with alopecia areata, and in this paper we report a case in whom the concomitant severe alopecia areata was associated with autoimmune thyroid disease and primary IgA deficiency – a quadruple complex which, to our knowledge, has never been previously described. The occurrence of multiple immune disorders in the same patient affected by pili annulati could represent a key to understanding the high prevalence of alopecia areata in this condition. Specifically, in individuals predisposed to autoimmune disease, the molecular alterations that cause the anatomical changes of pili annulati could prompt the immune response against the hair root that underlies alopecia areata.

Introduction

The designation pili annulati refers to a rare hair disorder characterized by alternating light and dark bands of the hair shafts which give them a shiny appearance. This feature is caused by the periodic occurrence of air-filled cavities along the hair

cortex, which scatter the light. The condition is transmitted with an autosomal dominant pattern whose susceptibility gene locus maps to the telomeric region of chromosome 12q. It has sometimes been observed in concurrence with alopecia areata, and in this paper we report on a case of pili annulati in a 17-year-old patient with alopecia areata, autoimmune thyroid disease and primary IgA deficiency – a complex which, to our knowledge, has never been previously described in concomitance with pili annulati. A maternal aunt of the patient was affected by banded hair as well, but she did not suffer from any immunologic disorders.

Clinical Case

A 17-year-old girl presented with a 3-month history of alopecia areata, which had not responded to topical high-potency steroid therapy. The patient was affected by documented primary selective immunoglobulin A deficiency 1 (IgA D1) with recurrent respiratory and gastrointestinal infections dating from infancy. She had had stunted growth with menarche at the age of 15 and was considerably slight, with a height of 1.41 m and a weight of 39 kg, her height and weight parameters scoring below the third percentile.

Dermatological examination revealed two large patches of hair loss at the scalp with angular contours and without signs of inflammation. The patches were localized at the vertex and the occipital region, respectively ([fig. 1](#)), the latter showing a typical pattern of ophiasis. Characteristic exclamation point hairs were present on their periphery. In addition, the patient's uninvolved hair had a spangled appearance, due to a pattern of transverse bright and dark bands regularly alternating along the shafts and resulting in a striking ringed configuration of the single hairs ([fig. 2](#)). This feature had been present since infancy, looking more or less pronounced in the course of the patient's life.

The diagnosis of alopecia areata concurrent with pili annulati was issued and the subsequent determination of serum thyroid hormones and thyrotropin showed an increase of free T₃, thyroglobulin and thyroid peroxidase, with remarkable reduction of thyroid-stimulating hormone (TSH), associated with high-titer antibodies for TSH receptor (TSH-R), thus revealing the presence of subclinical Graves' disease.

A banded pattern identical to the one observed in our patient was present in her 50-year-old maternal aunt's hair, who was, however, not affected by any immunological disorder and was in generally good health.

Laboratory investigation: Blood count, erythrocyte sedimentation rate and anti-streptolysin O antibody were normal. The determination of serum thyroid hormones and thyrotropin showed the following results: free T₃: 4.470 pg/ml (normal: 2.00–4.400 pg/ml), TSH: 0.043 μIU/ml (normal: 0.279–4.200 μIU/ml), anti-TSH-R antibodies: 5.0 IU/l (normal: 0.0–1.0 IU/l), anti-thyroglobulin antibodies: 800.30 IU/ml (normal: 100–115.00 IU/ml), and anti-thyroid peroxidase antibodies: 586.30 IU/ml (normal 5.00–34.00). Serum IgA and Serum IgE levels were 6.5 mg/dl and 962 IU/ml, respectively. An array GCH test on peripheral lymphocytes did not show segmental aneuploidies. HLA serological typing showed A1, A2, B51, B18 Class I and DR8, DR14, DQ5 [1], DQ4 Class II phenotypes.

Thyroid disease was treated with tiamazol in a dose of 5 mg/day. In regards to alopecia, in view of the patient's immunodeficiency, the option of administering any systemic immunosuppressive therapy, either steroids, or cyclosporine, or infliximab, was discarded. Instead, after a further ineffective attempt with local steroids, local tacrolimus was chosen. In spite of the treatment, the hair loss progressed inexorably, and in the course of few months it extended to the whole scalp ([fig. 3](#)), to which, however, it remained localized, sparing the eyelashes, brows, and axillary hair. At the present time, a year after our first observation, alopecia totalis still persists with the same aforementioned clinical features.

Discussion

Pili annulati (ringed hair) is a rare autosomal dominantly inherited abnormality of the hair, clinically characterized by a periodic pattern of light and dark bands (rings, if viewed in three-dimensional space) which impart the shafts a characteristic spangled appearance. If the hair is examined by transmitted light microscopy, the pattern is inverted and the regions seen as bright when viewed by the unaided eye or under a reflected light microscope appear dark. These biphasic bands result from the serial occurrence of clusters of air-filled cavities along the hair cortex whose uneven, keratin-lined inner surface totally scatters and reflects the light, preventing it from being transmitted [1].

According to electron microscopic studies, these cavities seem to arise in the bulb as abnormal intracellular empty areas, initially filled with fluid material, which set apart otherwise morphologically normal keratin fibrils [2]. Correspondingly, the normal immunohistochemical expression of the common known cytokeratins in the altered hair shafts suggests that the changes are not caused by a structural defect of keratins, but by failure in the assembly of these or other structural proteins, which results in an insufficient formation of macrofibrils [3]. These hypothetical disorders of protein metabolism have been functionally related to the changes observed in the distribution of free ribosomes in the hair [4]. On the other hand, pathogenically significant alterations of the basement membrane zone have been observed in the region of the root, both with electron microscopy (reduplication of the lamina densa) and with immunohistochemistry (wavy basement membrane zone) [5].

Recently, a gene locus for pili annulati has been mapped through a linkage study to chromosome 12q24.32–24.33, with a critical interval of 3.9 Mb [6]. This interval was subsequently narrowed to a 2.9-Mb region on chromosome 12q24.33-ter, and its candidate genes were sequenced. However, no mutations possibly responsible for the condition were identified, either in the coding, or in the promoter sequences analyzed, a result suggesting that other, noncoding, regulatory elements, may be implied in the pathogenesis of ringed hair [7, 8]. It is interesting that the regions sequenced included the exons, but not the introns, of Frizzled 10 gene, whose product is the transmembrane receptor for Wnt proteins, and that, in another study, pili annulati has been reported as a possible phenotypic expression of nonsense Wnt mutations. This suggests that the changes could lie either in the receptor or in its ligand because of mutations in the still unexplored noncoding regions of Frizzled gene or in a coding region of Wnt gene, respectively [8, 9].

In our case, pili annulati was concomitant with alopecia areata, autoimmune thyroid disease and primary IgA deficiency. These three conditions have been frequently observed in association to each other but, out of the three, only alopecia areata has been found in coincidence with pili annulati [10–16]. Thus, to our knowledge, the simultaneous presence of pili annulati and more than one immunological disorder in the same patient is being reported for the first time in this paper. This occurrence is worthy of attention since it could shed light on the puzzling issue of a possible relationship between ringed hair and the immunologic disorder underlying alopecia areata.

Alopecia areata has been repeatedly described in patients with pili annulati, but studies performed on extended family pedigrees indicate that the two disorders are likely to occur independently of each other and thus they should be considered as coincidental, rather than associated [17, 18]. In fact, in spite of the significantly higher prevalence of alopecia areata in individuals affected by pili annulati in comparison to the general population, in none of the studied families could the concomitance of the two conditions be detected in more than one individual [18]. In addition, none of the known susceptibility loci for pili annulati corresponds either to the candidate region for alopecia areata detected through linkage studies or to the single nucleotide polymorphism-containing regions more recently identified through a genome-wide association study in this disorder [19–21].

Our observation seems to confirm this view, since out of two family members affected by pili annulati only one, i.e., the girl studied by us, suffered from immunological disorders. Yet, it cannot be excluded that, in pili annulati, genetically inscribed molecular, and thus, antigenic alterations of the hair root would make it prone to the autoimmune response underlying alopecia areata, if predisposing mutations of the immune system are present [19–21]. Consistently, the putative locus for pili annulati contains the gene *Frizzled 10* [8], which is involved in development and organogenesis, whereas the regions significantly associated with alopecia areata contain genes controlling T cell-mediated immunity as well as genes expressed in the hair follicle [20, 21].

As far as the comorbidity alopecia areata/thyroid autoimmunity is concerned, it should be underlined that the thyroid disorder detected in our case was Graves' disease, whereas the form usually reported is Hashimoto thyroiditis [10–22], the two conditions sharing only three genetic loci out of several candidate regions identified for them [23, 24]. However, a wide-ranging comparison between our case and the literature was precluded by the lack of data about the type of thyroid involvement in most statistical studies.

Surprisingly, the patient's HLA phenotype resulting from serological typing did not show any correspondence either with the haplotypes usually associated with alopecia areata or with the ones characteristic of autoimmune thyroid disease [14, 25]. GCH microarray, performed in consideration of the patient's complex clinical situation, did not reveal any major genetic defect.

In conclusion, the simultaneous presence of pili annulati and a complex of three immune disorders in the same patient reported in the present paper suggests that a coincidental as well as synergic combination of an autoimmune trait and molecular/antigenic changes of the hair bulb, induced by distinct genes with different locations, may represent a key to understanding the frequent concomitant occurrence of pili annulati and alopecia areata in the absence of common susceptibility loci.



Fig. 1. Aphlegmatic patch of alopecia with angular contours.



Fig. 2. Hairs with a pattern of transverse bright and dark bands regularly alternating along the shafts.



Fig. 3. Hair loss on the whole scalp.

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