Novel Association of Trichothiodystrophy with Autoimmune Thyroiditis and Autoimmune Hemolytic Anemia: A Case Report

Dear Editor,

Trichothiodystrophies (TTD) are a heterogeneous group of genetic disorders characterized by abnormal synthesis of sulfur-containing keratins affecting organs of neuroectodermal origin. We report a novel association of the PIBIDS (photosensitivity, ichthyosis, brittle hair, intellectual impairment, decreased fertility, and short stature) complex with autoimmune thyroiditis and autoimmune hemolytic anemia (AIHA) in a five-year-old Indian child.

A five-year-old female child was referred by a pediatrician for evaluation of skin lesions. Mother gave a history of severe dryness of skin with pruritus gradually progressing from one year of age. The child was born out of a non-consanguineous marriage at full-term by normal delivery, had a low birth weight, and had a clinical picture of nonbullous ichthyosiform erythroderma.

On cutaneous examination, generalized ichthyosis with fine, translucent scales over the trunk and arms and thick, darker scales over the legs was seen. Well-defined erythematous hyperpigmented plaque with accentuation of scaling was present over the malar area, signifying photosensitivity [Figure 1a]. Scalp and eyebrow hair were brittle, short, and lusterless. All nails were yellowish, dystrophic, and had subungual hyperkeratosis. Single, fibrofatty remnant of an old hemangioma lesion was observed over the occipital scalp [Figures 1b and 2a-c]. Hair mount analysis revealed trichoschisis and 180° twists of the hair shaft as seen in pili torti [Figure 3a].

On examination under polarizing light microscopy, alternating light and dark bands, the eponymous "tiger tail" or "zigzag" pattern, were evident [Figure 3b]. Based on the above findings, a clinical diagnosis of TTD, subtype PIBIDS syndrome, was made. At presentation, hemoglobin level was 3 g/dL, which along with grade 4 positivity of direct and indirect Coombs test, positive anti-nuclear antibodies, elevated reticulocyte count, and direct and indirect bilirubin levels led to the diagnosis of AIHA. Additionally, positive antithyroid peroxidase, elevated thyroid stimulating hormone, and low T3, T4 levels pointed toward a diagnosis of autoimmune thyroiditis, with the following levels: TSH-32 mIU/L (Normal: 0.6–8 mIU/L), T3-95 ng/dL (Normal: 105–269 ng/dL), and T4-5.6 µg/dL (Normal: 7.3–15 µg/dL).

A further systemic evaluation revealed the following clinical findings: intellectual disability (Binet Kamat test: IQ35), developmental quotient of 33.5%, short height for

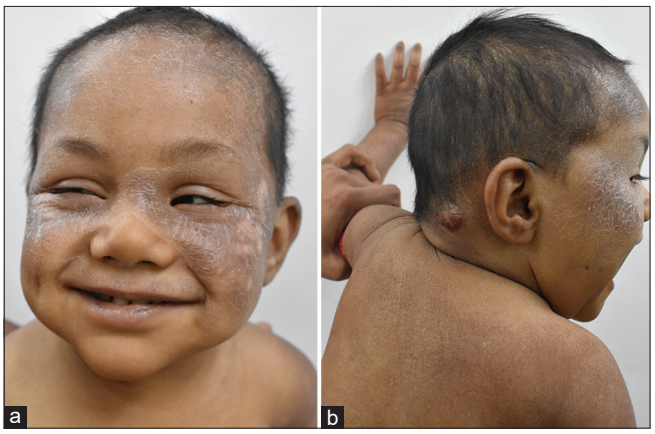

Figure 1: (a) A five-year-old female child with fine generalized scaling, hyperpigmented plaque over malar area with dyschromia suggesting photosensitivity and sparse lusterless hair. (b) Generalized fine scaling over face and trunk with sparse hair. Fibrofatty remnant of hemangioma is evident over occipital area

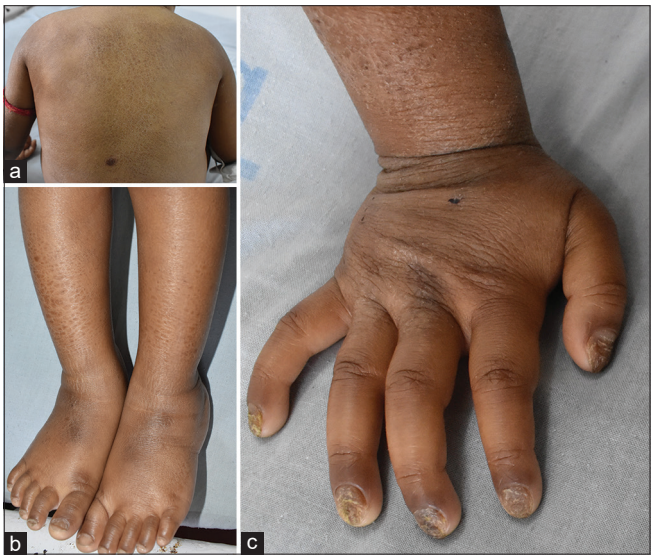

Figure 2: PIBIDS symptom complex showing: (a) Diffuse, fine scaling over trunk. (b) Ichthyotic scales over bilateral legs with toenail dystrophy. (c): Fine scales over hands along with dystrophic yellowish fingernails with subungual hyperkeratosis

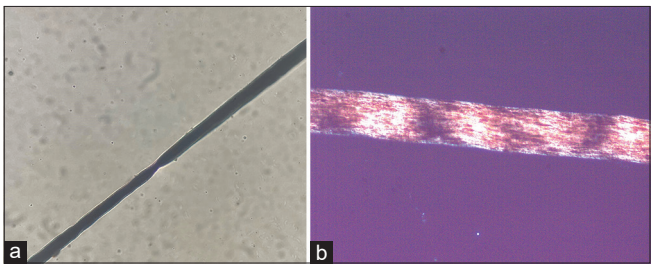

Figure 3: (a) Twisting of hair along its axis by 180º, i.e., pili torti seen on dibutylphthalate polystyrene xylene mountant at 10x magnification. (b) Polarizing microscopy examination at 40x magnification, showing alternate light and dark bands, i.e., "tiger tail" or "zigzag" pattern

age (>2SD below mean for age), bone age<chronological age on wrist bone radiography, and bilateral sensorineural hearing loss (on brainstem evoked response audiometry). Genetic studies could not be performed due to financial constraints. The patient was managed in liaison with pediatrician. For cutaneous lesions, topical emollients, sunscreen, and strict avoidance of sunlight were advised. Autoimmune thyroiditis was managed by levothyroxine supplementation, started at a low dose and was stepped up weekly to 1.6 µg/kg/day. The dose was further titrated as per repeat thyroid function tests at three months, in liaison with pediatric endocrinologist. For the management of AIHA, 1 g/kg of intravenous immunoglobulin and packed cell volume infusions were given.

TTD results from mutations in DNA repair genes (*ERCC2/XPD* and, less frequently, *ERCC3/XPB* and *GTF2H5)*.[1] A number of symptom complexes in which TTD is a feature have been described and several acronyms have been used (PIBIDS, IBIDS, and BIDS). Other reported associations include neurological abnormalities like microcephaly, ataxia, and spastic paralysis; MRI brain showing dysmyelination, cerebellar atrophy, and dilated ventricles.[2] Progeria-like facies, cataracts, joint contractures, recurrent infections, gonadal abnormalities, and osteosclerosis are rarer associations.[3]

A systematic review of 112 published cases of TTD reported haematologic abnormalities in 24 patients, out of which anemia was seen in 13 cases. The causes described were hematologic features of beta-thalassemia trait in eight cases, iron deficiency in two cases, Coombs positive hemolytic anemia, sideroblastic anemia, and unspecified in one case each.[4] Therefore, only a single case report has described the association of TTD with AIHA and none have reported autoimmune thyroiditis.

Photosensitivity in patients with TTD is due to mutations in two genes that encode helicase subunits of general transcription factor IIH (TFIIH), i.e., *ERCC2/XPD* and *ERCC3/XPB*, or rarely *GTF2H5* gene, which encodes the TFIIH subunit p8/TTD-A.[1] These genes are responsible for the repair of UV and oxidative agent induced DNA damage. Downregulation of ATP-dependent *ERCC* genes has been implicated in the pathogenesis of systemic lupus erythematosus, a photosensitive autoimmune disorder.[5] This may possibly explain the novel autoimmune associations seen in our case, and further research is warranted.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Harshita R. Vyas, Yashika J. Doshi, Shikha R. Shah, Bela J. Shah

Department of Dermatology, B. J. Medical College and Civil Hospital, Ahmedabad, Gujarat, India

Address for correspondence:
Dr. Shikha R. Shah,
Wing Number 3, OPD Building, Department of Dermatology, B. J. Medical College and Civil Hospital, Ahmedabad, Gujarat, India.
E-mail: srs4894@gmail.com

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