Ichthyosis Follicularis, Alopecia, and Photophobia (IFAP) Syndrome: A Case Report and Review of Cases Reported from India

Abstract

Ichthyosis follicularis, alopecia, and photophobia (IFAP) syndrome is characterized by the triad of follicular keratotic papules, total to subtotal alopecia, and photophobia. We hereby report a case of IFAP syndrome in a 1-year-old boy who presented with all these classical features along with hyperkeratotic plaques over knees, plantar keratoderma, and umbilical hernia. Also, literature review of cases reported from India is being presented.

Keywords: *Alopecia, ichthyoses follicularis, photophobia*

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Introduction

Ichthyosis follicularis, alopecia, and photophobia (IFAP) syndrome is an extremely rare X-linked oculocutaneous genetic disorder with only 37 cases reported in literature till 2011.[1] It is characterized by the triad of follicular keratotic papules, total to subtotal alopecia, and photophobia.[1] Missense mutation in gene MBTPS2 at Xp22.11.3 has been identified in many patients affected with this syndrome.[2] This causes functional deficiency of membrane-bound transcription factor protease, site 2 (MBTPS2), an intramembrane zinc metalloprotease which further disturbs either sterol or endoplasmic reticulum homeostasis and may impair the differentiation of epidermal structures.[1] We hereby report a case of IFAP syndrome.

Case Report

A 1-year-old boy born to nonconsanguineous parents presented with alopecia over scalp and dry rough skin since birth. There was also history of difficulty in opening the eyes and watering from eyes in exposure to light since birth. His antenatal and perinatal history was unremarkable. There was no history of mental retardation and developmental delay. There was no neurological and hearing deficit. There was no history of similar complaints in the family. On cutaneous examination, there were multiple follicular keratotic papules over whole body predominantly involving scalp, trunk, and extensors of extremities [Figure 1]. Over both knees there were two well-defined mildly erythematous to skin colored lichenified plaques of size approximately 3×2 cm one on each side [Figure 2]. Both soles showed thickened and fissured skin [Figure 3]. Palms were normal. The hair over scalp were sparse, short and thinned out, light brown with complete loss of eyebrows and eyelashes and body hair [Figure 4]. Alopecia was nonscarring in nature. Microscopic examination of hair did not show any abnormality. Ophthalmological examination revealed dry eyes. There was also presence of umbilical hernia [Figure 1]. Oral mucosa, nails, teeth, and sweating were normal. Ophthalmological examination of mother was normal. Skin biopsy from keratotic papule showed occasional plugging of the follicle by a thick deposition of the keratinous material and absence of hair shaft [Figure 5]. In view of above clinical and histopathological features diagnosis of IFAP syndrome was made. Genetic analysis was not done because of financial constraints. Patient was prescribed topical urea-based emollients along with lubricating eye drops. This was followed by mild to moderate improvement in cutaneous lesions and ocular symptoms. Parents were counselled regarding the genetic basis of disease.

How to cite this article: Bains A, Vedant D, Verma A, Bhardwaj A, Nalwa A. Ichthyosis follicularis, alopecia, and photophobia (IFAP) syndrome: A case report and review of cases reported from India. Indian Dermatol Online J 2019;10:686-91.

Received: February, 2019. **Accepted:** April, 2019.

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Access this article online

Website: www.idoj.in

DOI: 10.4103/idoj.IDOJ_19_19

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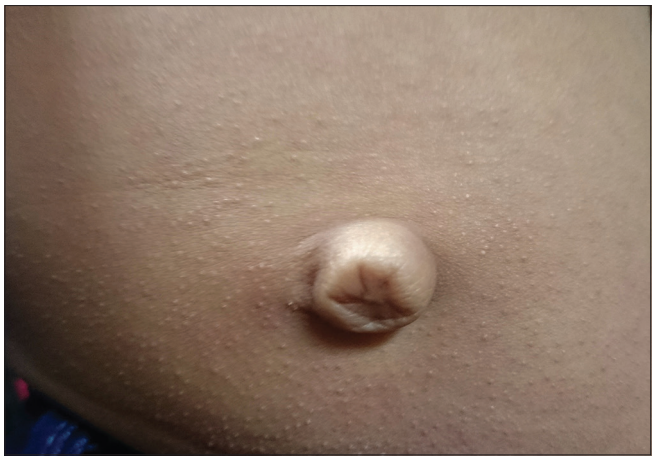

Figure 1: Multiple follicular keratotic papules over abdomen with umbilical hernia

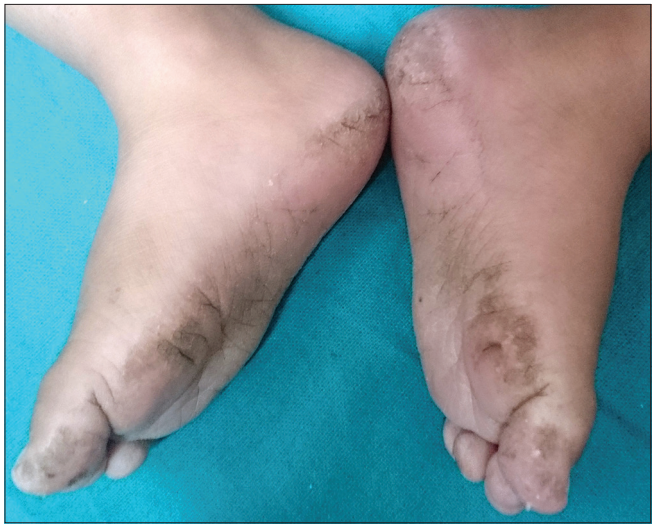

Figure 3: Plantar keratoderma

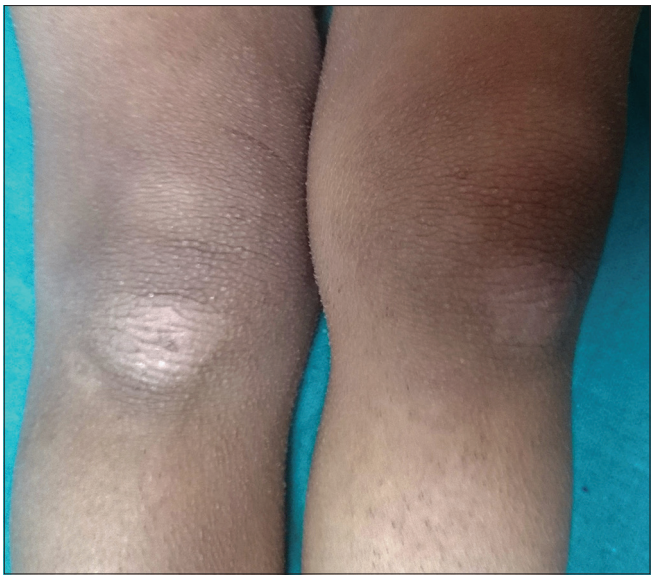

Figure 2: Hyperkeratotic plaques over both knees

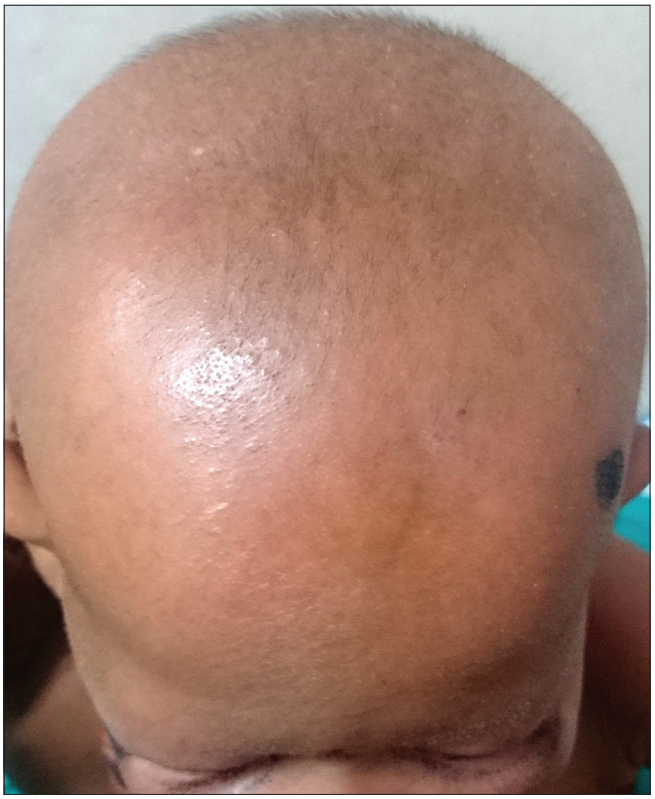

Figure 4: Sparse, short, and thinned out scalp hair

Discussion

First case of IFAP syndrome was reported by Mcleod in 1909.[3] Common manifestations of this syndrome are follicular keratotic papules, alopecia, and photophobia. Follicular papules usually involve scalp, extensor aspect of extremities, and give sandpaper-like texture to skin. Alopecia is congenital, nonscarring, involves scalp, eyebrows, eyelashes, and sometimes is universal.[1] Photophobia is caused by corneal defects like erosions, ulcers, scars, and neovascularization.[4] Other ocular changes can be scarring atopic keratoconjunctivitis, nystagmus, and myopia. Retinal vascular tortuosity may be a clinical sign in carrier females.[5] Ocular examination in our patient revealed dry eyes. Similar changes were reported by Lal *et al*.[6]

The disease may manifest from mild to severe form. Mild form is limited to skin, while BRESHECK is the severe form which manifests as multiple extracutaneous features like brain anomalies, retardation, ectodermal dysplasia, skeletal deformities, Hirschsprung disease, ear/eye anomalies, cleft palate/cryptorchidism, and kidney dysplasia/hypoplasia.[7] Other additional features which may be present are growth retardation, psychomotor development delay, seizures, recurrent pneumonia, inguinal, and umbilical hernia.[1] In our patient, there was presence of associated umbilical hernia.

Patient can have psoriasiform plaques, cheilitis, hypohidrosis, nail dystrophy, atopic dermatitis, and

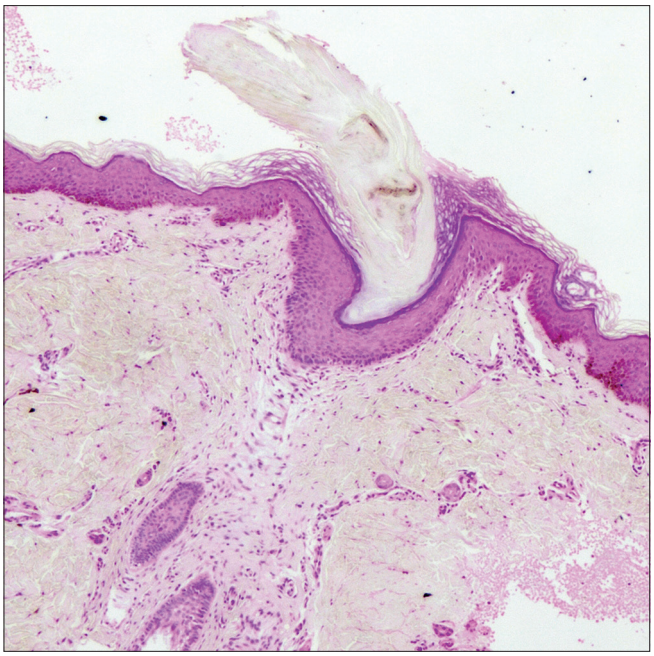

Figure 5: Skin biopsy from keratotic papule showed occasional plugging of the follicle by a thick deposition of the keratinous material and absence of hair shaft. (H and E original magnification 4×)

keratoderma.[4] Hyperkeratoses over elbows and knees have been described earlier in few case reports.[8] Associated palmoplantar keratoderma have been described by Rai and Shenoi and Alshami *et al*.[9,10] In our patient, hyperkeratotic plaques were present over both knees along with plantar keratoderma.Carrier females may have hyperkeratotic lesion along Blashko's lines and asymmetric distribution of body hair.[11] Histopathology from cutaneous lesions show follicular plugging, acanthotic infundibular epidermis, and hypoplasia of sebaceous glands.[1]

To the best of our knowledge only ten cases have been reported from India. Review of these cases showed that the disease manifested predominantly in males. Only one female was reported with this disease. This suggests X-linked recessive inheritance of disease. Onset of cutaneous lesions was since birth in almost all cases. Follicular papules, alopecia, and photophobia were nearly present in all patients. Follicular papules were predominantly distributed over scalp, trunk, and extremities. Alopecia involved scalp, eyebrows, and eyelashes except in one case where scalp hair was normal. Photophobia was absent in one patient. Ocular examination showed abnormal findings in fivepatients and was in the form of corneal xerosis, vascularization, keratitis, opacity, and meibomitis.Hyperkeratotic plaques over elbows and knees were present in two patients, palmoplantar keratoderma in threepatients, nail dystrophy in threepatients, angular cheilitis in twopatients, retarded physical growth in threepatients, delayed milestones in twopatients, seizures in twopatients, family history in twopatients, inguinal hernia in onepatient, and recurrent respiratory infection in twopatients.Skin biopsy showed follicular plugging in most of the patients. Mutation analysis was not done in any patient [Table 1].[6,8,9,12-18]

IFAP syndrome needs to be differentiated from other diseases. Mutations in MBTPS2 have also been found keratosis follicularis spinulosa decalvans (KFSD) and X-linked Olmsted-like syndrome. There is overlap of clinical features in IFAP and KFSD. Both are distinguished by presence of scarring and patchy alopecia in KFSD, also the alopecia is not congenital in KFSD.[7] KFSD usually manifests in early childhood. Symptoms tend to decrease with age and the long-term prognosis for vision is usually good.[19] It has to be differentiated from keratitis ichthyosisdeafness syndrome where there is erythrokeratoderma and congenital hearing loss.[20] Other differentials include papular atrichia and hereditary mucoepithelial dysplasia (HMD). Congenital atrichia with papular lesions presents with hair loss with papules which on histopathology are small keratinous cysts.[21] HMD consists of triad of nonscarring alopecia, well-demarcated fiery red mucosa, and psoriasiform perineal lesions.[19]

There is no permanent cure and genetic counselling of patients is important. Though initially thought to be X-linked recessive disorder but there are some reports in literature where females were also affected. This may reflect genetic heterogeneity of this disorder or autosomal dominant mode of inheritance.[22,23] Heterozygous female carriers can present with patches of alopecia over scalp, linear hyperkeratotic plaques, follicular atrophoderma, and hypohidrosis. However, findings of atrophoderma and hypohidrosis are absent in male patients.[24]

Temporary reduction in cutaneous lesions can be seen with topical keratolytics like urea, topical tretinoin, and topical steroids. Systemic therapy in the form of oral vitamin A, 250 000 units/day, administered for 6 months was used in in one case which led to improvement in photophobia and cutaneous lesions.[25] Moderate response to oral retinoids has been seen in some patients. In one case oral acitretin 1 mg/kg/day was given for 6 months which resulted in flattening of cutaneous lesions, but there was no response in alopecia and ocular symptoms.[12] Similarly, oral isotretinoin 0.5 mg/kg/day for 4 months resulted in marked improvement in cutaneous lesions in one case. However, there was reoccurrence after discontinuation of treatment.[16] Life expectancy of patients can vary from normal survival to death in the neonatal period from cardiopulmonary complications.[4]

Conclusion

The index patient presented with characteristic triad of follicular keratotic papules, atrichia, and photophobia syndrome along with hyperkeratotic plaques over both knees, plantar keratoderma, and umbilical hernia. This case is being reported to increase the clinician's awareness regarding diagnosis of this rare disease.

Table 1: Review of cases reported from India

Author	Rai and Shenoi *et al.*[9]	Khandpur *et al.*[12]	Rai and Shenoi *et al.*[8]	Laway *et al.*[13]	Bhattacharjee and Yadav[14]	Fatima *et al.*[15]	Chauhan *et al.*[16]	Lal *et al.*[6]	Kumar *et al.*[17]	Nagakeerthana *et al.*[18]
Year	2005	2005	2006	2012	2013	2014	2015	2016	2017	2017
Sex	Male	Male	Male	Male	Male	Female	Male	Male	Male	Male
Onset of cutaneous lesions	Since birth	Since birth	Since birth	Since birth	NM*	Since birth	Since birth	Since birth	NM	Since 3 months of age
Follicular papules	Trunk, extremities	Generalized, more prominent on scalp, neck	Face, trunk, extremities	Abdomen	Extensors of extremities	Icthyoses generalised	Abdomen, Icthyotic patches over scalp, face, shins	Generalised	Icthyoses generalised	Face, trunk, extremities, gluteal area
Hyperkeratotic plaques	absent	Cheeks, upper trunk, elbows, knees	Elbows, knees	absent	Ear lobe	NM	NM	NM	NM	NM
Palmoplantar keratoderma	present	Present	NM	absent	absent	absent	absent	absent	present	absent
Alopecia	Since birth, nonscarring, universal	Since birth, universal, developed fine, light brown scalp hair at 3 months of age.	Devoid of eyelashes, Eyebrows since birth Non scarring Sparse scalp hair	Since birth Scalp hair sparse, loss of eyebrows and eyelashes	Scalp, Eyebrows, eyelashes	Since birth, Universal, Non scarring	Since birth Non scarring Scalp, eyebrows	Since birth Non Scarring universal	present	Loss of eyebrows at 1 year age. Scalp hair normal
Nails	Twenty nail dystrophy	Normal	NM	Normal	NM	NM	Normal	Onycholysis, trachonychia, dystrophy	Dystrophy	Normal
Oral mucosa	Linear hyperpigmentation buccal mucosa	Normal	NM	Normal	Angular cheilitis	Angular cheilitis	Normal	Normal	SCC**	Normal
Sweating	Normal	Reduced but not objectively tested	Normal	Normal	NM	NM	NM	NM	NM	NM
Photophobia	Absent	Started at 6 months of age	Since birth	Since birth	Started at 2.5 yrs of age	Since nearly 3 yrs of age	present	Since birth	NM	present
Ocular examination	Normal	Corneal opacity and vascularisation	NM	Normal	Corneal vascularisation	Bilateral severe meibomianitis Punctate keratitis in one eye	Normal	Conjunctival, Corneal Xerosis	NM	Bilateral posterior blepharitis
Hearing	Impaired in left ear due to otitis media	normal	normal	normal	NM	normal	NM	normal	NM	NM

Contd...

Table 1: Contd...

Author	Rai and Shenoi *et al.*[9]	Khandpur *et al.*[12]	Rai and Shenoi *et al.*[8]	Laway *et al.*[13]	Bhattacharjee and Yadav[14]	Fatima *et al.*[15]	Chauhan *et al.*[16]	Lal *et al.*[6]	Kumar *et al.*[17]	Nagakeerthana *et al.*[18]
Physical growth	Normal	Retarded	Normal	Retarded	NM	NM	Retarded	Normal	NM	NM
Mental retardation	Absent	Borderline intelligence	Absent	Absent	NM	NM	NM	Absent	NM	Absent
Developmental milestones	Normal	Delayed	normal	Normal	NM	Normal	Delayed	Normal	NM	Normal
Seizures	NM	Absent	Absent	Absent	NM	Absent	Present	Present	NM	Absent
Skeletal anomaly	Absent	Absent	NM	Suggestive of rickets	NM	NM	Absent	Absent	NM	NM
Dentition	Normal	Normal	NM	Normal	NM	NM	Normal	Normal	NM	Normal
Family history	Absent	Absent	Absent	Absent	NM	Present in father	Absent	Present in brother, maternal uncle	NM	Absent
Atopy	NM	Absent	NM	NM	NM	NM	NM	Present	NM	Absent
Consanguineous parents	Absent	Absent	Absent	Absent	NM	Absent	Absent	Absent	NM	Absent
Hair microscopy	NM	Normal	Normal	NM	NM	NM	NM	NM	NM	Normal
Skin biopsy from follicular papule	Follicular plugging	Follicular plugging, abortive hair follicles, absent Sebaceous glands, normal eccrine glands	Follicular plugging	Scalp biopsy showing hyperkeratoses, Acanthosis, vacuolar degeneration, scant perivascular lymphoid infiltrate	NM	NM	Follicular plugging	Follicular plugging, Absence of follicles and sweat glands	NM	Keratoses pilaris
Serum IgE	Not done	Increased	Not done	NM	NM	NM	NM	NM	NM	NM
Karyotyping	Not done	Normal	Not done	NM	NM	NM	Not done	NM	NM	NM
Mutation analysis	Not done	Not done	Not done	Not done	NM	NM	Not done	NM	NM	Not done
Associated disease or finding	Absent	Absent		Non nutritional rickets	NM	NM	Recurrent respiratory infection, regurgitation, inguinal hernia	Eczematous plaques cubital fossa	CML†, SCC** Oral cavity	Recurrent respiratory tract infection

Abbreviations *not mentioned, †chronic myeloid leukemia, **squamous cell carcinoma

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Kamo M, Ohyama M, Kosaki K, Amagai M, Ebihara T, Nakayama J, *et al.* Ichthyosis follicularis, alopecia, and photophobia syndrome: A case report and a pathological insight into pilosebaceous anomaly. Am J Dermatopathol 2011;33:403-6.
2. Izumi K, Wilkens A, Treat JR, Pride HB, Krantz ID. Novel MBTPS2 missense mutation in the N-terminus transmembrane domain in a patient with ichthyosis follicularis, alopecia, and photophobia syndrome. Pediatr Dermatol 2013;30:263-4.
3. McLeod JM. Three cases of 'ichthyosis follicularis' associated with baldness. Br J Dermatol 1909;21:165-89.
4. Ferrari B, Morita L, Choate K, Hu RH. Ichthyosis follicularis with alopecia and photophobia syndrome (IFAP): A case report. Dermatol Online J 2017;23.
5. Traboulsi E, Waked N, Mégarbané H, Mégarbané A. Ocular findings in ichthyosis follicularis-alopecia-photophobia IFAP syndrome. Ophthalmic Genet 2004;25:153-6.
6. Lal NR, Bandyopadhyay D, Misra S, Sarkar AK, Rao S. Ichthyosis follicularis, atrichia and photophobia (IFAP) syndrome affecting two successive generations in an Indian family. Indian J Dermatol Venereol Leprol 2016;82:537-9.
7. Fong K, Takeichi T, Liu L, Pramanik R, Lee J, Akiyama M, *et al.* Ichthyosis follicularis, atrichia, and photophobia syndrome associated with a new mutation in MBTPS2. Clin Exp Dermatol 2015;40:529-32.
8. Rai VM, Shenoi SD. Ichthyosis follicularis with alopecia and photophobia (IFAP) syndrome. Indian J Dermatol Venereol Leprol 2006;72:136-8.
9. Rai VM, Shenoi SD. Ichthyosis follicularis with congenital atrichia, nail dystrophy and palmoplantar keratoderma. Variant of IFAP syndrome or a new entity? Dermatol Online J2005;11:36.
10. Alshami M, Bawazir MA, Atwan AA. Photoletter to the editor: A new variant of ichthyosis follicularis with alopecia and photophobia (IFAP) syndrome with coexisting psoriasiform lesions and palmoplantar keratoderma. IFAP-PPK syndrome? J Dermatol Case Rep 2011;5:14-6.
11. Megarbane H, Megarbane A. Ichthyosis follicularis, alopecia, and photophobia (IFAP) syndrome. Orphanet J Rare Dis 2011;6:29.
12. Khandpur S, Bhat R, Ramam M. Ichthyosis follicularis, alopecia and photophobia (IFAP) syndrome treated with acitretin. J Eur Acad Dermatol Venereol 2005;19:759-62.
13. Laway BA, Verma SK, Bashir MI, Ganie MA, Mir SA, Ahmad SM, *et al*. IFAP Syndrome with rickets and normal vitamin D status. Indian J Dermatol 2012;57:161-3.
14. Bhattacharjee H, Yadav A. A rare case of ichthyosis follicularis, alopecia & photophobia syndrome. Indian J Med Res 2013;138:1033.
15. Fatima T, Mathur U, Acharya M. Meibomian gland dysfunction in a case of ichthyosis follicularis with alopecia and photophobia syndrome. Indian J Ophthalmol 2014;62:365-7.
16. Chauhan S, Gahalaut P, Chandra K. Ichthyosis follicularis alopecia and photophobia syndrome: Transient improvement with oral isotretinoin. Indian J Paediatr Dermatol 2015;16:39-41.
17. Kumar U, Singh A, Reddy A, Vidyasgar MS, Prahlad HY. Oral cavity squamous cell carcinoma in a case of ichthyosis follicularis, alopecia, and photophobia syndrome with chronic myeloid leukemia on longtermhydroxyurea: A rare presentation. Asian J Pharm Clin Res 2017;5:1-3.
18. Nagakeerthana S, Rangaraj M, Karthikeyan K. Ichthyosis follicularis, alopecia, and photophobia syndrome. Int J Trichol 2017;9:67-9.
19. Tang L, Liang J, Wang W, Yu L, Yao Z. A novel mutation in MBTPS2 causes a broad phenotypic spectrum of ichthyosis follicularis, atrichia, and photophobia syndrome in a large Chinese family. J Am Acad Dermatol 2011;64:716-22.
20. Patel V, Sun G, Dickman M, Khuu P, Teng JM. Treatment of keratitis-ichthyosis- deafness (KID) syndrome in children: A case report and review of the literature. Dermatol Ther 2015;28:89-93.
21. Nomura K, Hashimoto I, Takahashi G, Ito M. Atrichia with papular lesions: Electron microscopic observations of cystic lesions. Am J Dermatopathol 2001;23:227-31.
22. Rothe MJ, Weiss DS, Dubner BH, Weitzner JM, Lucky AW, Schachner L. Ichthyosis follicularis in two girls: An autosomal dominant disorder. Ped Dermatol 1990;7:287-92.
23. Tsolia M, Aroni K, Konstantopoulou I, Karpathios T, Tsoukatou T, Paraskevakou H, *et al*. Ichthyosis follicularis with alopecia and photophobia in a girl with cataract: Histological and electron microscopy findings. Acta Derm Venereol 2005;85:51-5.
24. Konig A, Happle R. Linear lesions reflecting lyonization in women heterozygous for IFAP syndrome (ichthyosis follicularis with atrichia and photophobia). Am J Med Genet 1999;85:365-8.
25. Eramo LR, Esterly NB, Zieserl EJ, Stock EL, Herrmann J. Ichthyosis follicularis with alopecia and photophobia. Arch Dermatol 1985;121:1167-74.