

# Concomitant extraspinal hyperostosis and osteoporosis in a patient with congenital ichthyosis

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## Summary

**Ichthyosiform dermatosis is a term referred to a group of disorders that have as their basis a disorder of keratinization (1). These conditions which are present at birth result in a generalized dry, scaly skin without any inflammation. There are several types of ichthyosis based on their clinical presentation and mode of inheritance. The most common types are: ichthyosis vulgaris, X-linked recessive ichthyosis, epidermolytic hyperkeratosis (bullous), lamellar ichthyosis and non-bullous ichthyosiform erythroderma. Lamellar ichthyosis, which is inherited in an autosomal recessive pattern, shows genetic heterogeneity with the most severe type being due to mutations in the transglutaminase-1 gene. This condition presents with skin changes at birth and cases are referred to as collodion babies. Initially, the stratum corneum is smooth and appears as though it is covered with cellophane. This layer is discarded a few days after birth, leaving a generalized inflamed and scaly appearance. The skin is tight at this stage and may cause ectropion, and difficulties in feeding and temperature regulation. Lamellar ichthyosis is characterized by plate-like scales that last for life and can significantly impact the patient's quality of life (2). We report here a case of multiple extraspinal hyperostoses concomitant with marked osteoporosis and vitamin D deficiency in a patient taking acitretin for 20 years due to severe congenital lamellar ichthyosis.**

**KEY WORDS:** lamellar ichthyosis; extraspinal hyperostosis; osteoporosis; retinoids.

## Case report

A 27-year-old man was initially referred in 2008 to a tertiary children's hospital for evaluation and management of severe osteoporosis first diagnosed in 2005. This was in the context of congenital lamellar ichthyosis diagnosed at birth, borderline low BMI, sedentary life style and poor dietary habits. Low vitamin D levels were also detected on review. Treatment including diet modification, lifestyle change, exercise advice and also calcium and vitamin D supplements was initiated at that stage. It was elected not to start bisphosphonates due to his young age and lack of any prior major fractures.

The patient failed to return for follow up until he represented with long standing pain in his forearms, wrists, right leg and also the hip. His symptoms had been present for 7 years and had increased in intensity resulting in limited range of motion. His congenital lamellar ichthyosis had been treated with oral acitretin since the age of seven, his current treatment dose being 50mg daily, together with multiple topical emollients, which adequately controlled his skin condition. He had been reviewed by multiple specialists for restricted pronation of the right forearm since 2008 which was initially thought to be due to a buckle fracture after sustaining a fall but he had later developed similar symptoms in his left forearm, hip and right leg. On review, the patient was thin with a BMI of 18. Clinically he had low muscle mass. Most recent bone densitometry results demonstrated marked osteoporosis ( $T < -2.5$ ) (Table 1). He was not able to pronate his right forearm at all, and had negative 10° supination and 40° on pronation that was associated with pain. He also complained of hip and right leg pain which did not limit his daily function. Radiographs of the upper and lower limbs demonstrated bridging ossification within the intraosseous membrane between the mid ulnar and radial diaphysis with an oblique orientation bilaterally (Figure 1 a, b). This bridging ossification consisted of mature non-aggressive appearing new bone. Moreover, similar bridging ossification was identified between the right distal fibular and tibial diaphysis (Figure 1 c, d). A trial of acitretin dose reduction together with life style and dietary modifications were initiated for the patient.

## Discussion

Lamellar ichthyosis in less severe forms can be treated using various topical lubricating, keratolytic and hydrating agents. In more severe cases that do not respond to these treatment options, oral retinoids have been found to be effective. Acitretin, a synthetic vitamin A analogue, is the treatment of choice for severe keratinization disorders (3). Moreover, vitamin A analogues can be used in the treatment of severe psoriasis and nodulocystic acne (3). The patient reported here had multiple extraspinal hyperostoses concomitant with marked osteoporosis and vitamin D deficiency and had taken acitretin for 20 years due to severe congenital lamellar ichthyosis. Concomitant presence of severe early onset osteoporosis and hyperostoses as seen in the current reported case has not been reported previously in association with retinoids.

Table 1 - Bone density studies demonstrating significant osteoporosis (BMD studies from 2012).

	Bone Density gms/cm <sup>2</sup>	Z score (compared with age-sex matched mean value)	T score (compared with young normal mean value)
Lumbar spine average	0.684	-3.7	-3.7
Total Hip	0.680	-2.87	-3.02
Femoral neck	0.554	-3.6	-3.86

The simultaneous presence of these two paradoxical phenomena together with the fact that the nature, incidence and severity of skeletal changes with retinoids is yet to be established raises the question whether factors other than retinoids have contributed.

There is limited and conflicting evidence available regarding retinoid-related bone changes. The main effect of retinoids on the skeletal system is axial hyperostosis (4). This usually occurs with high doses of retinoids and long term treatment (>10 years). This mostly affects the cervical and thoracic spine. Retinoids have been reported to be associated with extraspinal hyperostosis as well (4). Remarkable ossification of both iliolumbar ligaments has been reported in a patient with congenital lamellar ichthyosis who had been treated with etretinate and acitretin for 10 years (5). Van Dooren-Greebe et al. (1995) reported ossification of the interosseous membrane in the right ankle of a patient with pityriasis rubra pilaris who had been treated with oral retinoids for a long time (6). Extensive periosteal hyperostoses and bridging exostosis between the left acetabulum and greater femoral trochanter has also been reported after 13 years of oral acitretin in a patient with psoriasis (7). Although the exact mechanisms for these changes are unknown they are thought to be mostly due to excess vitamin A levels (7). It would be useful to determine whether monitoring of vitamin A and insulin-like growth factor 1 levels would be informative in patients on long term retinoids in order to monitor the side effects and minimize them as retinoic acid which is the active metabolite of vitamin A controls growth hormone production by triggering its production in the GH1 pituitary cells (6, 8). High levels of vitamin A have been shown to induce bone fragility by increasing osteoclast formation and decreasing cortical bone mass (9). Retinoids have also been suggested to have osteopo-

rotic effects. There are inconsistent reports and studies in this area and the data remain unconvincing. While long term retinoid therapy has been shown to be associated with osteoporosis in some older studies (10, 11) more recent investigations have denied any association (12). Short term acitretin has not been shown to result in decrease in bone density (13). Isotretinoin was shown to have no effect on bone density in a recent double-blind randomized study which followed 358 teenagers for 5.5 months (14). Progressive extraspinal hyperostosis can also be seen in bone dysplasia disorders such as *osteogenesis imperfecta* type 5 (OI type V). OI type V, which is a rare hereditary disease associated with increasing bone fragility, is also characterized by calcification of the interosseous membranes in limbs and hyperplastic callus formation. OI Type V has been shown to be associated with low bone density and patients tend to suffer recurrent fractures from an early age and as a result have short stature (15). OI type V generally presents at an early age (onset under age of 5) and late onset presentation is rare. To exclude this diagnosis genetic testing for a recurrent mutation in the 5' UTR of the Interferon-induced transmembrane protein5 (IFITM5) gene which is seen in all OI type V patients will be required (15). The five gene defects associated with lamellar ichthyosis include mutations in transglutaminase 1 gene (TGM1), ABCA12, two lipoxigenase genes, ALOXE3 and ALOX12B and ichthyin (1). No association between these two conditions has been reported in our knowledge. Other differential diagnoses for hyperostosis include post-traumatic, metabolic conditions such as diabetes mellitus (16), acromegaly (17). Treatment options for osteoporosis in this patient include dietary and life style modification and vitamin D and calcium supplements. Bisphosphonates remain a potential treatment option but considering his young age, concomitant hyperostoses and lack of prior

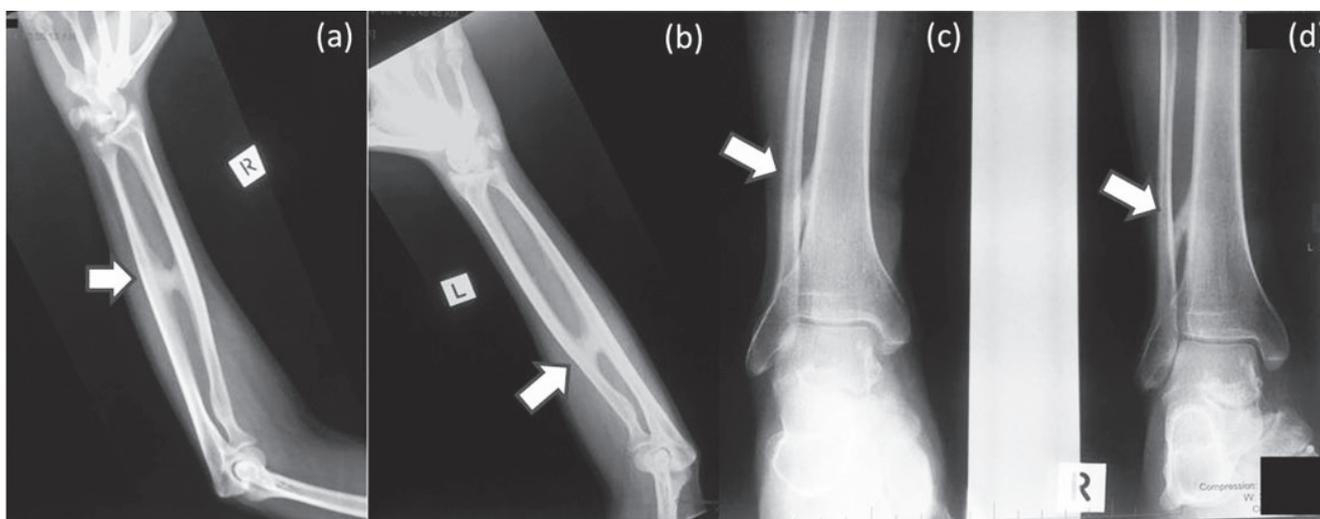


Figure 1 - (a, b) Prominent bridging ossification within the intraosseous membrane (arrow) between the mid ulnar and radial diaphysis with an oblique orientation bilaterally. (c, d) Similar bridging ossification (arrow) was identified between the right distal fibular and tibial diaphysis (X-ray taken in 2012).

fractures, the use of this medication has currently been postponed to after a trial of acitretin dose reduction. When given the option of stopping acitretin or continuing treatment, the patient chose to continue treatment at a lower dose due to concerns of compromising treatment of the ichthyosis. Management of hyperostoses is also a challenge as the exact pathophysiology is yet to be identified. Surgical intervention is not deemed to be an effective option due to the possibility of recurrence at the operative sites and extent of lesions. Palovarotene is a new retinoic acid receptor (RAR) gamma agonist which is currently being trialed in patients with heterotopic ossification due to fibrodysplasia ossificans progressiva (FOP). Mouse models of FOP have demonstrated the ability of RAR gamma agonists to prevent heterotopic ossification (HO) following injury (18). The aforementioned trial is at early stages and possible effects of this agent on bone mineral density and bone strength is not known yet. This might be a possible treatment option to consider in the future.

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