LICHEN AMYLOIDOSIS ASSOCIATED WITH PRIMITIVE BILLIARY CHOLANGITIS

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Summary

Primary cutaneous amyloidosis is a rare disease, characterized by the deposition of amyloid in the dermis, in the absence of systemic involvement. It has been linked especially to autoimmune diseases, such as systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, primitive biliary cholangitis. We present a case of a patient with primitive biliary cholangitis who developed lichen amyloidosis. This association has been rarely reported in the literature.

Keywords: *lichen amyloidosis, primitive biliary cholangitis, pruritus, primary cutaneous amyloidosis*

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Introduction

Primary cutaneous amyloidosis (PCA) consists of the deposition of amyloid in the dermis, with no systemic involvement. It is classified into three major forms, lichen amyloidosis – the commonest type, macular, and a rare nodular form. Macular and papular forms may co-exist in the same patient and is known as biphasic amyloidosis. Typically, PCA presents as an eruption with brownish macules (macular form), pruriginous brownish papules or plaques (lichen amyloidosis) on the trunk and extremities. [1]

Extracellular deposition of altered autologous protein (amyloid protein) within the dermis is the hallmark of cutaneous amyloidoses and systemic amyloidoses with cutaneous involvement. Many proteins and peptides have been identified as amyloid precursors and the pathogenic alteration of normal human proteins can be induced by chronic inflammation, malignancies, various mutations. [2]

In both lichen amyloidosis and macular form, amyloid consists of aggregates of keratin filaments formed as a result of defective degeneration of keratinocytes[3]. Nodular amyloidosis is characterized by the presence of crusted nodules, frequently located on the face and extremities.[1] It is associated with blood disorders, amyloid being derived from immunoglobulins and consists of light lambda or kappa chains.

Macular amyloidosis has a higher incidence in Asia, the Middle East and South America. Lichen amyloidosis is a rare disease in Europe and North America and is more common in Southeast Asia and South America[4]. Most cases are sporadic, but an autosomal dominant condition may be present in up to 10% of cases[5]. Pruritus is a common symptom, but may be absent in 10-40% of patients, suggesting that PCA is not secondary to chronic scratching[4].

The diagnosis is confirmed by histopathological examination where the amyloid is showed as an eosinophilic material on the usual staining with hematoxylin-eosin. Using congo red, amyloid shows characteristic green birefringence when viewed under polarized light

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and in ordinary light the amyloid appears brown-reddish. In lichen amyloidosis and macular amyloidosis, amyloid can be found in the papillary dermis and the overlying epidermis often shows acanthosis and hyperkeratosis[2].

Primitive biliary cholangitis (PBC) is an autoimmune liver disease characterized by progressive destruction of the intrahepatic bile ducts leading to cholestasis. Over time, liver fibrosis occurs which can lead to cirrhosis and liver failure[6]. Antimitochondrial antibodies have high specificity, they are found in over 90% of diagnosed patients and are a diagnostic criteria along with cholestasis syndrome and histopathological examination[6, 7]. PBC, like most autoimmune diseases, has a female predisposition with female-to-male ratio of 10 to 1[6]. Fatigue and pruritus are the most common symptoms that affects 80% of patients and are not related to with disease stage or activity[6, 8]. Up to 73% of patients have extrahepatic manifestations, especially autoimmune, the most common being Sjogren's syndrome, thyroid dysfunction and systemic sclerosis[6].

The association between PCA and other diseases has been documented for connective tissue disease as systemic sclerosis, systemic lupus erythematosus and rheumatoid arthritis[9].

We report a case of a 48-year-old woman with primary biliary cholangitis who developed lichen amyloidosis, a rare association reported in the literature.

Clinical case

A 48-year-old female patient, known for many years with primitive biliary cholangitis, presents in November 2020 for a disseminated, intensely pruriginous rash, with an evolution of about 1 year. She followed intermittent treatment with antihistamines and dermatocorticoids, without improvement.

The patient was diagnosed with primary biliary cholangitis at the age of 21 (cholestasis syndrome and positive antimitochondrial antibodies), being regularly followed up in the gastroenterology clinic.

The last check-up, in November 2020, showed cholestasis syndrome with elevated levels of alkaline phosphates (243 U/l, max. 104 U/l) and conjugated bilirubin 0.88 mg/dL (max. ≤ 0.5 mg/dl), total bilirubin within normal limits, hepatocytolysis syndrome (TGP 83.5 U/l max. 31 U/l, TGO 54.6 U/l max. 32 U/l). The hemoleukogram showed eosinophilia (1.01 thousand/μL, max. 0.4 thousand/μL) and basophilia 0.1 thousand/μL). Also, the ESR value is slightly increased (51 mm/h, max. ≤20 mm/h). Currently, the patient is being treated with ursodeoxycholic acid 1250 mg/day. From the patients history we also mention asthma, aspirin intolerance and rhinosinusitis. The patient has no significant hereditary history, there are no cases of PBC or cutaneous amyloidosis in the family.

The dermatological clinical examination reveals an erythematous-violet papules eruption, intensely pruriginous, some forming plaques, located on the forearms (fig.1), calves (fig2), thighs (fig. 3), abdomen (fig. 4) and lower back, with symmetrical arrangement. In addition, there is diffuse hyperpigmentation and severe skin xerosis. Otherwise, the general examination is within normal limits.

Considering the dermatological clinical aspect and the presence of the associated autoimmune pathology - primitive biliary cholangitis, we focused on the diagnoses of lichen planus or lichen amyloidosis. The differential diagnosis was made with prurigo nodularis (severe pruritus, typical lesions are papules covered with hematic crusts), chronic simplex lichen and lichen planus.

To confirm the diagnosis, a skin biopsy was taken and a histopathological examination was performed. Histopathological examination (Fig. 5,6) showed thickened epidermis, orthokeratotic stratum corneum with areas of hyperparakeratosis containing small interlamellar spaces filled with fluid; irregular elongated interpapillary ridges, some dilated at the extremity and coalescing with congeners at this level; areas of spongiosis; the cells of the basal layer are hyperpigmented. It also showed perivascular inflammatory infiltrates (composed of lymphocytes, histiocites and rare eosinophils), which sometimes include melanophagous. The special coloration with Congo Red (fig. 7) highlights the presence of amyloid deposits in the reticular dermis. The histopathological aspects support the clinical diagnosis of cutaneous amyloidosis,

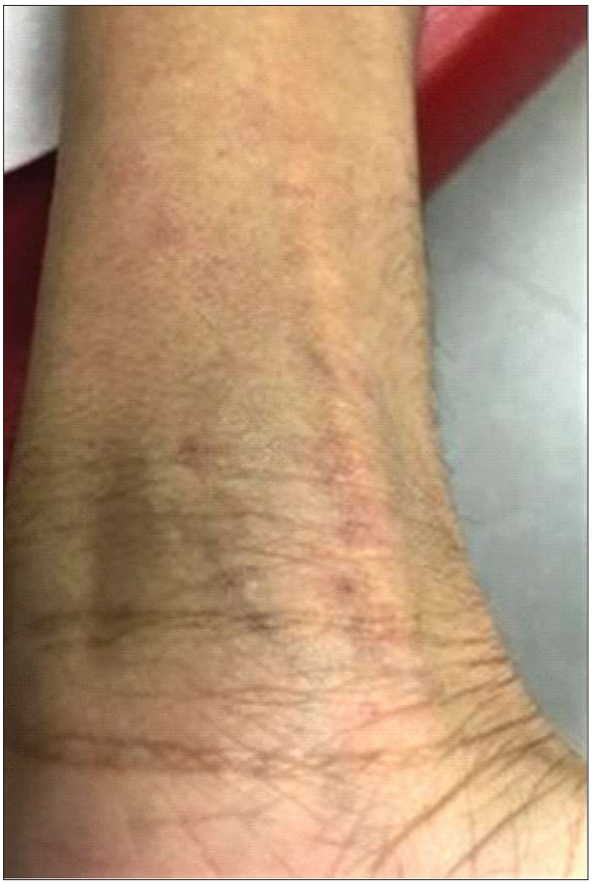


Figure 1. Hyperpigmented papules located on the forearm.

with dermo-epidermal changes of the "spongiotic dermatitis".

The main goal of the treatment was to relieve the itching, to improve skin lesions and prevent the appearance of new ones. The patient was treated with emollients for the intense skin xerosis and calcipotriol/betamethasone ointment, one application per day on skin lesions. The patient also received systemic corticosteroid therapy (Prednisone 30 mg/day for 4 weeks, followed by gradual dose reduction for another 4 weeks). In our case, the association of lichen amyloidosis with another disease (PBC) that causes pruritus, makes it even more important to control it. So, the patient continued treatment with ursodeoxycholic acid 1250 mg/day, according to the recommendations of the gastroenterologist.

After treatment, the itching was gone, the lesions flattened and no new lesions appeared and neither the pruritus nor the lesions reappeared. The patient remains in our records for follow-up visits. She will continue gastroenterological follow-ups and treatment for her associated disease.

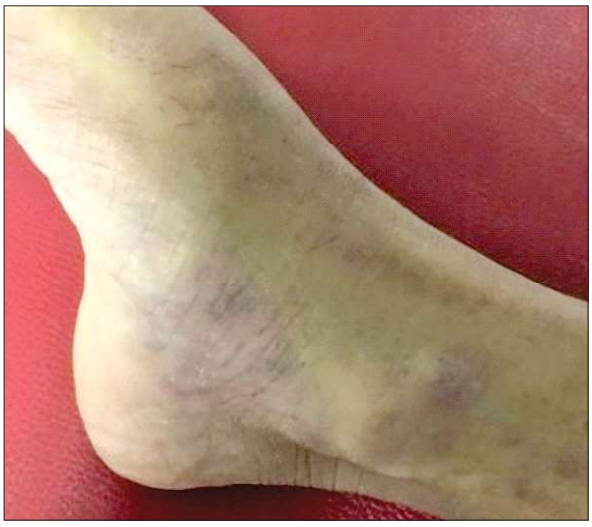


Figure 2. Erythematous-violet papules plaques, located at the plantar and retromaleolar level.

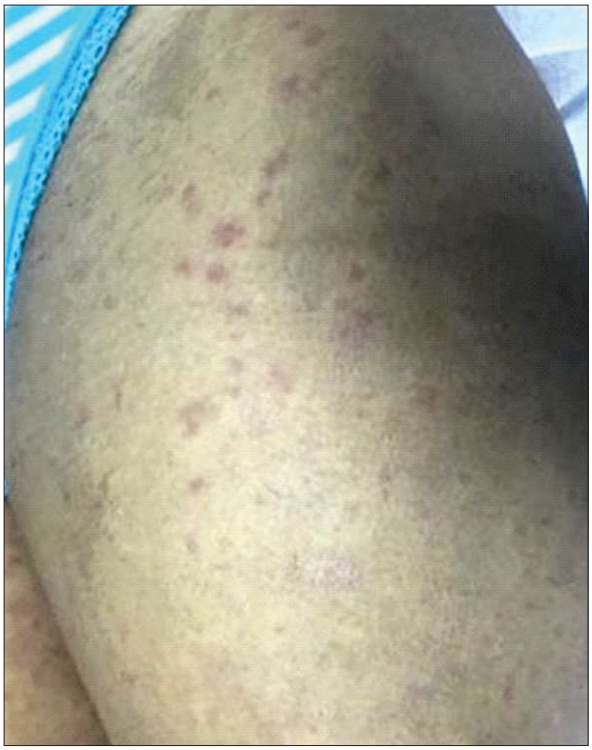


Figure 3. Erythematous-violet papules located on the thighs.

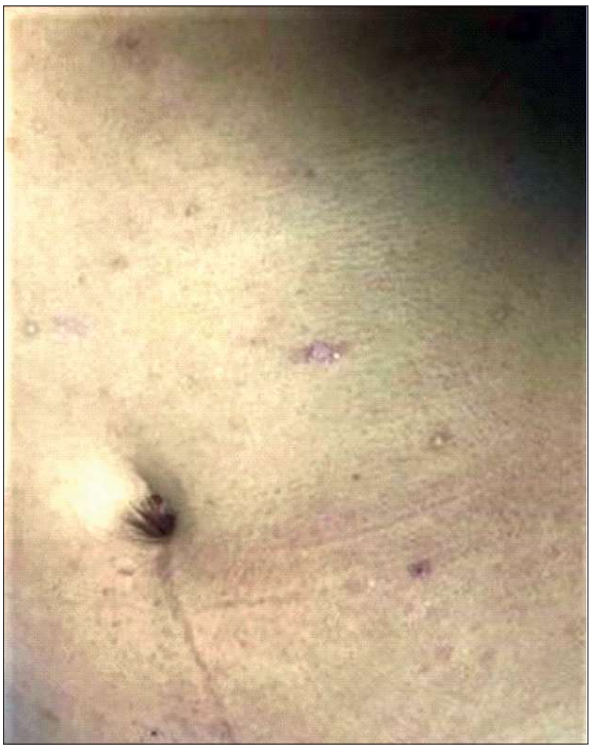


Figure 4. Violet scaly papules, well delimited, located at the abdominal level.

Discussion

Lichen amyloidosis is the most common form of primary cutaneous amyloidosis, with a higher incidence in South America and Asia, compared to Europe and the USA. In addition, women are more likely to develop PCA than men (female: male ratio is 2-3: 1).[10]

Lichen amyloidosis is generally sporadic, but cases of familial presentation by autosomal dominant transmission have also been reported, possibly caused by a mutation in the short arm of chromosome 1[11]. Other studies have shown the association with mutations located on chromosome 5 that cause changes in the structure of the oncostatin M receptor (OSMR), but also in the IL-31 receptor. These changes lead to increased keratinocyte apoptosis and amyloid deposition[4].

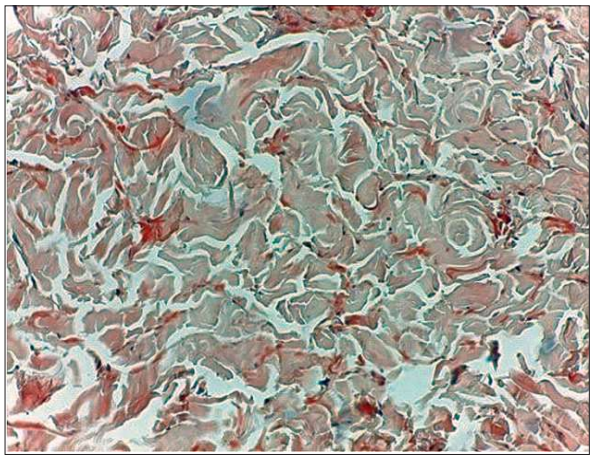
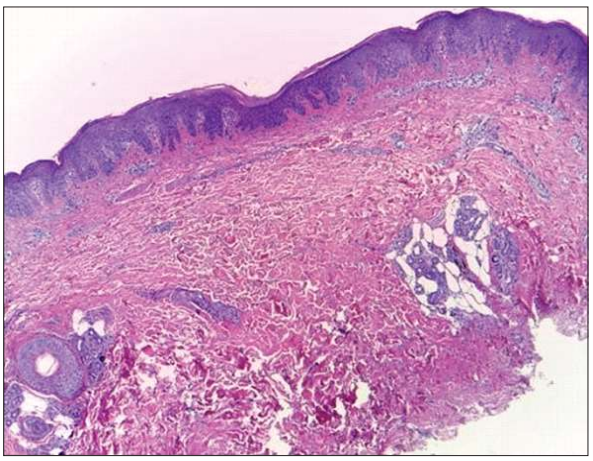


Figure 7. HP, x100 Congo Red staining highlights the presence of amyloid deposits in the reticular dermis.



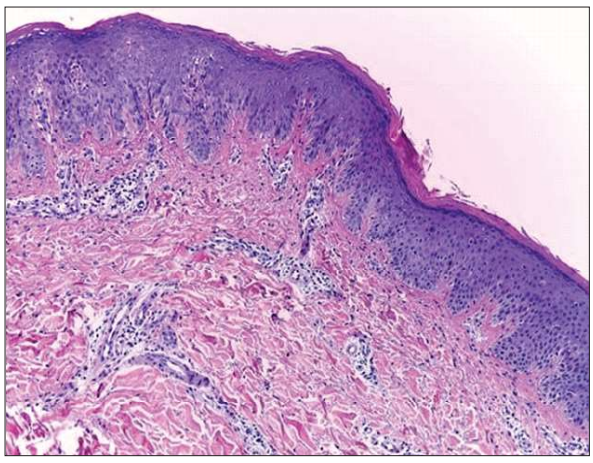


Figure 5, 6. HP, HE x 40, x100 (Fig.6) thickened epidermis, orthokeratotic stratum corneum with areas of hyperparakeratosis; irregular elongated interpapillary ridges; areas of spongiosis; perivascular inflammatory infiltrates (composed of lymphocytes, histiocites and rare eosinophils).

The etiopathogenesis of the disease is not fully known. Numerous cases of lichen amyloidosis associated with autoimmune diseases have been reported in the literature, suggesting the possibility of a common underlying immune-mediated mechanism [12]. Conditions like Sjogren, Behcet, IgA nephropathy, systemic lupus ery-thematosus and systemic sclerosis have been associated with PCA[1].

In macular and papular amyloidosis one of the accepted pathogenic theories is that amyloid results from the apoptosis of keratinocytes. Apoptotic basal keratinocytes release cytokeratins that are phagocytosed by macrophages and enzymatically degraded to amyloid K which deposits in the papillary dermis and is the major constituent of amyloid in lichen amyloidosis[12]. The reasons that cause keratinocyte apoptosis remain unknown.

The pathogenic mechanism of PBC is the loss of immune tolerance to certain cell components in the bile ducts[1].

Regarding the association between PBC and lichen amyloidosis, there are two hypotheses.

The first hypothesis is based on the effect that hyperbilirubinemia has on keratinocytes. It has been shown that cultivated keratinocytes are damaged by bilirubin, in addition hyperbilirubinemia can lead to extensive epidermal injury[13]. Thus, bilirubin deposition on the skin could cause keratinocyte apoptosis with cytokeratin release leading to amyloid formation[1].

The second hypothesis implies the possibility of a common autoimmune mechanism. Certain common components in keratinocytes and bile duct epithelium (common epitopes) may be the target of antibodies in a group of patients[14]. These autoantibodies cause the destruction of keratinocytes, developing PCA and the distruction of biliary epithelial cells determing PBC. Thus, the autoantibodies in these tissues cause different clinical manifestations and could explain the simultaneous appearance of the two patho-logies.[3]

Lichen amyloidosis is a chronic disease with no potential for malignant transformation[15]. The treatment of cutaneous amyloidosis remains a challenge for the dermatologist, but also for the other medical disciplines involved. In the case of the association of lichen amyloidosis with primitive biliary cholangitis there is no standard treatment. Pruritus is often the main reason for the patient to go to the doctor. Therefore, its control must be achieved in all treatment regimens. The most commonly used therapies are: topical treatment with topical steroids, tacrolimus 0.1%, phototherapy, systemic treatment with acitretin, prednisone, cyclosporine. Surgical treatments such as excision, dermabrasion, shave excision are also helpful[2].

The associated liver disease is treated with ursodeoxycholic acid, in combination with immunosuppressive therapy corticosteroids +/- azathioprine depending on the evolution, in advanced stages may require liver transplantation.

Our patient was treated with systemic corticosteroid - prednisone 0.5 mg/kgc for one month, with the dose lowered in the following month, and topically with calcipotriol/betamethasone ointment and emollients. The patient responded well to treatment, with remission of pruritus and significant relief of lesions. She remains in our care as well as gastroenterologicals.

Conclusions

PCA is a rare disease in the Caucasian population, with sporadic onset or familial transmission (autosomal dominant transmission in up to 10% of cases[5]). The etiopathogenic mechanism is still unknown, it is frequently associated with collagen diseases. PCA seems to be linked to autoimmunity, therefore, in the case of a patient with PCA, the presence of other conditions with the same pathophysiology should be considered and investigated. The association with primitive biliary cholangitis has been rarely described in the literature, but the etiopathogenic implications deserve to be studied further.

The multitude of therapies used in trying to control the signs and symptoms of PCA shows how difficult is to control this condition[16]. Recent research has led to the discovery of new treatments in hereditary PCA. It remains to be seen whether they are useful in sporadic forms. Thus, patients with PCA as well as those with other pruritic dermatoses may receive treatment with anti-IL-31. Reducing its bioactivity has a marked antipruritogenic effect.

Bibliography

1. González-Moreno EI, Cámara-Lemarroy CR, Borjas-Almaguer DO, Martínez-Cabriales SA, Paz-Delgadillo J, Gutiérrez-Udave R, Ayala-Cortés AS, Ocampo-Candiani J, Cortéz-Hernández CA, Maldonado-Garza HJ. Cutaneous amyloidosis associated with autoimmune hepatitis-primary biliary cirrhosis overlap syndrome. *Ann Hepatol.* 2015 May-Jun;14(3):416-9. PMID: 25864224.
2. Schreml S, Szeimies RM, Vogt T, Landthaler M, Schroeder J, Babilas P. Cutaneous amyloidoses and systemic amyloidoses with cutaneous involvement. *Eur J Dermatol.* 2010 Mar-Apr;20(2):152-60. doi: 10.1684/ejd.2010.0842. Epub 2010 Jan 14. PMID: 20071301.
3. Tafarel JR, Lemos LB, Oliveira PM, Lanzoni VP, Ferraz ML. Cutaneous amyloidosis associated with primary biliary cirrhosis. *Eur J Gastroenterol Hepatol.* 2007 Jul;19(7):603-5. doi: 10.1097/MEG.0b013e32811ec024. PMID: 17556910.
4. Chia B, Tan A, Tey HL. Primary localized cutaneous amyloidosis: association with atopic dermatitis. *J Eur Acad Dermatol Venereol.* 2014 Jun;28(6):810-3. doi: 10.1111/jdv.12144. Epub 2013 Mar 12. PMID: 23489336.
5. Breathnach SM. Amyloid and amyloidosis. *J Am Acad Dermatol.* 1988 Jan;18(1 Pt 1):1-16. doi: 10.1016/s0190-9622(88)70001-8. PMID: 3279077.
6. Chalifoux SL, Konyn PG, Choi G, Saab S. Extrahepatic Manifestations of Primary Biliary Cholangitis. Gut Liver. 2017 Nov 15;11(6):771-780. doi: 10.5009/gnl16365. PMID: 28292174; PMCID: PMC5669592.
7. Gershwin ME, Mackay IR. Primary biliary cirrhosis: paradigm or paradox for autoimmunity. *Gastroenterology.* 1991;100:822–833. doi: 10.1016/0016-5085(91)80033-6.
8. Carey EJ, Ali AH, Lindor KD. Primary biliary cirrhosis. *Lancet.* 2015;386:1565–1575. doi: 10.1016/S0140-6736(15)00154-3
9. Azón-Masoliver A. Widespread primary localized cutaneous amyloidosis (macular form) associated with systemic sclerosis. *Br J Dermatol* 1995; 132:65–67.
10. Ollague W, Ollague J, Ferretti H. Epidemiology of primary cutaneous amyloidoses in South America. *Clin Dermatol* 1990; 8: 25-9.
11. Lin MW, Lee DD, Lin CH, Huang CY, Wong CK, Chang YT, et al. Suggestive linkage of familial primary cutaneous amyloidosis to a locus on chromosome 1q23. *Br J Dermatol* 2005; 152: 29–36.
12. Dahdah MJ, Kurban M, Kibbi AG, Ghosn S. Primary localized cutaneous amyloidosis: a sign of immune dysregulation? *Int J Dermatol* 2009; 48: 419-21.
13. Kamada N, Yoneyama K, Togawa Y, Suehiro K, Shinkai H, Yoko-ta M, Matsuda K, et al. Toxic epidermal necrolysis with severe hyperbilirubinemia: complete re-epithelialization after bilirubin reduction therapies. *J Dermatol* 2010; 37: 534-6.
14. Fujiwara K, Kono T, Ishii M, Goto H, Nishigushi S, Kawada N, et al. Primary localized cutaneous amyloidosis associated with autoimmune cholangitis. *Int J Dermatol* 2000; 39:768
15. Ladizinski B, Lee KC. Lichen amyloidosis. CMAJ. 2014 Apr 15;186(7):532. doi: 10.1503/cmaj.130698. Epub 2013 Oct 15. PMID: 24130236; PMCID: PMC3986318.
16. Tanaka A, Arita K, Lai-Cheong JE, Palisson F, Hide M, McGrath JA. New insight into mechanisms of pruritus from molecular studies on familial primary localized cutaneous amyloidosis. *Br J Dermatol.* 2009 Dec;161(6):1217-24. doi: 10.1111/j.1365-2133.2009.09311.x. Epub 2009 May 26. PMID: 19663869.

Conflict of interest
NONE DECLARED

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