

Macular Amyloidosis: A Case Report

Jaka Radoš, Sandra Marinović Kulišić, Jasna Lipozenčić, Dragomir Budimčić, Davorin Lončarić

University Department of Dermatology and Venereology, Zagreb University Hospital Center and School of Medicine, Zagreb, Croatia

Corresponding author:

Jaka Radoš, MD, MS
University Department of Dermatology
and Venereology
Zagreb University Hospital Center and
School of Medicine
Šalata 4
HR-10000 Zagreb
Croatia
sodarakaj@yahoo.com

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SUMMARY Macular amyloidosis is a major cause of skin pigmentation and a rare form of localized primary cutaneous amyloidosis in western countries, with a higher prevalence in Asia and South America. The etiopathogenesis of macular amyloidosis has not yet been fully clarified; a number of risk factors are involved, among them chronic friction in particular. A 54-year-old patient with macular amyloidosis is presented. The diagnosis of macular amyloidosis was based on history data on long-term persistence of the disorder, localized pruritus and constant scratching urge, grayish-brown pigmentation over the scapula, and detection of amyloid in histologic slides. Three-month tretinoin therapy resulted in pruritus alleviation, with no change in the appearance of hyperpigmentation. The exact incidence of macular amyloidosis in Croatia is not known, however, the issue appears to be underestimated or neglected in dermatology routine.

KEY WORDS: macular amyloidosis, primary localized cutaneous amyloidosis, friction, amyloid AK

INTRODUCTION

Macular amyloidosis is a localized, primary form of cutaneous amyloidosis, which has been rarely tackled in western countries, probably because of its rather low prevalence. Clinically, it manifests with characteristic, readily recognizable brownish pigmentation mostly on the upper back (1). The disorder has been mostly described in Asia and in South and Central America, in women aged 40-70 (1).

Amyloid AK is exclusively accumulated in the skin (2). It may be difficult to detect on hematoxylin-eosin stained histologic slides, thus requiring

additional testing by use of histologic or immunohistochemical methods, or electron microscopy (2). The etiopathogenesis of the disease remains obscure; however, most authors tend to associate its onset to some form of mechanical trauma, constant friction in particular (3-5). As amyloid deposits show high chemical resistance, all therapeutic approaches attempted to date have produced rather poor and only transient results (1).

We present a patient with a clinically characteristic manifestation of macular amyloidosis, with the diagnosis made on the basis of history data

on long-term duration of the disease, clinical appearance of lesions and amyloid detected by skin histology.

CASE REPORT

In May 2007, a 54-year-old man, otherwise healthy, presented to the Department outpatient clinic for dark skin pigmentation in the left scapular region. The pigmentation had developed 15 years before and gradually enlarged to the present size. The patient did not complain of any discomfort except for pruritus in the region that used to intensify with warm weather. He could not recollect any inflammation at the site in the past. Dermatologic examination showed a grayish-brown pigmented area of irregular shape, 20x15 cm in size, of indistinct margins on the skin over the left scapula and paravertebral region, with slightly reticular and ruffled surface (Fig. 1).

The patient complained of no discomforts or neurologic disturbances other than pruritus that made him rubbing every now and then the skin through the clothes or even scratching it with his nails. During the last year he was taking statins for elevated blood lipids. He denied any atopic disease, chronic disease, or similar lesions in his family history.

Diagnostic work-up revealed normal routine biochemistry findings except for elevated plasma triglycerides and cholesterol, normal electrophoresis and immunoelectrophoresis, normal urine finding, negative urinary Bence-Jones protein, negative stool parasites, normal thyroid function tests and normal serum calcitonin and adrenal gland hormone levels, whereas x-ray of the spine showed no degenerative changes.



Figure 1. Poorly delineated, hyperpigmented patches with slightly rippled and reticulated surfaces on the skin of the upper back.

Histologic slides showed mild enlargement of dermal papillae containing a homogeneous, amorphous material corresponding to amyloid (Fig. 2). The presence of amyloid was confirmed by histochemical Congo red stain, when amyloid stained light-red at the sites of accumulation. Melanophages and scant lymphohistiocytic infiltrate were found in papillary dermis.

The patient was recommended local application of retinoids (Zorac gel, 0.01%). At 3-month follow up visit, the lesion looked unchanged but the patient reported pruritus alleviation.

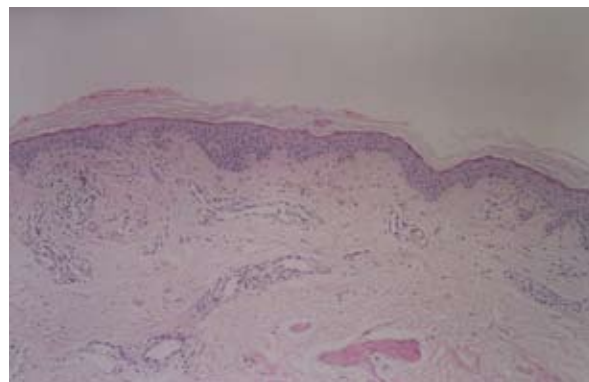


Figure 2. Circumscribed deposit of amyloid is present in superficial dermis. Hyaline material is barely distinguishable from collagen. The diagnosis may be easily missed. There are some melanophages in papillary dermis and scant lymphohistiocytic infiltrate (HE stain, original magnification X80).

DISCUSSION

Amyloidosis is a group of rare disorders characterized by the accumulation of fibrillar material (amyloid). Chemically, amyloid is not a uniform substance but a group of substances consisting of 16 different fibrillar proteins described to date (2). Primary cutaneous amyloidosis characterized by amyloid accumulation exclusively in the skin should be differentiated from systemic amyloidosis where amyloid is deposited in internal organs in addition to the skin (1,2). In primary cutaneous amyloidosis, mostly clinically represented by macular amyloidosis and lichen amyloidosis, amyloid AK originates from keratinocytes, i.e. from keratin intermediary filaments, as demonstrated by immunohistochemical studies (2,6). The presence of a typical clinical picture obviates the need of extensive diagnostic work-up to rule systemic amyloidosis out (7). In systemic amyloidosis, the precursor amyloid proteins are immunoglobulin light chains that are deposited in tissues in myeloproliferative diseases, multiple myeloma in particular

(2). In systemic amyloidosis associated with the presence of chronic diseases (e.g., rheumatoid arthritis, tuberculosis), the C-reactive protein-like amyloid AA produced from serum proteins is deposited in tissues (2). In systemic amyloidosis, when skin lesions suggestive of amyloidosis are absent, biopsy specimens are obtained from other sites (e.g., rectum, gingiva, abdominal subcutaneous fat or kidney) (7).

Amyloidogenesis in macular amyloidosis depends on a number of factors. Prolonged friction, atopy, itching, genetic predisposition, racial and familial factors, Epstein-Barr virus and environmental factors (humidity, temperature and light) have been reported as major etiological factors (8).

Most authors believe that localized trauma in the form of continuous friction, scratching or manipulation on taking bath or skin cleansing with the use of various gloves, sponges, brushes, plant stalks or leaves plays a role in the genesis of amyloid due to mechanical damage to keratinocytes or their apoptosis (3-5). It has been proposed that basal layer keratinocytes die due to apoptosis or release keratin bodies to the dermis, where they are lined with antikeratin antibodies. Upon being phagocytosed by macrophages, they are believed to take active part in the formation of AK, transforming proteins with previously α structure into β pattern proteins (2-5). The disease has been described by various terms such as friction melanosis, friction amyloidosis, macular amyloidosis and towel melanosis (5); all these authors emphasize the role of mechanical trauma in the disease onset. In their epidemiological study, Rasi *et al.* found no association between macular amyloidosis and friction but postulated the role of female hormones in the disease genesis because of its predominant occurrence in young age females (9). The association of macular amyloidosis with multiple endocrine neoplasia syndrome 2 (MEN2) was observed in some families (10). This hereditary syndrome includes some endocrine manifestations such as medullary thyroid carcinoma and pheochromocytoma (10). On differential diagnosis, it may be difficult to discriminate residual hyperpigmentation and macular amyloidosis, or some forms of circumscribed atopic dermatitis, which may occasionally precede the onset of macular amyloidosis (1). In these conditions, not only amyloid but also melanophages and scant inflammatory infiltration are found in histologic slides (2). Differentiation of notalgia paresthetica and macular amyloidosis may also pose a problem. In the former, sensory neuropathy usually induced by spinal nerve com-

pression due to degenerative changes of the spine (which results in hyperpigmentation of the skin in the dermatome innervated by the nerve involved) is regularly present in addition to hyperpigmentation on the back (11). Some authors consider notalgia paresthetica as a separate entity, whereas others believe that it is a transitory stage in the development of macular amyloidosis (1).

Therapeutic effects are only partial and short-lasting (transient) because amyloid is hard to dissolve (1). Attempts can be made with moderate strength corticosteroids by use of occlusive technique or intralesional application (1). There are reports on the beneficial effect of retinoids; however, data on long-term follow up are lacking (12). The mechanism of action of acitretin is not known. Retinoids are strong inducers of apoptosis and can also stimulate macrophages for phagocytosis and elimination of amyloid AK deposits. These two effects may reduce the formation of amyloid (12).

In case of severe itching, distractors (mentholate lotions or creams) and capsaicin (which is efficacious in notalgia paresthetica) can be administered (1). In clinical studies, the effect of topical dimethyl sulfoxide (DMSO) was assessed in patients with persistent and unbearable itching. The mechanism of action of DMSO is explained by blockade of the nerve or mediators released from mastocytes. The mechanisms proposed may prevent signal transfer in synapses to type C nerve fiber, thus causing interruption of the vicious circle of pruritus – amyloid deposition – pruritus (13). The opinions on therapeutic effects of DMSO are contradictory (13,14).

CONCLUSION

Macular amyloidosis is a rare disease in Europe, however, with a slightly higher prevalence in Mediterranean countries, as evidenced by individual reports by Italian (3,5) and German (15) authors. In Croatia, exact data on the incidence of macular amyloidosis are lacking. The issue may have been underestimated in clinical routine since discoloration can be primarily considered as a cosmetic problem unless associated with severe itching, thus the problem proceeds unrecognized or neglected by dermatologists. In case of severe itching, the disease poses a serious therapeutic problem and challenge. Additional studies are definitely needed in the field of the disease etiopathogenesis. This case report may hopefully stimulate further studies of this intriguing disease in Croatia as a Mediterranean country.

References

1. Braun Falco O, Plewig G, Wolff HH, Burgdorf WHC. Amyloidoses. In: *Ibidem. Dermatology*. Second, completely revised edition. Berlin: Springer-Verlag;2000. pp. 1278-88.
2. Weedon D. Cutaneous deposits. In: *Skin pathology*. Second edition. Edinburgh: Churchill Livingstone;2002. pp. 429-34.
3. Siragusa M, Cavallari V, Schepis C. Macular amyloidosis due to friction by a horsehair glove. *Dermatology* 2000;200:82-3.
4. Venkataram MN, Bhushnurmath SR, Muirhead DE, Al-Suwaid AR. Frictional amyloidosis: a study of 10 cases. *Austral J Dermatol* 2001;42:176-9.
5. Siragusa M, Ferri R, Cavallari V, Schepis C. Friction melanosis, friction amyloidosis, macular amyloidosis, towel melanosis: many names for the same clinical entity. *Eur J Dermatol* 2001;11:545-8.
6. Apaydin R, Gürbüz Y, Bayramgürler D, Müezzinoğlu B, Bilen N. Cytokeratin expression in lichen amyloidosis and macular amyloidosis. *JEADV* 2004;18:305-9.
7. Steciuk A, Domp Martin A, Troussard X, Veneuil L, Macro M, Comoz F, *et al.* Cutaneous amyloidosis and possible association with systemic amyloidosis. *Int J Dermatol* 2002;41:127-32.
8. Eswaramoorthy V, Kaur I, Das A, Kumar B. Macular amyloidosis: etiological factors. *J Dermatol* 1999;26(5):305-10.
9. Rasi A, Khatami A, Javaheri SM. Macular amyloidosis: an assessment of prevalence, sex, and age. *Int J Dermatol* 2004;43:898-9.
10. Baykal C, Buyukbabani N, Boztepe H, Barahmani N, Yazganoglu KD. Multiple cutaneous neuromas and macular amyloidosis associated with medullary thyroid carcinoma. *J Am Acad Dermatol* 2007;56:533-7.
11. Şavk E, Şavk Ö, Bolukbasi O, Culhaci N, Dikiçioğlu E, Karaman G, *et al.* Notalgia paresthetica: a study on pathogenesis. *Int J Dermatol* 2000;39:745-59.
12. Hernández-Núñez A, Daudén E, Vega de M, Fraga J, Aragues M, Garcia-Diez A. Widespread biphasic amyloidosis: response to acitretin. *Clin Exp Dermatol* 2001;26:256-9.
13. Özkaya-Bayazit E, Kavak A, Güngör H, Özarmagan G. Intermittent use of topical dimethyl sulfoxide in macular and papular amyloidosis. *Int J Dermatol* 1998;37:949-54.
14. Pandhi R, Kaur I, Kumar B. Lack of effect of dimethylsulphoxide in cutaneous amyloidosis. *J Dermatol Treat* 2002;13(1):11-4.
15. Abels C, Karrer S, Lanthaler M, Szeimes RM. Truss-induced macular amyloidosis. *Hautarzt* 2001;52(10 Pt 2):970-3.