Primary localised cutaneous amyloidosis – systematic review

Britta Kaltoft[1], Grethe Schmidt[1], Anne Falensteen Lauritzen[2] & Peter Gimsing[3]

ABSTRACT

INTRODUCTION: Amyloidosis is defined as extracellular deposits of heterogenic, misfolded proteins, amyloid fibrils, in various tissues. The aim of our study was to review the literature and to evaluate the risk of developing systemic amyloidosis (SA) and the risk of local recurrence of primary localised cutaneous amyloidosis (PLCA). The method of treatment was compared to the risk of local recurrence.

METHODS: A literature search produced 77 articles with localised cutaneous amyloidosis, 23 articles were excluded; thus, a total of 54 articles were included.

RESULTS: A total of 94 patients were included with a male:female ratio of 1.2:1.0. The median age was 57 years (range 24-87 years). The most common tumour localisation was in the head and neck region with a total of 38 lesions (34%), and 20 patients (22%) had two or more lesions in different locations. The nodular subtype was reported in 65 patients (69%). Only 29 patients received therapy with eight patients having two or more treatments (28%). Eight patients (9%) had local recurrence and all were nodular PLCA, which were mainly seen in males and localised in the face. One patient developed SA (1%); in fact, this was the only patient who was positive for monoclonal amyloid light chain amyloidosis by immunoelectrophoresis of the serum.

CONCLUSION: Our review suggests that PLCA is a benign disease that has a good prognosis and that it is associated with a low risk of developing SA (1%).The risk of developing local recurrence or developing new lesions was 9%, and no significant differences were found when compared to the primary treatment.

Amyloidosis is defined as extracellular deposits of heterogenic misfolding proteins, amyloid fibrils, in various tissues. The condition is classified either based on localisation or biochemical structure [1-4].

When based on localisation, the disease is classified into four groups: localised versus systemic and primary versus secondary. A fifth group comprises some rare hereditary forms of amyloidosis. Three primary localised subtypes have been described in the skin: macular, lichen and nodular. In this article, we focus on primary localised cutaneous amyloidosis (PLCA) [1, 5].

The biochemical structure of the involved proteins includes amyloid light chain (AL) amyloidosis, amyloid A, transthyretin (TTR) and beta-2-microglobulin (β_2M). The two latter are associated with a somewhat different clinical presentation (e.g. TTR often involves the nerves and hearth and β_2M tendons and joints). When classified based on their biochemical structure, the most common forms of amyloidosis are immunoglobulin AL amyloidosis, also known as primary systemic amyloidosis, and serum amyloid A secondary amyloidosis which accounts for more than 90% of the cases of systemic amyloidosis (SA) [6].

The aim of our study was to review the literature and to evaluate the risk of development of SA and the risk of local recurrence of PLCA. Furthermore, local recurrence was evaluated according to the method of primary treatment.

METHODS

A literature search was performed by the author at PubMed using the terms “localised amyloidosis” and adopting a broad search strategy on all patient series (limitations “English”, “Abstract available” and “Human”). All abstracts were evaluated for inclusion. This resulted in 185 articles of which 77 included patients with amyloidosis localised to the skin. We evaluated the full length of 77 articles and a total of 23 articles were excluded (three could not be obtained, six were reviews with insufficient patient data, seven articles were on secondary localised amyloidosis or SA, seven were excluded for other reasons). This left a total of 54 articles for the analysis.

The following data were registered: number of patients, gender (male/female), age (years), localisation(s) (head/neck, trunk, genitalia, arms, legs, no information available), subtype (nodular, macular, lichen, mixed, no information available), ethnic origin (Asian, Indian, Caucasian, African, no information available), other diseases, treatment (excision, dermabratio, cryotherapy, laser evaporation, steroid treatment, other medical treatment, oncological treatment), tested for SA (yes, no, no information available), tested for AL amyloidosis (yes, no, no information available), local recurrence (yes, no, no information available) and follow up (months) (**Table 1**).

RESULTS

A total of 94 patients were included from the 54 articles

SYSTEMATIC REVIEW

1) Department of Plastic Surgery, Breast Surgery and Burns Treatment, Rigshospitalet
2) Department of Pathology, Herlev Hospital
3) Department of Haematology, Rigshospitalet

Dan Med J 2013;60(11):A4727

TABLE 1

Demographic data and tumour characteristics.

Articles/patients, n	54/94
Male/female, n	52/42
Age, years, median (range)	57 (24-87)
Localization	
Lesions, n (%)	
Head and neck	38 (34)
Trunk	26 (23)
Genitalia	9 (8)
Upper extremity	15 (13)
Lower extremity	24 (22)
≥ 2 localizations, n (%)	20 (22)
No information available, n (%)	5 (5)
Subtypes	
Lesions, n (%)	
Nodular	65 (69)
Lichen	7 (7)
Macular	4 (5)
Mixed	7 (7)
No information available	11 (12)
Ethnic origin, n	
Asian	
Nodular	12
Macular/lichen/mixed	10
No information available	1
Total	23
Caucasian	
Nodular	15
Macular/lichen/mixed	3
No information available	3
Total	21
Indian	
Nodular	1
Mixed	2
Total	3
African	
No information available	1
Total	1
No information available about ethnicity, total	46

TABLE 2

Methods of treatment. The values are n (%).

Treatment, total	
Excision	15 (41)
Dermabratio	6 (15)
Cryotherapy	1 (3)
Laser evaporation	4 (4)
Steroids	6 (15)
Other medical treatment	2 (5)
Radiation or chemotherapy	2 (5)
Psoralen and ultraviolet A treatment	1 (3)
≥ 2 treatments per patient, total	8 (28)

TABLE 3

Immunoglobulin amyloid light chain (AL) amyloidosis: positive for AL amyloidosis, total.

	Positive/ not tested, n
Blood	1/13
Urine	0/57
Immunohistochemistry	19/48
Bone marrow	0/71

with a ratio of 1.2:1.0 (male:female). The median age was 57 years (range 24-87 years) (Table 1).

The most common tumour localisation was the head and neck region with a total of 38 lesions (34%), and 20 patients (22%) had two or more lesions in different locations (Table 1).

The nodular subtype was reported in 65 patients (69%), and no information about subtype was available for 11 patients (12%) (Table 1).

In patients of Asian origin, 12 out of 23 had the nodular subtype and ten had either the macular, lichen or mixed subtype. Patients of Caucasian origin had a nodular subtype in 15 out of 21 cases, and three patients had either the macular, lichen or mixed subtype. No information about ethnicity was available for 46 patients. The other minor ethnical groups are listed in Table 1.

Three patients had Kimura's disease which can be seen as subdermal lesions in the head and neck caused by chronic inflammation. Another six patients had diabetes, four had one or several symptoms of CREST syndrome (calcinosis, Raynaud's phenomenon, dysfunction of the oesophagus, sclerodactyly, telangiectasia), four had or were later diagnosed with Sjögren's syndrome and one had a low-grade malignant lymphoma.

In total, 29 patients received therapy with eight patients having two or more treatments (28%). The remaining 53 patients were only observed and 12 patients had no information available regarding treatment or observation (**Table 2**).

Only 48 out of 94 patients had follow-up data with a median follow-up period of 72 months (range 10-288 months).

Tests for AL amyloidosis were positive by immunohistochemistry of the biopsy in 19 patients and one patient was positive by immunoelectrophoresis of the serum. In many cases, the data on AL amyloidosis were insufficient (**Table 3**).

Eight patients had local recurrence or recurrent disease (9%). Three of these patients had recurrent disease distant from the primary site, including one patient with local recurrence in the same region as the primary lesion and rectal biopsies containing amyloid. The second pa-

tient had amyloid deposits in the prostate gland and larynx, and the third had PLCA in a region distant from the primary site. The time of recurrence was verified from six months to 23 years after the diagnosis. Seven out of eight patients were males. The median age was 54.5 years (range 35-75 years). All the lesions were of the nodular subtypes. Five were localised in the face, one in the genital area, one at the upper extremity and one had an unknown location. In half of the patients, the primary tumour was not or only partly removed. Five were positive for AL amyloidosis by immunohistochemistry of the biopsy; no information regarding AL amyloidosis was available for the remaining cases.

One patient developed clinical signs of SA (1%); in fact, this was the only patient who was positive for AL amyloidosis by immunoelectrophoresis of the serum. In total, nine patients were not tested for SA (10%).

DISCUSSION

Our review of the literature found a male:female ratio of 1.2:1.0 with a median age of 57 years. Previous studies have reported that the disease is predominantly found in females in the sixth and seven decades, but another study found that men and women are equally affected and that the disease predominates in middle-aged patients [7].

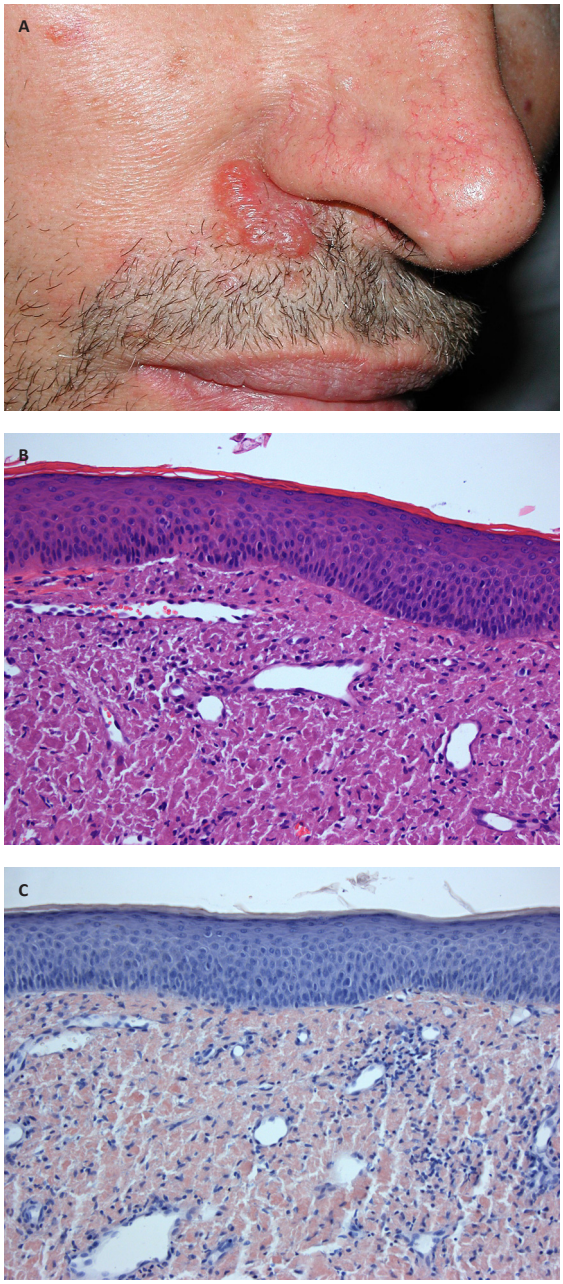
The pathogenesis of the nodular subtype is different from that of the lichen and the macular subtypes, and the macular subtype is thought to be a variant of the lichen subtype [5]. In our study, 65% of the patients had the nodular subtype. This does not necessarily indicate that this is the most common subtype, but it is the most interesting one as far as the development of SA is concerned, which may explain the nodular predominance in our study.

The nodular subtype can be seen as one or several noduli, and the epidermis above the tumour can become atrophic and simulate bullae. Telangiectasia can be seen and may result in bleeding (**Figure 1**A). By histopathology, large deposits of amyloid are located in the dermis and subcutaneously with accentuation around the vessels and adnexa [1, 5]. The nodular subtype is not positive when tested for anti-keratin antibodies (Figure 1B and C) [1]. Monoclonal plasma cells can often be seen. The pathogenesis is not fully understood, but the monoclonal light-chain immunoglobulin from the plasma cells could indicate a local dysfunction of the plasma cells [1, 8].

The lichen and the macular subtypes are uniform on histopathology. Lichen is often seen as an itching, firm, painless and hyperkeratotic lesion with a yellow-brown appearance. The macular subtype is slightly less visible. On histopathology, the epithelium is focally thickened and the amyloid deposits are found in small globuli in the underlying dermis. The pathogenesis, also known as the "keratinocyte-theory", is believed to be caused by inappropriate apoptosis of the keratinocytes with a filamentous "degeneration", which can be seen as amyloid [2]. The lichen and the macular subtypes are both positive on immunohistochemistry aimed at detecting anti-

FIGURE 1

A. Clinical photography of nodular primary localised cutaneous amyloidosis localised at the right nasolabial fold. **B.** Skin biopsy from the patient seen in the clinical photo with subepithelial nodular amyloid deposits (haematoxylin eosin staining × 20). **C.** Skin biopsy from the patient seen in the clinical photo with subepithelial nodular amyloid deposits (Congo red × 20).



FACTS

Primary localised cutaneous amyloidosis (PLCA) is a benign disease with a good prognosis if there is no evidence of systemic amyloidosis (SA) at the time of the diagnosis.

In our study of the literature, only one patient developed SA (1%).

We found a 9% risk of local recurrence with a predominance among males with a facial lesion of the nodular subtype.

All patients with PLCA should be referred to a Department of Haematology for examination of amyloid light chain amyloidosis and SA.

bodies against different keratin subtypes, in particular CK5. Prior trauma, rubbing and scratching of the skin is often confirmed by the patient. In our literature search, patients of Asian origin had a higher rate of the lichen and the macular subtypes than patients of Caucasian origin, which has been suggested to be associated with a more frequent use of nylon cloth for exfoliation of the skin (Table 1) [9, 10].

We found a risk of 9% for local recurrence with a predominance of males with a facial lesion of the nodular subtype [1, 11-16]. We found no previous studies that had estimated the risk of local recurrence. Although our data might be biased by our insufficient follow-up data, which involves a potential risk of estimating a higher or a lower local recurrence, we still believe that the risk of local recurrence is low. Although some studies have recommended CO2 laser evaporation [11], we observed no correlation between the type of treatment and a potentially reduced risk of local recurrence (Table 2). The risk of morbidity and the risk of local recurrence should be taken into consideration before planning any treatment.

The presence of AL amyloidosis can be examined in the blood, urine, bone marrow and on immunohistochemistry stains for kappa and lambda light chains in the biopsy. Many of the studies had no or insufficient data concerning AL amyloidosis (Table 3). Examination for AL amyloidosis is important; in fact, the only patient positive for AL amyloidosis by immunoelectrophoresis of the serum was diagnosed with SA and died shortly after [7]. However, the present literature study does not allow us to conclude that AL amyloidosis can be considered a predictive factor for development of SA or local recurrence.

The development of SA after the patient was diagnosed with PLCA has been reported in 7-50% of cases [5, 12]. SA has a poor prognosis and SA symptoms will often not show until the amyloid deposits involve many organs. Affection of the heart and the kidneys may be life-threatening, but early treatment of the patients can markedly decrease their mortality [3]. In our study, we found that patients with PLCA had a 1% risk of developing SA; however, our results were biased by potential lack of information and follow-up data. The present study indicates that PLCA only rarely develops into SA [7] if there are no clinical or laboratory evidence of SA at the time of the PLCA diagnosis.

CONCLUSION

Our review suggests that PLCA is a benign disease with a good prognosis that is associated with a low risk of developing SA. One patient (1%) developed SA; in fact, this was the only patient who tested positive for AL amyloidosis in the serum obtained by immunoelectrophoresis. The risk of developing local recurrence or developing new lesions was 9% and no significant differences were found when compared to the primary treatment.

We recommend that patients diagnosed with cutaneous amyloid deposits should be referred to a Department of Haematology for examination of AL amyloidosis and SA.

CORRESPONDENCE: *Britta Kaltoft,* Hostrups Have 46, 5. th., 1954 Frederiksberg C, Denmark. E-mail: E-mail: brittakaltoft@hotmail.com

ACCEPTED: 9 September 2013

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk.

LITERATURE

1. Borowicz J, Shama L, Miller R. Nodular cutaneous amyloidosis. Skin 2011;9:316-8.
2. Glenner GG. Amyloid deposits and amyloidosis. The beta-fibrilloses. Second of two parts. N Engl J Med 1980;302:1333-43.
3. Merlini G, Seldin DC, Gertz MA. Amyloidosis: Pathogenesis and new therapeutic options. J Clin Oncol 2011;29:1924-33.
4. Brambilla F, Lavatelli F, Silvestre DD et al. Reliable typing of systemic amyloidoses through proteomic analysis of subcutaneous adipose tissue. Blood 2012;119:1844-7.
5. Brownstein MH, Helwig EB. The cutaneous amyloidosis. Localized forms. Arch Derm 1970;102:8-19.
6. Magy-Bertrand N, Dupond JL Mauny F et al. Incidens of amyloidosis over 3 years: the AMYPRO study. Clin Exp Rheumatol 2008;26:409-11.
7. Moon AO, Calamia KT, Walsh JS. Nodular amyloidosis. Arch Dermatol 2003;139:1157-9.
8. Hagari Y, Mihara M, Konohana I et al. Nodular localized cutaneous amyloidosis: further demonstration of monoclonality of infiltration plasma cells in four additional Japanese patients. Br J Dermatol 1998;138:652-4.
9. Macsween RM, Saihan EM. Clin Exp Dermatol 1997;22:28-9.
10. Hashimoto K, Ito K, Taniguchi Y et al. Keratin in cutaneous amyloidosis. Clin Dermatol 1990;8:55-65.
11. Truhan AP, Garden JM, Roenigk HH. Nodular primary localized cutaneous amyloidosis: immunohistochemical evaluation and treatment with the carbon dioxide laser. J Am Acad Dermatol 1986;14:1058-62.
12. Woollons A, Black MM. Nodular localized primary cutaneous amyloidosis: a long term follow-up study. Br J Dermatol 2001;145:105-9.
13. Bart RS, Kopf AW. Tumor conference #56. Localized cutaneous nodular amyloidosis. J Dermatol Surg Oncol 1985;11:582-4.
14. Northcutt AD, Vanover MJ. Nodular cutaneous amyloidosis involving the vulva. Case repost and literature review. Arch Dermatol 1985;121:518-21.
15. Trau H, Shpiro D, Schewash-Millet M et al. Nodular cutaneous amyloidosis. Am J Dermatopathol 1991;13:414-7.
16. Vestey JP, Tidman MJ, Mclaren KM. Primary nodular cutaneous amyloidosis – long term follow-up and treatment. Clin Exp Dermatol 1994;19:159-62.