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Original contribution

Localized amyloidosis of the vulva with and without vulvar intraepithelial neoplasia: report of a series☆,☆☆

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Summary Localized primary cutaneous amyloidosis is uncommon in Europe and North America and is infrequently reported in the English literature. The constituents of such deposits have not been previously examined; this series characterizes amyloid deposits in localized vulvar amyloidosis and their association with vulvar intraepithelial neoplasia. All biopsies and excisions of vulva over 18 months were reviewed. Cases with suspected amyloidosis were retrieved after institutional review board approval. Twenty cases mimicking amyloidosis were selected as controls. All study and control cases were stained with Congo red. Four Congo red–positive study cases were studied by liquid chromatography–tandem mass spectrometry. Of 27 Congo red–positive study cases, 25 were then examined by immunohistochemical stains with antibodies to cytokeratin 5 (CK5) and cytokeratin 14 (CK14). Of 149 cases reviewed, 26 localized and 1 systemic vulvar amyloidosis were identified. Liquid chromatography–tandem mass spectrometry analysis of the deposits revealed unique peptide profile consistent with CK5 and CK14. Immunohistochemical staining with antibodies to CK5 and CK14 also detected these components in the deposits. The vulvar deposit of systemic amyloidosis consisted of amyloid light chain (λ)–type amyloid deposit. All control cases were negative for Congo red. Keratin-associated amyloid materials (CK5 and CK14) were found to be unique in localized vulvar amyloidosis. Leakage of keratins from the basal layer of the epithelium into the superficial dermis may have been the possible source of the deposits. It appears to be associated with both high-grade and low-grade vulvar intraepithelial neoplasias and, rarely, lichen sclerosus, seborrheic keratosis, and benign vulvar skin.

1. Introduction

Primary cutaneous amyloidosis is characterized by the amyloid deposition predominantly in the papillary dermis in the absence of systemic amyloidosis. Although common in south east Asia including Japan and Taiwan [1], it is uncommon in Europe and North America. Localized vulvar amyloidosis is infrequently reported in the English literature. Most available reports in the literature are based on a single case or, at most, handful of cases.

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Localized cutaneous amyloidosis has been described in association with a spectrum of malignant and benign lesions, including basal cell carcinoma, discoid lupus erythematosus, and cellular dermatofibroma [2]. Various other body sites have also been reported to show localized amyloidosis, for example, lungs [3], larynx [4], urinary bladder [5], tongue [6], and eye [7].

It has been speculated that most of the deposits are derived from keratin epithelial elements. Electron microscopy of the deposits also suggested keratin-derived materials [8]. Gondo et al [9] described the electron microscopic features of localized amyloid deposits associated with squamous cell carcinoma to be slightly whorled fibrils, measuring 7 to 10 nm in width. The authors suggested that the deposits may have been derived from the degradation of these whorled fibrils. An acantholytic variant of well-differentiated squamous cell carcinoma of the uterine cervix with amyloid deposition is also reported in the literature. Amyloid deposits mimicking giant condyloma have been described [10,11]. Northcutt and Vanover [12] reported a case of vulvar amyloidosis that recurred after 6 years. The lesion was ulcerated and had brisk plasma cell infiltration with numerous Russell bodies. The amyloid was thought to be derived from immunoglobulin light chain origin based on the presence of abundant plasma cells [12]. No attempts were made to further characterize the deposits in that study.

The deposits of localized cutaneous amyloidosis, especially in the female lower genital tract, although thought to be cytokeratins, were never studied by liquid chromatography–tandem mass spectrometry (LC-MS/MS). The current study was undertaken to identify the constituents of the amyloid deposits in the localized cutaneous amyloidosis of vulva, with and without vulvar intraepithelial lesion.

2. Materials and methods

All vulvar biopsies and excisions done for inflammatory, benign, and/or malignant lesions from January 1, 2012, to June 30, 2013, were reviewed. All the cases of suspected amyloidosis were retrieved after institutional review board approval.

All the hematoxylin and eosin–stained slides were reviewed by 1 pathologist (M.R.Q.) for the presence of amyloid deposits, and identified cases were confirmed by a second pathologist (W.D.L., C.J.S., or R.A.S.). The associated lesions such as vulvar carcinoma, low-grade or high-grade intraepithelial lesion, and lichen sclerosis were noted. Unique epidermal morphological changes when present were also recorded.

Twenty cases mimicking amyloidosis on hematoxylin and eosin stains were selected as controls. All study and control cases were stained with Congo red. Four Congo red–positive cases (3 localized and 1 systemic) were studied by LC-MS/MS. LC-MS/MS was performed at Mayo Medical Laboratories, Mayo Clinic, Rochester, MN. All Congo red–positive and 5 Congo red–negative control cases were then studied by immunohistochemistry using antibodies to cytokeratin 5 (CK5) and cytokeratin 14 (CK14) (Cell Marque, Rocklin, CA; CK5 [EP 16014, cat no. 305-R-18], CK14 [LL 002, cat no. 314-M-18]). The immunohistochemical staining was done by Dako Autostainer (Ft. Collins, CO) using manufacturer's instruction, and appropriate positive controls were run with each batch of staining.

3. Results

A total of 149 cases were reviewed, and 27 incidental cases, 26 localized and 1 vulvar deposits of a systemic amyloidosis, were identified. Of these 27 cases, 6 cases were invasive squamous cell carcinoma, 17 cases of high-grade vulvar intraepithelial neoplasia (VIN 3), 1 case of low-grade vulvar intraepithelial neoplasia (VIN 1), 1 case of seborrheic keratosis, and 2 cases of squamous hyperplasia. Of 27 cases, 2 were consultation cases, and remaining cases were in-house cases. All 27 cases were stained appropriately with Congo red and polarization. No Congo red–positive deposits were identified in any of the 20 control cases.

Immunohistochemical staining with antibodies to CK5 and CK14 were done on 25 cases, where adequate tissue was available in the paraffin block for staining, and the findings are tabulated in Table 1. Of 27 study cases, 2 did not have adequate material in the paraffin block for further staining. No CK5 and CK14 components were identified in the vulvar deposits of the systemic case in this series. Keratin immunohistochemical staining (CK5 and CK14) was also negative in all 5 control cases.

LC-MS/MS study of all 3 localized amyloidosis cases identified unique peptide profile consistent with keratin-associated amyloid deposition (CK5 and CK14). In addition, serum amyloid P components, apolipoprotein E, and apolipoprotein A4 were also identified in 2 cases. LC-MS/MS study of vulvar deposit of the only systemic amyloidosis yielded amyloid light chain (λ)–type amyloid. The keratin components were not detected in this systemic case. The findings of LC-MS/MS are tabulated in Table 2.

The age range and median age of the patients in this series were 38 to 96 years and 57.5 years, respectively.

Table 1 Immunohistochemical staining results of CK5 and CK14

	n	Types of deposit	
		CK5	CK14
Total no. of cases	25		
Localized Congo red positive	24		
With VIN	22	17	10
Without VIN	2	2	2
Systemic amyloidosis	1	0	0
With VIN	0	n/a	n/a
Without VIN	1	0	0

Abbreviations: VIN, vulvar intraepithelial neoplasia; n/a, not applicable.