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A case of high-grade vulvar dysplasia with underlying spherules of amyloid deposition

Christopher P Julien, John Ekledaus, Ihab Lamzabi

ABSTRACT

Introduction: High-grade vulvar intraepithelial neoplasia (VIN3) is a common pathologic diagnosis. Usually, the lesions are associated with human papillomavirus (HPV), as demonstrated by block positivity on p16 staining. The lesions are not typically associated with amyloid deposition. It is even more rare to find amyloid spherules associated with high-grade vulvar dysplasia. The clinicopathologic significance of the amyloid spherules is unclear. Case Report: In this article, we discuss a case of a 59-year-old female with VIN3-associated underlying amyloid spherules that are present primarily only where there is high-grade dysplasia, and absent in other portions of the specimen. The patient of our study did not have a history of amyloidosis, and the lesion represented the only area of known amyloid deposition in this patient. Conclusion: These findings support the association between amyloid deposition and HPV-related cases of high-grade VIN. We postulate that the presence of high-grade dysplasia was the causative factor of the amyloid deposition in this case.

Keywords: Amyloid, Congo red, High-grade squamous intraepithelial neoplasia, High-grade vulvar intraepithelial neoplasia, Human papillomavirus, Localized cutaneous amyloidosis, Spherule, VIN3, Vulvar dysplasia

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INTRODUCTION

Squamous neoplasia of the vulva is a common pathologic occurrence. It is now appreciated that squamous intraepithelial neoplasia can be subclassified into HPV-associated and HPV-independent forms, which differ with respect to etiology, age at diagnosis, natural history, and morphology. In North America, most preinvasive lesions are associated with HPV [1]. Localized primary cutaneous amyloidosis of the vulva, on the other hand, is uncommon in Europe and North America and is infrequently reported in the English language literature [2]. Localized cutaneous amyloidosis (LCA) of the vulva has been described in association with a spectrum of malignant and benign lesions, including VINs, lichen sclerosus, seborrheic keratosis, and benign vulvar skin [2] in a single case series in which 26 cases had localized amyloidosis and 1 case had systemic vulvar amyloidosis. Spherule-like amyloid deposition has not been previously reported in the vulva, nor in association with vulvar intraepithelial neoplasm (VIN).

CASE REPORT

The patient was a 59-year-old female, G2P1 (one prior vaginal delivery) with a history of VIN2 diagnosed

on a prior vulvar biopsy. Her medical history was also remarkable for breast cancer status post right lumpectomy and lymph node biopsy 10 years ago. She was treated with radiation therapy, Tamoxifen for one year, and Anastrozole for five years, which was completed four years ago. In 2011 and 2012, she had a thickened endometrium on imaging, which prompted endometrial and endocervical sampling with features suggestive of endometrial and endocervical polyps in 2011. In 2014, multiple small-scattered condylomata were noted on physical examination. Human papillomavirus testing at that time was negative. In September 2018, she had a biopsy that was read as VIN2.

A vulvectomy was performed on October 2018 for management of the patient's high-grade squamous intraepithelial neoplasia. The vulva was submitted in three specimens. The skin had an irregular surface with multiple tan-colored, raised, fleshy plaques ranging from 0.6 to 1.1 cm in largest dimension. The specimen was entirely submitted.

Microscopic evaluation of the specimens revealed high-grade squamous intraepithelial neoplasia (VIN2 and VIN3) with spherule-like deposition of amyloid (Figures 1D, 2A, and 2B). The amyloid deposition consisted of spherules resembling corpora amylacea. The amyloid exhibited a band-like dermal distribution (including the papillary dermis) (Figure 1A). A special stain for Congo red confirmed that the deposition is amyloid (Figure 1B and C). Immunostain of amyloid P (AP) and immunohistochemical stain for pan-cytokeratin (PANCK) was positive while the immunostain for amyloid AA was negative. Immunohistochemical stains with adequate controls demonstrated the dysplastic epithelium to have block-like positivity for p16 and Ki-67 was increased, supporting the diagnosis of HPV-associated VIN and high-grade squamous intraepithelial lesion.

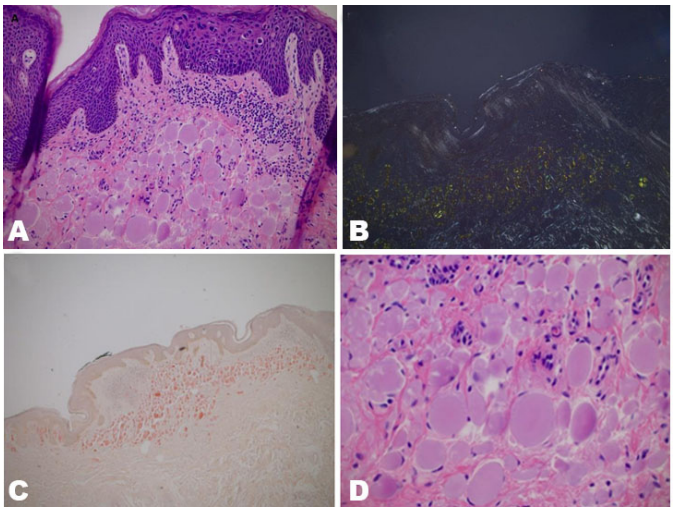

Figure 1: (A) Band-like dermal distribution of amyloid spherules; (B) Apple-green birefringence on Congo red immunostain; (C) Positive Congo red immunostain; (D) High power image of the amyloid spherules.

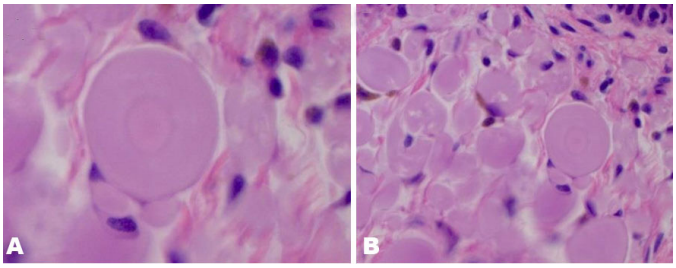

Figure 2: (A) Additional high power image of an amyloid spherule; (B) Additional high power image of multiple amyloid spherules.

DISCUSSION

The association between HPV infection and amyloid deposition has been previously studied. It is known that abundant E4 protein assembles into amyloid fibrils that disrupt keratin structure and compromise the normal assembly of the cornified envelope [3]. It has been postulated that E4 amyloid fibers may contribute to virion release and infectivity in the upper layers of the epithelium [3]. It is known that E4 self-association allows the protein to form structures resembling amyloid fibers, which is critical in the pathogenesis of HPV [4]. Researchers have even performed structural analysis which revealed an amyloid form of the HPV type 16 E1×E4 protein and provided a molecular basis for its accumulation [5] (N-terminal deletion results in the assembly of the 16E1×E4 protein into ordered amyloid-like fibrils). These findings represent a growing body of literature that is bridging the gap between localized amyloid deposition and HPV infection.

Localized cutaneous amyloidosis is a condition characterized by the deposition of amyloid or amyloid-like proteins in the dermis. Amyloid is defined as *in vivo* deposited material characterized by an amorphous eosinophilic appearance on hematoxylin and eosin staining. It is classified chemically. All types of amyloid consist of one major fibrillary protein that defines the type of amyloid. Amyloidosis is referred by AL in which the fibril protein is an immunoglobulin light chain or light chain fragment. In AA amyloid, the "A" protein is a normal-sequence apo-SAA (serum amyloid A protein), which is an acute phase reactant produced mainly in the liver in response to certain cytokines [6]. The AP component is a nonfibrillar normal plasma protein that is common to all forms of amyloid. Regardless of the protein precursor of amyloid fibrils in the different potential clinical scenarios, all amyloid deposits always contain abundant serum AP. Serum amyloid P binds avidly but reversibly to all types of amyloid fibrils and is thus specifically concentrated in all amyloid deposits [7, 8].

Amyloid spherules are a rare finding but have also been previously described. Notably, spherical amyloid is identified in the squash smear preparation of a patient with a pituitary prolactinoma [9]. Spherical amyloid aggregates have also been found to be neurotoxic, and may play a role in the neurodegeneration in Alzheimer's

disease [10]. However, to the best of our knowledge, it has not been described involving or in association with HPV-related lesions.

Localized cutaneous amyloidosis encompasses several conditions characterized by amyloid deposition, including but not limited to localized primary cutaneous amyloidosis of the vulva [11]. Primary cutaneous amyloidosis of the vulva is an entity that is very poorly described and understood in the English language literature. The only study that attempted to characterize the association between amyloid deposits in localized vulvar amyloidosis and their association with VIN concluded that the amyloid deposition appears to be associated with both high- and low-grade VINs. Like our case, these cases of amyloid deposition exhibited Congo red positivity. Our case also demonstrated block-like positivity for p16. Ki-67 was increased, supporting the diagnosis of HPV-associated VIN and high-grade squamous intraepithelial lesion. The immunostain for AP was positive while the immunostain for amyloid AA was negative. It is unclear (and unstudied) as to whether or not amyloid deposition is a causative factor in the development of high-grade VIN or is a consequence of the VIN, or if it plays a role in its pathogenesis. This rare and poorly studied association merits further research in order to provide additional insight on the nature of both LCA and high grade VIN.

CONCLUSION

In conclusion, spherule-like amyloid deposition has not been previously described in the vulva. However, localized amyloid deposition in the vulva has been seen in association with various benign and malignant lesions, including intraepithelial neoplasias. The full clinical significance of this finding is not certain at this time. We postulate that the presence of high-grade intraepithelial neoplasia is a causative factor in the formation of these amyloid deposits. Further research to elucidate the pathophysiology of these findings would be helpful in preventing the formation of these deposits and associated complications.

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Author Contributions

Christopher P Julien – Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

John Ekledaus – Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Ihab Lamzabi – Conception of the work, Design of the work, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The guarantor of submission is Ihab Lamzabi, MD.

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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