Epidermodysplasia verruciformis in Mohs micrographic surgery

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Key words: EDV; epidermodysplasia verruciformis; Mohs; SCC; squamous cell carcinoma.

Epidermodysplasia verruciformis (EDV) is a rare inherited or acquired dermatosis associated with an increased risk of squamous cell carcinoma (SCC).[1] We describe, for the first time to our knowledge, its frozen section pathologic characteristics and specific benefits of the use of Mohs micrographic surgery (MMS) in its setting.

EDV is characterized by an abnormal susceptibility to β-genotype human papillomavirus (HPV) infections causing persistent flat warts or pityriasis versicolor-like lesions with a tendency to be widespread over the body.[1] Approximately 75% of EDV patients have a homozygous inactivating mutation in *TMC6 (EVER1)* and *TMC8 (EVER2)*, creating susceptibility to HPV, notably the oncogenic subtypes HPV-5 and HPV-8, which increase the risks of keratinocyte atypia and SCC.[1] Tumors arising from EDV lesions are numerous and evolve progressively starting in childhood or early adolescence, eventually leading to the formation of nonmelanoma skin cancer, predominantly SCC, in 30% to 70% of patients in the fourth or fifth decade of life.[1,2] "Acquired EDV" is a term used to describe an EDV-like phenotype in immunocompromised hosts with defective cell-mediated immunity.[1]

Relevant publications indexed in electronic databases (PubMed, Embase, Web of Science, and Cochrane Library) between inception of the database and June 19, 2021, were searched using permutations of the terms "EDV," "epidermodysplasia verruciformis," "Mohs," "micrographic," and "frozen." The search revealed that EDV characteristics in MMS frozen sections have not been previously documented. We discuss 2 cases of EDV and EDV-like histopathologic findings identified in MMS frozen sections. In addition to describing the frozen section pathologic characteristics of EDV compared with those found in permanent sections, we indicate the differential diagnoses of similar clear cell changes in frozen section pathology to avoid diagnostic pitfalls.

Abbreviations used:

EDV: epidermodysplasia verruciformis
HPV: human papillomavirus
MMS: Mohs micrographic surgery
SCC: squamous cell carcinoma

CASE 1

A 52-year-old Caucasian man with a history of HIV-associated EDV that began 15 years previously and a significant history of EDV-associated SCCs presented for MMS of an SCC on the dorsal surface of the hand. In addition to the SCC, his intraoperative MMS frozen sections included classic histopathologic findings for EDV: acanthosis, gentle undulation, a thick granular layer with pronounced basophilic keratinohyaline granules, and large keratinocytes with correspondingly large nuclei in the granular and spinous layers with abundant blue-gray cytoplasm (Fig 1). Also noted were foci of parakeratosis isolated to the areas above the abnormal keratinocytes.

CASE 2

An 84-year-old Caucasian immunocompetent man without known EDV risk factors and a history

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Funding sources: None.
IRB approval status: Not applicable.

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JAAD Case Reports 2021;16:41-3.
2352-5126

https://doi.org/10.1016/j.jdcr.2021.08.004

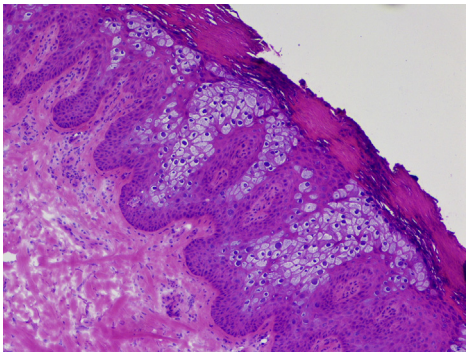

Fig 1. Frozen section histology of acquired epidermodysplasia verruciformis at ×10 magnification. Patient described in case 1 with known history of HIV and squamous cell carcinoma secondary to acquired epidermodysplasia verruciformis was being treated for a squamous cell carcinoma by Mohs micrographic surgery. Frozen section histology showing acanthosis, gentle undulation, a thick granular layer, and large epidermal keratinocytes with abundant blue-gray cytoplasm with large, deep purple, chunky granules and enlarged nuclei.

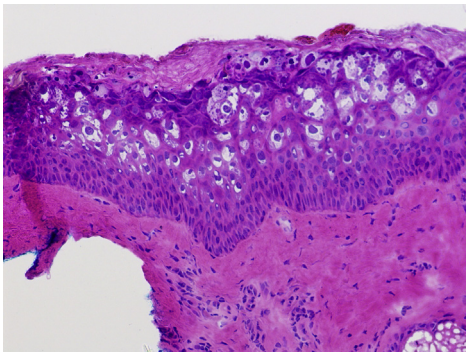

Fig 2. Frozen section histology of incidental epidermodysplasia verruciformis-like changes at ×20 magnification. Immunocompetent patient described in case 2 with incidental epidermodysplasia verruciformis-like changes while he was being treated for a squamous cell carcinoma by Mohs micrographic surgery. Frozen section histology revealed squamous cell carcinoma (not pictured), but also various foci of vacuolated epidermal cells with subtle blue-gray cytoplasm with purple granules and large nuclei.

of multiple nonmelanoma skin cancers presented for MMS of an SCC on the forehead. His intraoperative MMS frozen sections revealed atypical keratinocytes and keratin pearls consistent with SCC, but also various foci of vacuolated cells in the epidermis with subtle blue-gray cytoplasm with purple granules and large nuclei (Fig 2). Permanent sections submitted confirmed the frozen section findings of EDV-like changes (Fig 3).

DISCUSSION

Compared with permanent paraffin-embedded section histology (Fig 3), EDV and EDV-like changes observed in our laboratory on frozen section histology (Figs 1 and 2) appear to have a more subtle blue-gray cytoplasm. These findings may be even more challenging to interpret with other clear cell changes frequently observed in frozen sections. The differential diagnoses for the histologic changes found in EDV include other viral changes, Paget's disease, keratinocytic neoplasms with clear cell change, pagetoid spread SCC in situ, intraepithelial sebaceous neoplasms, and freeze artefact (Fig 4). A distinguishing characteristic is that the atypically enlarged clear cells in EDV are usually more present in the granular and spinous layers with enlarged, hyperchromatic, or centrally pyknotic nuclei. In comparison with case 1, the granules are more "dirty-appearing" and of different sizes; this could be related to differences in the granular layers themselves (ie, related to anatomic site) and/or HPV type.

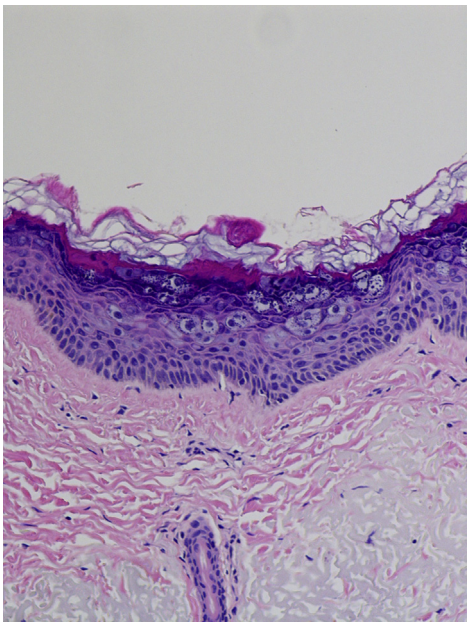

Fig 3. Permanent section histology of incidental epidermodysplasia verruciformis-like changes at ×20 magnification. Immunocompetent patient described in case 2 with incidental epidermodysplasia verruciformis-like changes while he was being treated for a squamous cell carcinoma by Mohs micrographic surgery. Permanent section histology of the same tissue as Fig 2, showing enlarged epidermal keratinocytes with blue-gray cytoplasm that is more obvious in permanent section than in frozen.

It is also important to remember that incidental EDV-like changes, like those found in case 2, can be found in patients without a known history of inherited or acquired EDV. This finding has been

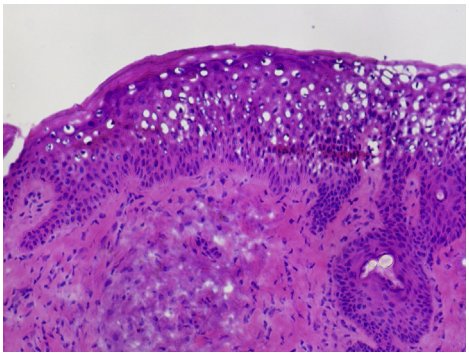

Fig 4. Frozen section histology of freeze artefact. Freeze artefact demonstrates numerous intraepidermal vacuoles on frozen histology mimicking clear cell change and making it a histologic differential diagnosis to epidermodysplasia verruciformis or epidermodysplasia verruciformis-like changes.

termed "EDV acanthoma" by dermatopathologists.[3] Our description of the frozen section histology of EDV in case 2 raises the possibility that subtle EDV-like changes in frozen sections may be commonly overlooked and compels consideration of the clinical relevance of these findings. A case series of incidental EDV found in benign biopsy specimens showed that 3 of 5 cases were positive for HPV-5, which could suggest that the patients were at increased risk of developing SCC; however, the investigators were not able to obtain the clinical history of skin cancers in these patients.[3] Nevertheless, EDV-HPV subtypes found in normal skin and eyebrow hairs have been linked to an increase in SCCs.[4,5]

There is no satisfactory treatment for congenital or acquired EDV to date. Topical and systemic retinoids, high-dose oral cimetidine, intralesional interferon, and cidofovir generally lead to recrudescent EDV warts. Electrodessication, cryotherapy, imiquimod, 5-fluorouracil, and podophyllotoxin, which are effective treatment options for common verrucae, have been applied to EDV lesions with inconsistent success.[1]

Although there is no reliable treatment for widespread EDV warts, we propose that MMS is a helpful modality in the setting of EDV. In addition to its inherent benefits of histologic confirmation of clearance while minimizing tissue loss and maximizing outcomes, MMS offers specific advantages in its context to EDV and EDV-like changes. First, it provides the advantage of recognizing the baseline EDV in constituent skin of patients with known EDV histories in order to differentiate cancer from baseline EDV. For example, the patient in case 1 had diffuse EDV in his intraoperative MMS frozen sections, which could make it challenging to differentiate clear cell keratinocyte carcinomas (eg, SCC in situ); however, MMS offered the advantage of seeing the baseline EDV in constituent skin. Additionally, when EDV-like changes are unexpectedly encountered, the Mohs micrographic surgeon can interpret the findings in the context of the patient and the histologic differential diagnoses we have described. We remind Mohs micrographic surgeons of EDV-like changes and encourage them to document them, even if small foci, as "EDV-like change" or "EDV acanthoma," as this may aid in studying these lesions in the future for any further implications.

The authors thank Benjamin Stoff, MD, dermatologist and dermatopathologist in the Department of Dermatology, Emory University School of Medicine, for his contributions to the histologic discussion.

Conflicts of interest

None disclosed.

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