JAPANESE DERMATOLOGICAL ASSOCIATION
THE JOURNAL OF DERMATOLOGY

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Journal:	*The Journal of Dermatology*
Manuscript ID	JDE-2020-1668.R1
Wiley - Manuscript type:	Letter to the Editor
Date Submitted by the Author:	n/a
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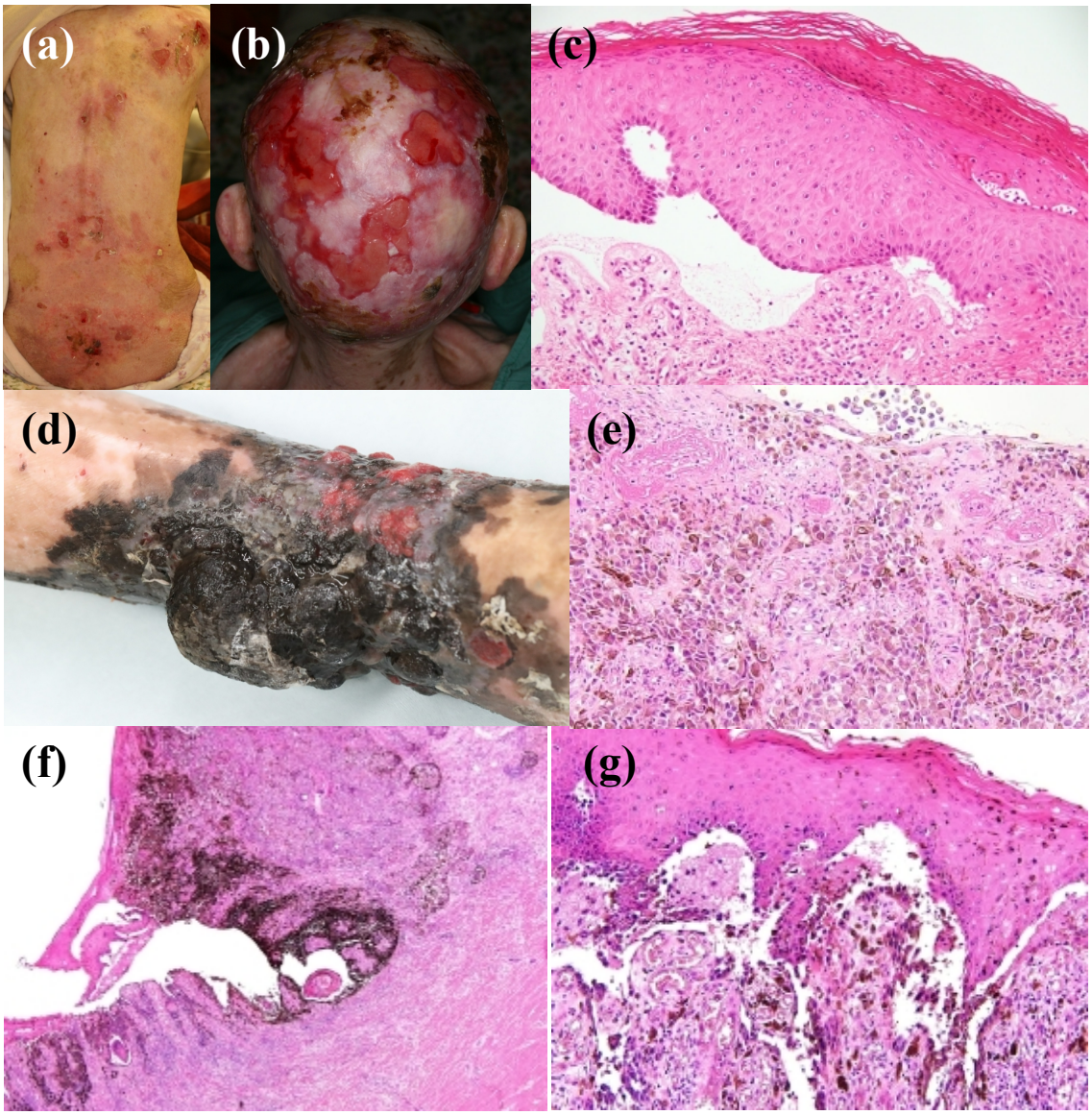
Keywords:	EB, JEB, intermediate JEB, epidermolysis bullosa nevi, collagen XVII, COL17A1
Abstract:	

Figure1



The Journal of Dermatology
Letters to the Editor

Cutaneous malignant melanoma in an elderly patient with intermediate junctional epidermolysis bullosa

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Acknowledgments: This work was supported by funding from the Japan Agency for Medical Research and Development (AMED) JP18ek0109295h0002 and 18ek0109281h0002 to M.A.
Conflicts of interest: None declared
Word count: ~~500~~ 496/500
References: 5/5
Figures: 1/1
Tables: 0

Dear Editor,

While an increased risk of squamous cell carcinoma has been well documented in patients with epidermolysis bullosa (EB),[1] malignant melanoma (MM) is not particularly common in any form of EB. ~~Junctional EB (JEB) is not considered to be associated with an increased risk of MM.[2] Here we report a case of JEB with cutaneous MM.~~

A 72-year-old woman had a recurrent history of blistering since birth. At her first visit, she had a large number of blisters, erosions/ulcers, ~~ulcers,~~ and scars on the whole body **(Fig. 1a, b)**. A skin ~~punch~~ biopsy ~~from the right thigh~~ revealed a subepidermal blister **(Fig. 1c)**. Ethical approval was obtained and all research was performed in accordance with the principles of the Declaration of Helsinki. Whole-exome sequencing ~~(WES) was performed for a definitive diagnosis. The WES~~ analysis found a previously unreported mutation, c.663G>A (p.Trp221*), and a previously reported mutation, c.3539dupC (p.Gly1181Argfs*61) in *COL17A1*. She was diagnosed with intermediate junctional EB (JEB).[3]

Physical examination also revealed a black node ~~of 5 x 10 cm~~ surrounded by dark pigmentation on the left lower leg. The lesion was noticed at a site of recurrent erosions/ulcers one year before her first visit **(Fig. 1d)**. ~~Computed tomography demonstrated swelling of the left inguinal lymph node, but no metastasis in other organs.~~ A skin biopsy from the node revealed sheets of dense infiltrates consisting of atypical epithelioid melanocytes with round, hyperchromatic nuclei **(Fig. 1e)**. ~~The patient was diagnosed with stage IIIC superficial spreading MM (pT4bN1bM0).[4]~~ She was diagnosed with MM and had a metastasis of the left inguinal lymph node. Wide local resection of the primary lesion and left inguinal lymph node dissection were performed. Histopathological examination revealed a dome-shaped nodule contiguous with the adjacent hyperplastic epidermis. There were atypical epithelioid melanocytes with hyperchromatic nuclei **(Fig. 1f, g)**. ~~The tumor thickness was 20 mm. The *BRAF* mutation p.Val600Glu was not detected in genomic DNA from the tumor cells.~~ Local recurrence, in-transit skin metastasis, and metastasis in the liver and the lungs were observed soon after surgery. She was treated initially with nivolumab and then with ipilimumab. However, she was unable to complete these treatments because of an immune-related adverse event. One year after resection of the primary MM lesion, she died of multiple organ failure due to the exacerbation of multiple organ metastases.

~~Intermediate JEB is caused by biallelic mutations in one of the three genes encoding the subunits of laminin 332 (*LAMA3*, *LAMB3* and *LAMC2)* or *COL17A1* coding collagen XVII, a binding ligand of laminin 332.[5] In the present case, two variants in *COL17A1* (p.Trp221* and p.Gly1181Argfs*61) were found and assessed to be "likely pathogenic" according to the ACMG guideline 2015.[6] The present patient had compound heterozygous truncation mutations of *COL17A1*, resulting in the complete or partial loss of function of collagen XVII, leading to intermediate JEB.~~

Patients with ~~various forms of~~ EB sometimes have EB nevi, which are benign pigmented lesions that resemble MM clinically and histopathologically.[2] ~~EB nevi typically arise within sites of previous EB-related bullae and erosions, EB nevi are frequently suspected to be MM; indeed, it is difficult to differentiate EB nevi and MM. However,~~ Irregular streaks, bluish-white veils, and black dots as dermoscopic features and architectural asymmetry, variability of melanocytic nests, and elongation of rete ridges as histopathological features are found more frequently in MM than in EB nevi.[3]

According to the National Epidermolysis Bullosa Registry (https://doi.org/10.1001/jamadermatol.2013.5628), the cumulative risk of MM arising in

EB is 0.65% for localized EB simplex (EBS), 1.79% for generalized EBS, 2.5% for severe generalized recessive dystrophic EB (RDEB), and 9.6% for dominant dystrophic EB. One patient with EBS and two patients with RDEB were reported to have MM.[3, 4, 5] We speculate that chronic inflammation and defective anti-tumor immunosurveillance due to EB lesions may be associated with the development of MM, although we do not have any evidence to support this hypothesis, and the development of MM in the patients with JEB might be coincidental.

~~In conclusion, to the best of our knowledge,~~ As far as we know, the present case is the first reported case of MM that developed in a JEB patient. The present patient suggests that we have to keep the possibility of both MM and EB nevus in mind when we see a pigmented lesion in a JEB patient~~s, especially in elderly patients with intermediate JEB due to *COL17A1* mutations~~.

Figure legends

Figure 1. Clinical and histopathological features of intermediate junctional epidermolysis bullosa and malignant melanoma in the patient

(a) Numerous blisters, erosions, ulcers and their scars are seen on the back. (b) Total scarring alopecia. (c) A skin punch biopsy from the right thigh reveals subepidermal blistering. (d) An irregularly shaped node of 5 x 10 cm surrounded by a dark, pigmented region on the left lower leg. (e) The initial punch biopsy specimen shows dense infiltration of atypical epithelioid melanocytes with round, hyperchromatic nuclei. (f, g) A resected specimen from the tumor reveals atypical epithelioid melanocytes with hyperchromatic nuclei, eosinophilic cytoplasm and melanin granules densely infiltrated in the nodular lesion ((f) the margin of the node; (g) the coexistence of subepidermal blistering and atypical epithelioid melanocytes).

References

1 ~~Fine JD, Johnson LB, Weiner M, Li KP, Suchindran C. Epidermolysis bullosa and the risk of life-threatening cancers: the National EB Registry experience, 1986-2006. *J Am Acad Dermatol* 2009; **60**(2): 203-211.~~

2 ~~Has C, Bauer JW, Bodemer C et al. Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. *Br J Dermatol* 2020.~~

3 ~~Balch CM, Buzaid AC, Soong S-J et al. Final Version of the American Joint Committee on Cancer Staging System for Cutaneous Melanoma. *Journal of Clinical Oncology* 2001; **19**(16): 3635-3648.~~

4 ~~Kiritsi D, Has C, Bruckner-Tuderman L. Laminin 332 in junctional epidermolysis bullosa. *Cell Adhesion & Migration* 2013; **7**(1): 135-141.~~

5 ~~Richards S, Aziz N, Bale S et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; **17**(5): 405-424.~~

1 Condorelli AG, Dellambra E, Logli E, Zambruno G, Castiglia D. Epidermolysis Bullosa-Associated Squamous Cell Carcinoma: From Pathogenesis to Therapeutic Perspectives. *Int J Mol Sci* 2019; **20**(22).

2 Hoss DM, McNutt NS, Carter DM, Rothaus KO, Kenet BJ, Lin AN. Atypical melanocytic lesions in epidermolysis bullosa. *J Cutan Pathol* 1994; **21**(2): 164-169.

3 Hocker TL, Fox MC, Kozlow JH et al. Malignant melanoma arising in the setting of epidermolysis bullosa simplex: an important distinction from epidermolysis bullosa nevus. *JAMA Dermatol* 2013; **149**(10): 1195-1198.

4 Chorny JA, Shroyer KR, Golitz LE. Malignant melanoma and a squamous cell carcinoma in recessive dystrophic epidermolysis bullosa. *Arch Dermatol* 1993; **129**(9): 1212.

5 Terrill PJ, Mayou BJ, McKee PH, Eady RA. The surgical management of dystrophic epidermolysis bullosa (excluding the hand). *Br J Plast Surg* 1992; **45**(6): 426-434.