remedy for extragenital LS triggered by the COVID-19 vaccine.

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The patients in this manuscript have given written informed consent to the publication of their case details. As this is a single case report, ethics committee approval is not required.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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REFERENCES

1. Almendro-Vazquez P, Laguna-Goya R, Paz-Artal E. Defending against SARS-CoV-2: the T cell perspective. Front Immunol. 2023;14:1107803. https://doi.org/10.3389/fimmu.2023.1107803
2. Khan Mohammad Beigi P. The immunogenetics of morphea and lichen sclerosus. Adv Exp Med Biol. 2022;1367:155–72. https://doi.org/10.1007/978-3-030-92616-8_7
3. De Luca DA, Papara C, Vorobyev A, Staiger H, Bieber K, Thaci D, et al. Lichen sclerosus: the 2023 update. Front Med (Lausanne). 2023;10:1106318. https://doi.org/10.3389/fmed.2023.1106318
4. Philips RL, Wang Y, Cheon H, Kanno Y, Gadina M, Sartorelli V, et al. The JAK-STAT pathway at 30: much learned, much more to do. Cell. 2022;185(21):3857–76. https://doi.org/10.1016/j.cell.2022.09.023
5. Kmietowicz Z. Covid-19: WHO recommends baricitinib and sotrovimab to treat patients. BMJ. 2022;376:o97. https://doi.org/10.1136/bmj.o97

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Multiple melanomas in ichthyosis with confetti: One more piece of evidence

Dear Editor,

Basal and squamous cell skin cancers have been described in patients with congenital ichthyoses,[1] whereas an increased incidence of melanoma in these diseases is not well established.

We describe the case of a 48-year-old Italian woman who referred to our dermatological department for ichthyosis with confetti (IWC). At birth, she presented a collodion phenotype with scaly erythroderma, while at the age of 10 years, she started developing isles of whitish non-ichthyotic skin spots (Figure 1a). During adolescence, a generalized hypertrichosis and brown-greyish macules at the dorsum of hands and feet occurred. Through the years, these hyperpigmented macules spreaded to the rest of the body, particularly localizing at the borders of healthy white spots, showing a benign melanocytic proliferation at histological examination.

A de novo heterozygous 2-base pair deletion NM_000421.5: c.1506_1507del (p.Ser503fs) in exon 7 of *KRT10* gene was identified from blood genomic DNA. No other causative variants were found in either lesional tissue or blood samples.

Our patient underwent acitretin at the dosage of 25 mg/day for the last 30 years, with moderate benefits.

In May 2018, at the age of 46 years, she showed an atypical melanocytic lesion on the right knee, developing from a healthy skin spot, that was excised and histologically confirmed as melanoma (pT2a) (Figure 1b,c). In the following 3 years, a new melanoma was excised on the left thigh (pT2b) (Figure 1d) and two new melanomas were excised on the right leg (pT3b and pT1a). The patient, in the absence of family history of both melanoma and non-melanoma skin cancers (NMSC), had never suffered from NMSC and, due to her underlying condition, she had

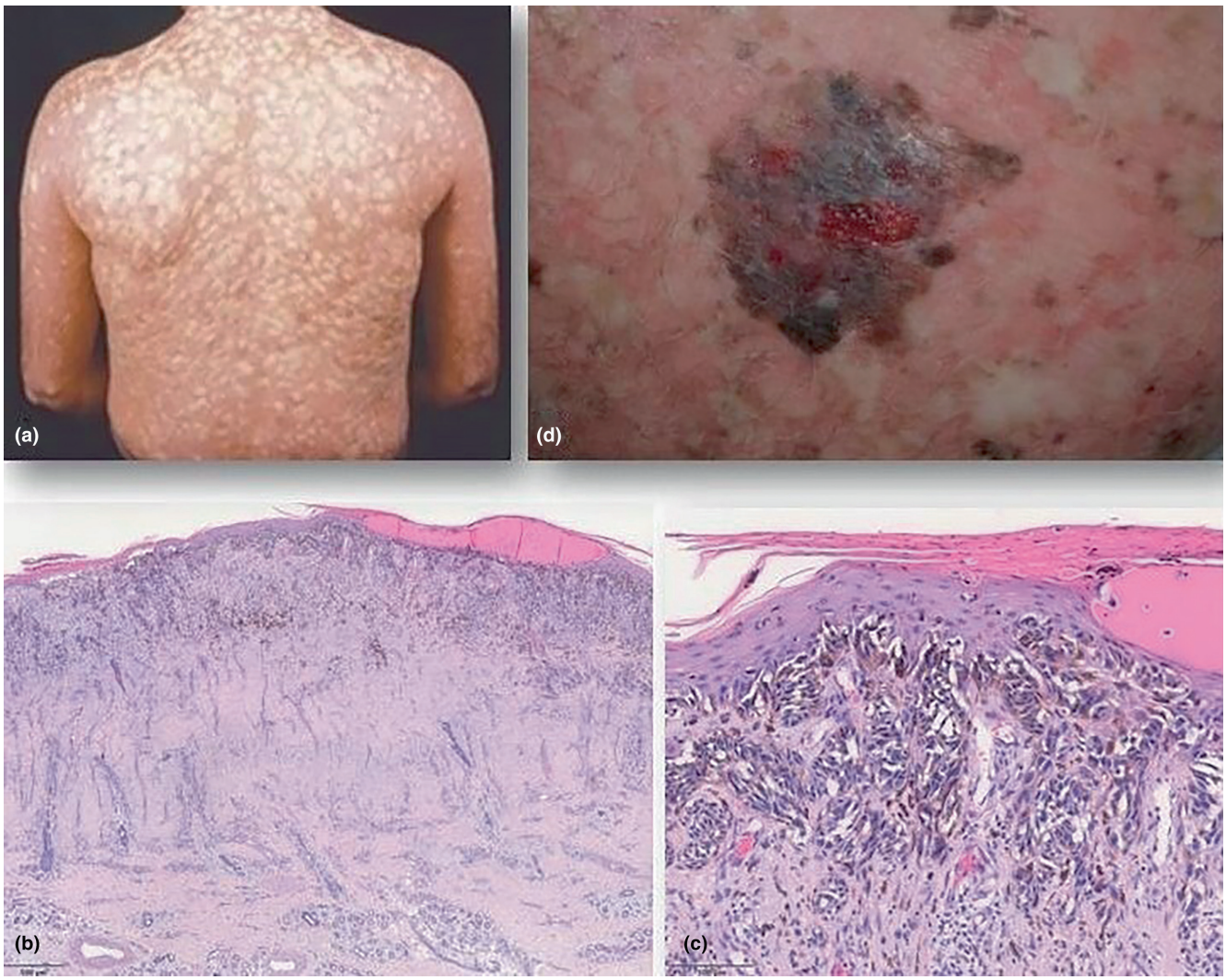

FIGURE 1 (a) Small patches of pale skin over the underlying scaling erythema in an Italian 48-year-old woman affected by ichthyosis with confetti (IWC), slowly enlarging during years. (b) Histopathology of melanoma (pT2a) with haematoxylin–eosin staining and (c) detail magnification. (d) Melanoma on the left hip (pT2b): the surrounding skin shows typical features of IWC.

never been exposed to sun since childhood, as confirmed by histological examinations.

In addition to our case just described two other cases of multiple melanomas in IWC, caused by *KRT10* gene mutations, have been recently described.[2,3]

IWC is an autosomal dominant congenital ichthyosis caused by heterozygous pathogenic variants in the *KRT10* or *KRT1* genes, in which healthy skin confetti-like spots represent 'repaired' skin due to a revertant mosaicism of keratin gene mutations via mitotic recombination.[4]

To explain skin carcinogenesis in congenital ichthyoses, mechanisms including incomplete cellular maturation due to a genetic defect, chronic inflammation caused by keratinocyte barrier deficiency and increased susceptibility to irritation caused by external agents have been hypothesized.[5]

In the context of IWC, moreover, it has been hypothesized that mutant KRT10 promotes carcinogenesis by increasing the frequency of revertant clones with the ability to cause coding errors and exerts a direct carcinogenic effect,[6] since the wild-type allele inhibits proteins involved in cell cycle regulation.[7] It has been in fact demonstrated that KRT10 acts as a negative modulator of cell cycle progression through sequestration of protein kinase B and zeta isotype of protein kinase C in the cytoskeleton.[7] All IWC pathogenic variants reported so far in *KRT10* result in a C-terminal (where its ability to suppress cell proliferation resides) frameshift into the same alternative reading frame, replacing a polyglycine tail with a polyarginine tail that redirects KRT10 from the cytoplasmic intermediate filament network to the nucleus.[8] The mitotic spindle instability caused by this mis-localisation may induce carcinogenesis and confer high frequency of revertant clones in IWC via mitotic recombination.[3] The specific absence of reversion of other dominant mutations in *KRT10* implicates KRT10 C-terminal frameshift peptide in the high

frequency of revertant mosaicism and melanoma proneness in IWC.[3,6]

In conclusion, we have reported a case of a patient affected by IWC who developed multiple melanomas, discussing the hypothesis of carcinogenic mechanisms. Based on this and other evidence,[2,3] careful monitoring of melanocytic lesions should be recommended in the routine follow-up for patients affected by IWC.

KEYWORDS

genetics, genodermatoses, ichthyosis, melanoma, skin cancer

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CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Natsuga K, Akiyama M, Shimizu H. Malignant skin tumours in patients with inherited ichthyosis. Br J Dermatol. 2011;165:263–8.
2. Takeichi T, Suga Y, Mizuno T, Okuno Y, Ichikawa D, Kono M, et al. Recurrent KRT10 variant in ichthyosis with confetti. Acta Derm Venereol. 2020;14:adv00209. https://doi.org/10.2340/00015555-3570
3. Ito Y, Takeichi T, NakagawaK K, et al. Case of ichthyosis with confetti caused by KRT10 mutation, complicated with multiple malignant melanomas. J Dermatol. 2022;49:e228–9. https://doi.org/10.1111/1346-8138.16348
4. Spoerri I, Brena M, De Mesmaeker J, et al. The phenotypic and genotypic spectra of ichthyosis with confetti plus novel genetic variation in the 3′ end of KRT10: from disease to a syndrome. JAMA Dermatol. 2015;151:64–9.
5. Tas F, Erturk K, Demirkesen C, Goktay F. Cutaneous melanoma in association with ichthyosis vulgaris. J Pediatr Hematol Oncol. 2017;39:630.
6. Choate KA, Lu Y, Zhou J, Choi M, Elias PM, Farhi A, et al. Mitotic recombination in patients with ichthyosis causes reversion of dominant mutations in KRT10. Science. 2010;330:94–7.
7. Paramio JM, Segrelles C, Ruiz S, Jorcano JL. Inhibition of protein kinase B (PKB) and PKCzeta mediates keratin K10-induced cell cycle arrest. Mol Cell Biol. 2001;21:7449–59.
8. Renz P, Imahorn E, Spoerri I, Aushev M, March OP, Wariwoda H, et al. Arginine- but not alanine-rich carboxy-termini trigger nuclear translocation of mutant keratin 10 in ichthyosis with confetti. J Cell Mol Med. 2019;23:8442–52.