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CASE REPORT

Verrucous epidermal nevus as a manifestation of a type 2 mosaic *PTEN* mutation in Cowden syndrome

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Abstract

Linear Cowden nevus, also known as linear PTEN nevus, is a type of epidermal nevus, first described in 2007, which is seen in patients with PTEN hamartoma tumor syndrome. It is considered to be a type 2 form of segmental mosaicism, and we suggest that it has certain clinical features that distinguish it from epidermal nevi seen in similar conditions, such as Proteus syndrome. We present a case of linear Cowden nevus in a 4-year-old boy and review the literature.

KEYWORDS
Cowden syndrome, epidermal nevus, lipoma, macrocephaly, mosaicism type 2, PTEN

1 | INTRODUCTION

PTEN is a tumor suppressor gene involved in the regulation of apoptosis and cycle arrest in the mammalian target of rapamycin (mTOR) pathway. Under normal conditions, it decreases the growth and survival of cells.[1] Numerous diseases have been linked to germline *PTEN* mutations in recent decades, including Cowden syndrome, Bannayan–Riley–Ruvalcaba syndrome, Lhermitte–Duclos disease in adults, macrocephaly/autism syndrome,[1] and SOLAMEN syndrome (segmental overgrowth, lipomatosis, arteriovenous malformation, and epidermal nevus syndrome).[2] Cowden syndrome is the most common phenotypic manifestation within this spectrum. Although each syndrome has characteristic features, they are all associated with intellectual disability, overgrowth, and predisposition to tumors. These manifestations often overlap and the conditions are grouped under the umbrella term *PTEN hamartoma tumor syndrome* (PHTS). Therefore, these patients can be diagnosed using the PTEN hamartoma syndrome clinical diagnostic criteria revised by Pilarsky et al in 2013,[3] although the diagnosis is usually subsequently confirmed by genetic testing. No clear genotype–phenotype correlations have yet been described.[1]

Happle[4] coined the term *linear Cowden nevus* (also called linear PTEN nevus)[4] to refer to a new clinical-genetic entity within the group of keratinocytic epidermal nevi.[4] He described it as a type 2 segmental manifestation (produced by the loss of the corresponding wild-type allele resulting in a pronounced segmental involvement

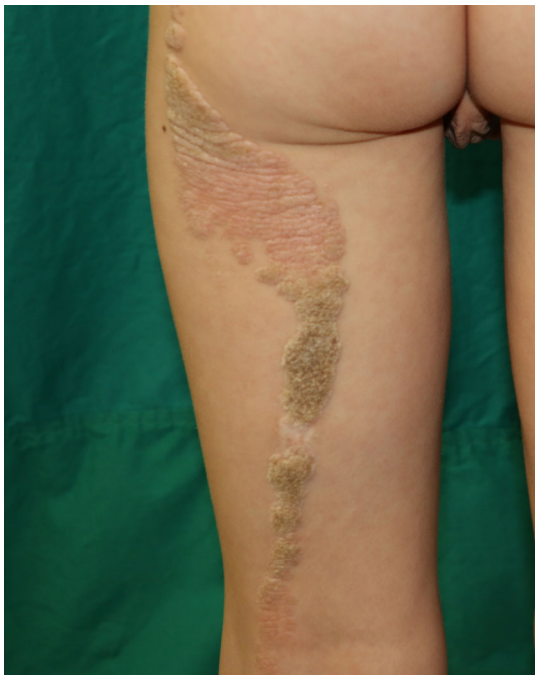

FIGURE 1 Brown lesion with a verrucous surface on the posterior aspect of the left thigh and buttock

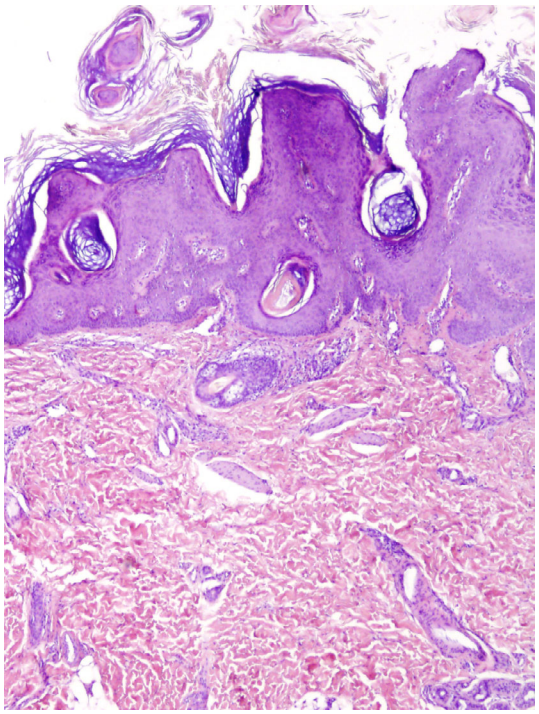

FIGURE 2 Biopsy from the epidermal nevus (H&E ×40) showing epidermal hyperplasia with marked acanthosis, hyperkeratosis, and papillomatosis

being superimposed on the ordinary nonsegmental phenotype) of Cowden disease in patients harboring a germline *PTEN* pathogenic variant and a second-hit mutation, usually a loss of heterozygosity early in embryonic development.[4]

We present the case of a patient diagnosed with PHTS manifesting a germline *PTEN* mutation and an epidermal nevus in which loss of heterozygosity was detected in DNA extracted from the lesion. We also review the literature.

2 | CASE REPORT

A 4-year-old boy was noted at birth to have a thick, linear, yellowish-white lesion with a verrucous surface on the posterior aspect of his left thigh and buttock diagnosed as an epidermal nevus (Figure 1). The child was born at 40 weeks gestation and had a history of macrocephaly with normal brain magnetic resonance imaging (MRI) findings. He has had delayed development and altered tooth morphology. Three subcutaneous tumors with an elastic consistency were observed in the trunk and groin areas between the ages of 2 and 4 years; both clinical and ultrasound findings were consistent with lipoma. Phimosis and bilateral cryptorchidism were also observed. Biopsy of the verrucous plaque on the left thigh (Figure 2) and one of the subcutaneous tumors confirmed the respective clinical diagnoses of epidermal keratinocytic nevus and lipoma. Given the history of macrocephaly and developmental delays, Cowden syndrome was suspected. This tentative diagnosis was confirmed genetically by next-generation sequencing of peripheral blood using a customized gene panel.[5] The results showed the heterozygous pathogenic *PTEN* variant c.367C>G (NM_000314.6), which causes a change in the protein without altering the reading frame (p.(His123Asp)). This variant has been described as pathogenic in other patients with clinical manifestations suggestive of PHTS, and has been found to inactivate the phosphatase function of *PTEN* (ClinVara: RCV000693998) in in vitro assays.

Subsequent analysis of DNA extracted from the epidermal nevus showed loss of heterozygosity following detection of the c.367C>G variant in heterozygosity in the affected tissue, confirming a diagnosis of linear Cowden (or PTEN) nevus.

3 | DISCUSSION

Linear Cowden (or PTEN) nevus was first described in 2007 in a 3-year-old boy with hydrocephalus, lipomas, limb asymmetry, unilateral macrodactyly and epidermal nevus. The boy was a carrier of a germline *PTEN* mutation and investigation of DNA extracted from the epidermal nevus showed loss of heterozygosity for this mutation.[4,6] Although the lesion was initially diagnosed as an epidermal nevus in the context of Proteus syndrome, Happle indicated that the patient probably had Cowden syndrome and that the nevus was a type 2 form of mosaicism.[4] Proteus syndrome was frequently confused with PHTS at this time as its genetic basis had not yet been discovered. In addition, approximately 50% of patients with Proteus syndrome have an epidermal nevus. It is now known, however, that Proteus syndrome is caused by lethal *AKT* mutations that survive in mosaic forms.[7] Accordingly, patients with clinical features of Proteus syndrome and a *PTEN* mutation described in early reports probably had PHTS.

In our review of the literature, we identified three additional cases of congenital epidermal nevi in which identification of a heterozygous germline pathogenic variant in the *PTEN* gene led to the detection of a second-hit mutation affecting the wild-type allele in DNA extracted from the lesions.[2,8,9] The first of these cases was described in 2000 by Zhou et al.[8] in a patient with hypertrophy of the lower right extremity, arteriovenous malformations, macrocephaly, lipomas, and epidermal nevi. The second-hit mutation was observed in DNA extracted not only from the epidermal nevus but also from a lipoma and an arteriovenous malformation. The second case was published by Tekin et al.[9] in 2006 and involved a 4-year-old boy with a germline *PTEN* mutation and a large congenital epidermal nevus; the authors detected a second somatic *PTEN* mutation within a lipoma (they did not investigate the epidermal nevus). The third and most recent case was published in 2007 by Caux et al.,[2] who described a 30-year-old woman with a germline *PTEN* mutation and left thigh overgrowth, lymphatic vascular malformations, macrocephaly, lipomas, and an epidermal nevus. Genetic evaluation demonstrated loss of heterozygosity in the second allele in epidermal nevus tissue and also in a lipoma.

In all the cases of PHTS reported the epidermal nevi are described as thick, markedly papillomatous lesions with a significant hyperkeratotic component. We propose that these clinical features could be useful for distinguishing PHTS-associated nevi from the flatter, softer, and more velvety nevi seen in Proteus syndrome. In addition, the histopathological changes seen in these lesions (epidermal hyperplasia with hyperkeratosis, acanthosis and papillomatosis) are probably more evident if we compare them with those of the Proteus syndrome. It is also important to keep in mind that some *PIK3A*-related overgrowth spectrum syndromes may also present with epidermal nevi. Epidermal nevi may thus be early markers of syndromes with multiple malformations.

Regarding treatment, although there are a few reports of non-syndromic epidermal nevi treated with topical rapamycin,[10] this has not been used to treat PHTS-associated nevi. Nevertheless, it could be a treatment to consider as these syndromes are caused by alterations in the mTOR pathway.

In conclusion, observation of a hyperkeratotic epidermal nevus in a patient with macrocephaly, intellectual disability, overgrowth, or tumors should raise suspicion for PHTS.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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