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Case Report

Papillon-Lefèvre Syndrome and Basal Cell Carcinoma: A Case Study

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Keywords
Papillon-Lefèvre syndrome · Cathepsin-C · Basal cell carcinoma · Palmoplantar keratoderma · Early-onset periodontitis

Abstract
Papillon–Lefèvre syndrome (PLS) is a rare autosomal recessive disorder characterized by palmoplantar keratoderma and early-onset periodontitis. It was first described by Papillon and Lefèvre in 1924. PLS is caused by mutations in the cathepsin-C *(CTSC)* gene. The development of malignant skin neoplasms in PLS patients is extremely rare. To date, there have been two cases of malignant melanoma (MM) in PLS patients reported in international journals. Further, only one case of squamous cell carcinoma (SCC) has been reported in PLS patients. To the best of our knowledge, no cases with basal cell carcinoma in PLS patients have been reported in literature. Thus, we report a case of a 55-year-old male from Arabic Saudi with PLS and basal cell carcinoma. The patient was homozygous for a G-to-C substitution at the nucleotide position 815 (*CTSC*, c.815G>Cp.(Arg272Pro), which is a pathogenic variant. Since this is not the first case of skin cancer in PLS patients, we are supporting the possibility that cathepsin-C play a role in cancer development.

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Introduction

Papillon-Lefèvre syndrome (PLS) is a rare autosomal recessive disorder characterized by two main features: palmoplantar keratoderma and early-onset periodontitis [1, 2]. Other features include hyperhidrosis, increased infection susceptibility, intracranial calcification, mental retardation, and arachnodactyly [1, 2]. The disease symptoms start appearing in the early few years of life between 2 and 3 years; hyperkeratosis on the palms and soles and sometimes on the elbows and knees as well as teeth inflammation appear during the same period [1–3]. The deciduous and permanent teeth are often lost by the ages of 5 and 16 years, respectively [1–3]. Globally, the condition is estimated to affect 1–4 in a million individuals [1]. PLS is caused by mutations in the cathepsin-C *(CTSC)* gene; >75 PLS-causing mutations have been discovered in this gene [2–4]. Homozygous or compound heterozygous pathogenic variants of *CTSC* cause the disease. Cathepsin C, also known as dipeptidyl peptidase I, removes the N-terminal dipeptide pro-domain from several serine proteases, activating their proteolytic function. Impairment in this process may affect important cell functions in the immune response and tumor suppression. Natural killer cells and cytotoxic T lymphocytes may be affected [5]. Malignant neoplasm development in PLS patients is extremely rare. To date, two cases of malignant melanoma (MM) in PLS patients have been reported in international journals [2]. Furthermore, only one case of squamous cell carcinoma (SCC) in PLS patients has been reported [6]. To the best of our knowledge, no cases of basal cell carcinoma have been reported in PLS patients. Moreover, among PLS patients reported in Saudi Arabia in various studies, only one with a liver abscess, one with skeletal, cardiac, and ophthalmic abnormalities, and no patients with cancer have been included [7, 8]. Thus, we report a case of PLS with basal cell carcinoma development.

Case Presentation

A 55-year-old retired male teacher with a history of hypertension presented to our dermatology clinic in 2017, complaining of one dark brown lesion on the face. The lesion had gradually increased in size in the past 3 years, was accompanied by a burning sensation in the area, and bled sometimes. There was no history of frequent sun exposure, phototherapy, radiation, or photosensitizer drug use and no sunburns or use of tanning beds. He was only on losartan for hypertension. On examination, the Fitzpatrick scale score was three; the patient had a dark brown plaque with a 1 × 3 × 0.3 cm depressed center and rolled border on the right lower eyelid (Fig. 1). He also had thick yellow hyperkeratotic plaques on the palms and soles, no teeth, and no psoriasiform lesions (Fig. 2). On further history-taking, the patient mentioned that he had the lesions on the palms and soles since he was 4 years old, but he was not sure, and they could have developed earlier. Further, he mentioned that he lost all his permanent teeth when he was 14. We suspected skin cancer and conducted a biopsy of the lesion. Regarding the other symptoms and presentations, we first suspected PLS; hence, we sent the patient's blood sample for genetic testing. The patient had not visited any dermatology clinic previously.

Biopsy results showed that the patient had pigmented basal cell carcinoma of the nodular type. Microscopically, sections showed an epithelial tumor arising from the basal cell layer of the epidermis, exhibiting a nodular growth pattern. The tumor comprised basaloid cells with scant cytoplasm and elongated hyperchromatic nuclei (Fig. 3). Peripheral palisading and peritumoral clefting were present in addition to melanin production by tumor cells (Fig. 4). Mitotic

figures and apoptotic bodies were clearly visible. Tumor cells showed intense cytoplasmic staining upon CK5/6 immunohistochemical staining (Fig. 4a). They were also positive for Ber EP-4 (Fig. 4b) and BCL2 (Fig. 4c). The tumor was excised, and full-thickness skin grafting was performed by plastic surgery, with regular follow-up every 6 months.

Targeted sequencing was performed on both DNA strands for the relevant *CTSC* region. The patient was homozygous for G-to-C substitution at nucleotide position 815 (CTSC, c.815G>Cp.(Arg272Pro). This variant causes an amino acid change from arginine to proline at position 272. This variant has previously been described as a cause of PLS by Toomes et al., 1999 and Kurban et al., 2009 [3, 10] and is classified as pathogenic. The parents and grandparents were found to be consanguineous. None of the other family members had palmoplantar keratoderma or periodontitis.

Discussion

To the best of our knowledge, this is one of the earliest reports of basal cell carcinoma and could be the second reported case of non-melanoma skin cancer in PLS patients. There have been two cases of melanoma in PLS patients published in international journals with two more published in Japanese journals [2]. All previous reports have shown that the tumor develops in the hyperkeratotic part of the skin; however, the basal cell carcinoma in our patient developed on the face [2, 6]. Whether mutations in the cathepsin C gene increase the risk of cancer in PLS patients or whether only the hyperkeratotic microenvironment is a risk factor remains unclear [2, 5]. However, in our patient, cancer developed on the face; this could be either be an incidental finding or cathepsin C may play a role in cancer development. Cook (2009) mentioned that although cathepsin C mutation impaired the cytotoxic lymphocyte activity in PLS, leading to immunodeficiency and the possibility of tumor progression at a cellular level, immunodeficiency was not one of the main clinical features for PLS, as explained by cathepsin C-independent pathways [5, 9]. The role of cathepsin C could be the reason for the multiple cancer cases and severe infections like liver abscess reported in PLS patients [5, 9]. The role of cathepsin C in the development of dermatological conditions in PLS is still unclear and may explain the nonsignificant correlation between the severity of skin disease and severity of oral infection [5, 7–9]. This study raises the question of the possibility of other functions of cathepsin C, which are not clear yet, and helps in explaining the association between PLS and cancer.

Statement of Ethics

Informed consent obtained from the patient.

Reviewed and approved by King Saud University College of medicine IRB; Approval No. E-18–3352.

Disclosure Statement

The authors have no conflict of interest to declare.

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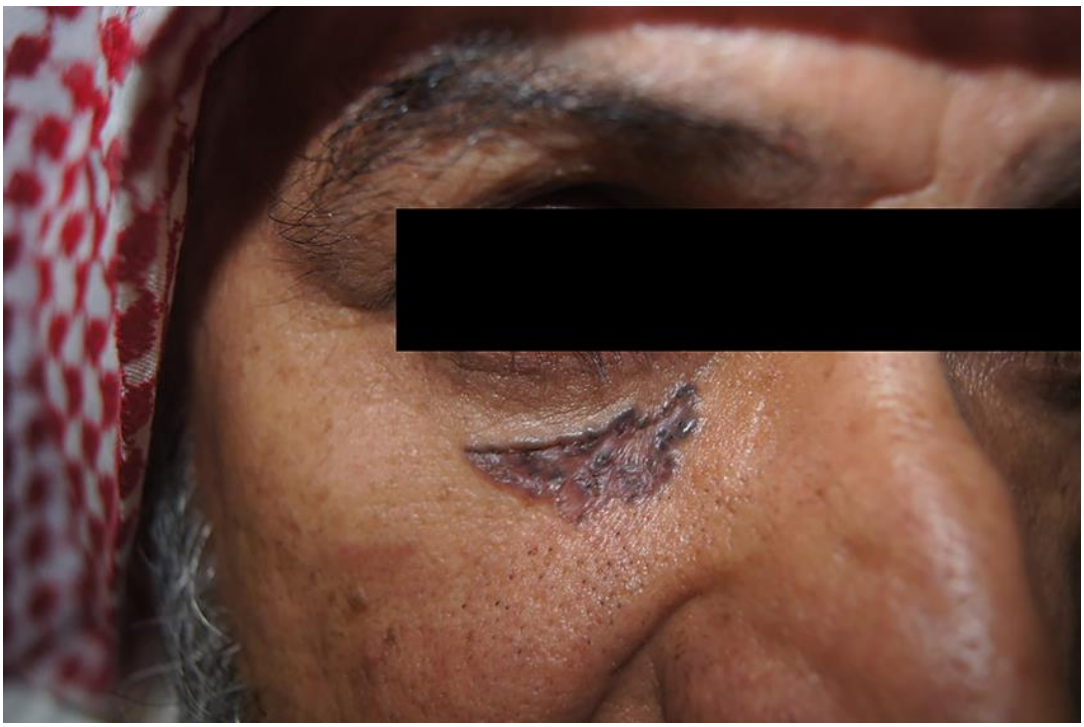

Fig. 1. Face. Basal cell carcinoma.

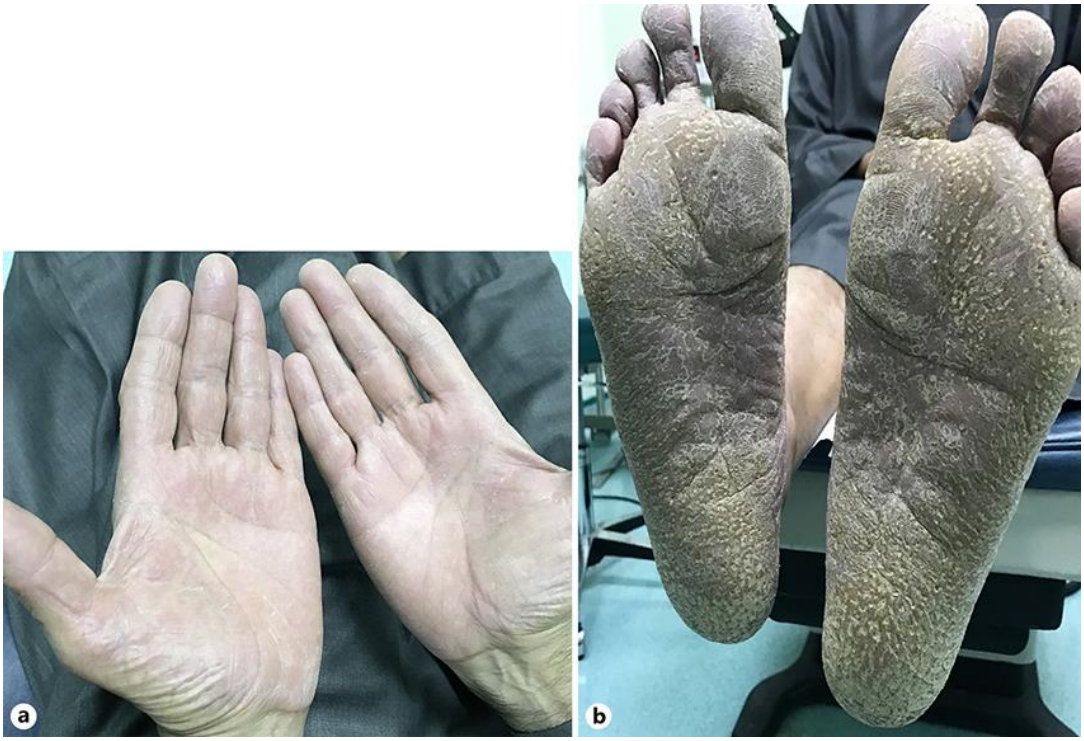

Fig. 2. Palm and sole. Thickened hyperkeratotic skin on the palms (**a**) and soles (**b**) with yellowish fishy scales more obvious on the soles.

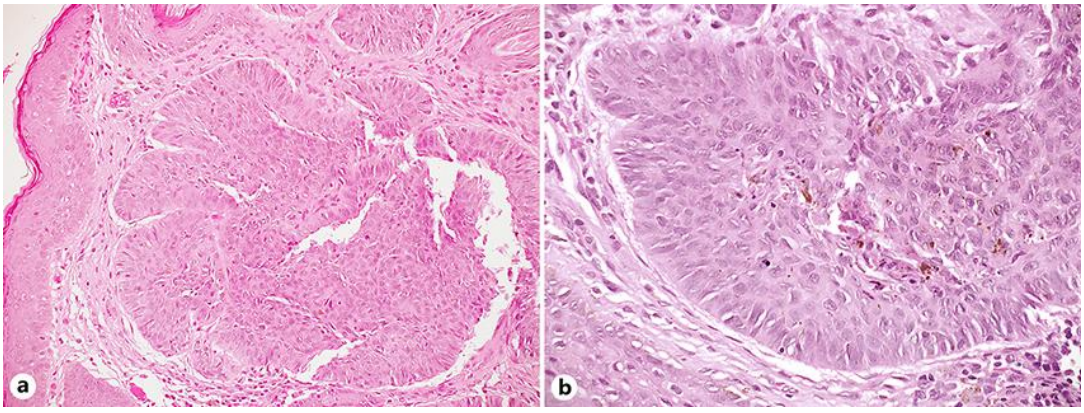

Fig. 3. H&E stain. A photomicrograph showing a nodular proliferation of basaloid cells (H&E stain, ×10) (**a**). Tumor cells showing peripheral palisading and melanin pigment deposition. Peritumoral clefting is seen in addition to few apoptotic bodies (H&E stain, ×20) (**b**).

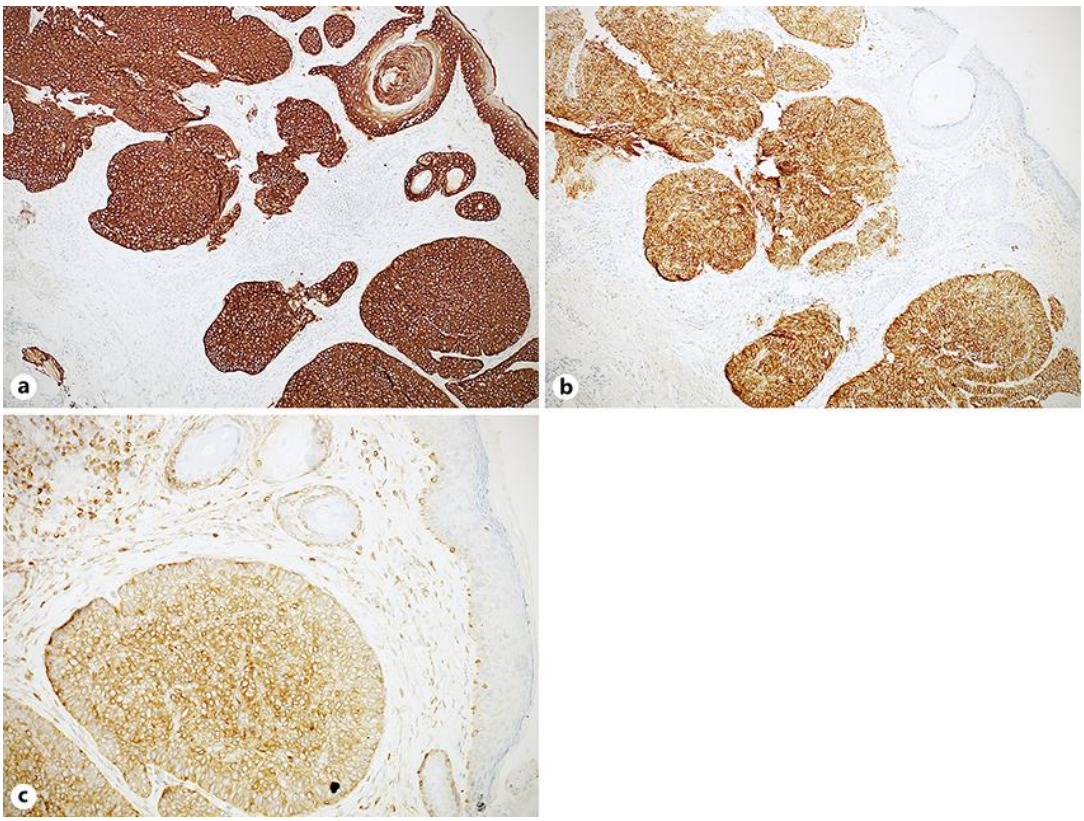

Fig. 4. Immunohistochemical stains. A panel of immunohistochemical stains showing (**a**) a strong cytoplasmic positivity to CK5/6 (CK5/6 immunostain, ×10), (**b**) a positive membranous staining to Ber EP4 (Ber EP4 immunostain, ×10) and (**c**) BCL2 (BCL2 immunostain, ×20).