SKIN

BRIEF ARTICLE

Cylindroma in a Young Woman with a Germline Checkpoint Kinase 2 Gene Mutation

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ABSTRACT

A cylindroma is a benign, slow-growing sweat gland neoplasm that tends to occur on the face or scalp. Cylindromas are often multiple in association with an underlying genetic abnormality such as the germline CYLD mutation seen in Brooke-Spiegler syndrome. Sporadic cylindromas are rare, tend to effect older individuals, and have been associated with MYB overexpression. We present a case report of a cylindroma developing in a young female patient with a known germline Checkpoint Kinase 2 (CHEK2) mutation. We hypothesize that her CHEK2 mutation resulted in cylindroma formation by way of CHEK2's downstream effects on p53 and MYB.

INTRODUCTION

A cylindroma is a slow-growing, benign sweat gland tumor that rarely undergoes malignant transformation.[1] They are often associated with genetic mutations, most commonly germline CYLD mutations.[1] To our knowledge, cylindroma associated with Checkpoint Kinase 2 (CHEK2) mutation has never been reported in the literature. We present a case report of a patient with a cylindroma and known germline CHEK2 mutation, as well as hypothesize a pathway in which a mutation in CHEK2 could lead to the development of cylindromas.

CASE REPORT

A 36-year-old female with a history of tanning bed use and a germline Checkpoint Kinase 2 (CHEK2) gene mutation was referred to the dermatology clinic by her geneticist for a baseline full body skin examination. The patient reported a pink bump on the right temple that had been present for the past 6 to 7 years. This lesion frequently became symptomatic, including pain and pruritus, whenever traumatized by her hairbrush. While the patient had a strong family history of breast cancer, she denied any personal or family history of skin cancer.

The patient's skin examination was notable for an 8 by 6-millimeter pink dome-shaped papule on the right temple with a positive wobble sign (**Figure 1**). On dermoscopy, the lesion had a homogenous pink to flesh colored pattern with scant arborizing vessels and was believed to most likely be a benign intradermal nevus. Due to the symptomatic nature of the lesion and to rule out the less favored differential diagnosis of basal cell

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carcinoma, an excisional biopsy with layered closure was performed (**Figure 2**).

Histologic evaluation revealed a dermal nodule comprised of tightly packed, geometrically shaped basaloid tumor islands separated by thin, acellular, eosinophilic septa. Around the periphery of the islands, the basaloid cells were darker and palisading, but without retraction artifact. The centers of the nodules contained lighter staining cells as well as scattered hyaline droplets (**Figure 3**). This led to a diagnosis of cylindroma.

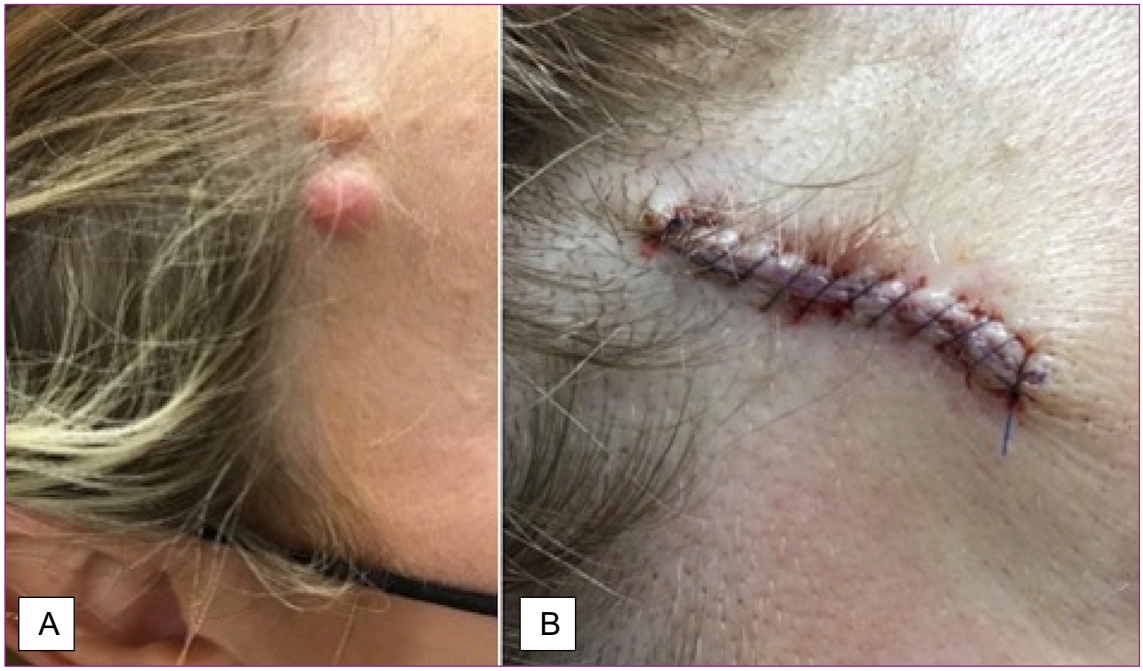

Figure 1. (A) Physical exam revealing an 8 by 6-millimeter pink dome-shaped papule with positive wobble sign on the right temple. (B) Post-operative photograph following excisional biopsy with layered closure on the right temple.

DISCUSSION

Cylindromas typically present as pink to red, smooth-surfaced papules or nodules and are most commonly found on the face and scalp. Clinically, they are often mistaken for intradermal nevi, cysts, or basal cell carcinomas.[1] Cylindromas are a benign entity but can rarely undergo malignant transformation, particularly when associated with an underlying genetic abnormality.[1] The pathogenesis of cylindromas is poorly understood. Isolated lesions may develop as a result of a sporadic mutation, whereas multiple cylindromatosis is typically associated with an inherited germline mutation. Sporadic cases most often occur secondary to transcription factor MYB overexpression.[2,3] As noted by Ramsay and Gonda, MYB is a leucine zipper transcription factor that plays an important role in the control of cell proliferation, apoptosis and differentiation.[4]

The most common cause of multiple cylindromatosis is Brooke Spiegler syndrome (BSS), which results from a germline mutation in the CYLD tumor suppressor gene located on chromosome 16q12.[5] This condition is inherited in an autosomal dominant fashion and may result in multiple

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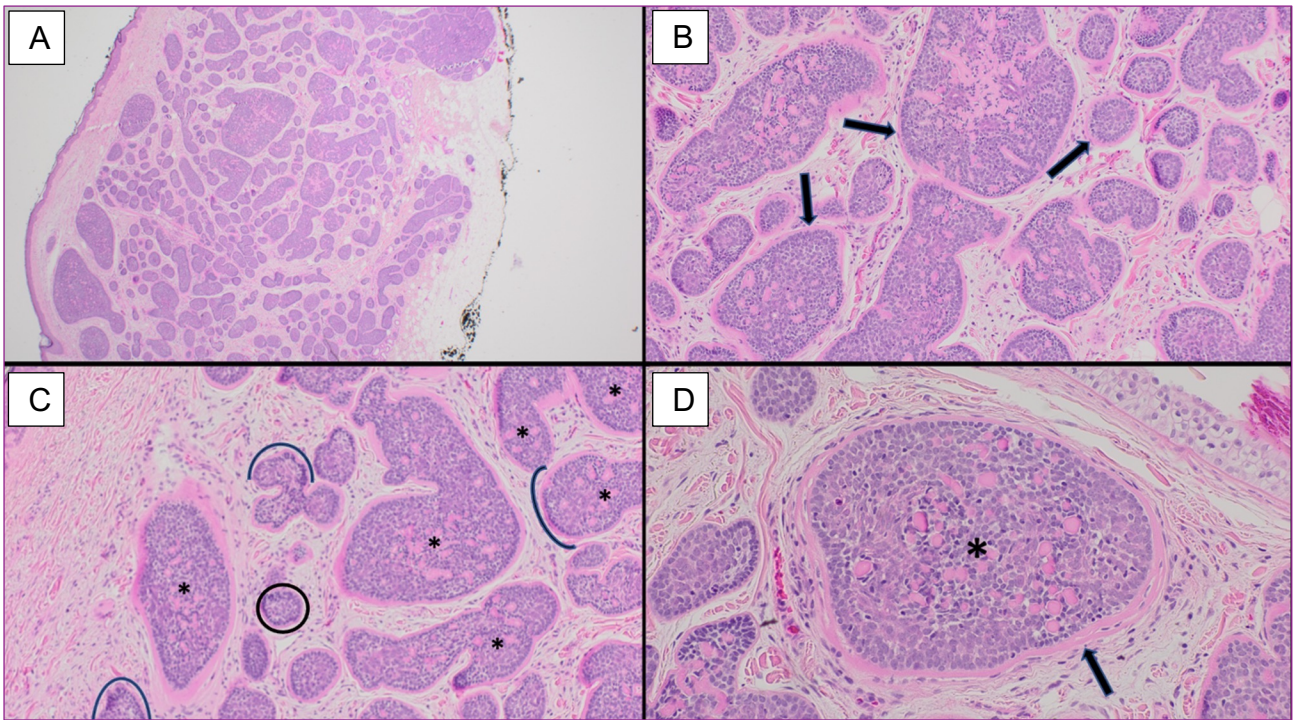

Figure 2. Histology photomicrographs from the right temple excisional biopsy specimen exhibiting proliferations of epithelial cells and cellular nests of basaloid cells deiminated by eosinophilic septate. (A) Excisional biopsy of the patient's papule at 4X magnification. (B) Proliferations of epithelial cells along with basaloid cells organized as cellular nests demarcated by thin, acellular, eosinophilic septate (arrow) at 10X magnification. (C) Basaloid cells with dark nuclei and scant cytoplasm palisaded around the edges of the nests (outlined). The centers contained larger cells with lighter staining nuclei and moderate eosinophilic cytoplasm (*) at 10X magnification. (D) A cellular nest at 25X magnification with clear eosinophilic septate and basaloid cells.

cylindromas coalescing to form large plaques on the scalp known as turban tumors.[5] Individuals with BSS are also prone to developing other adnexal neoplasms, such as trichoepitheliomas, spiradenomas, trichoblastomas, follicular cysts, and milia, as well as basal cell carcinomas. The CYLD gene controls the activity of the transcription factor NF-kB and negatively controls histone deacetylases that alter MYB locuses.[6,7] Fehr et al did not detect MYB–NFIB fusion transcripts or rearrangements of the MYB locus in CYLD-defective familial tumors, but immunohistochemical analysis revealed strong nuclear expression of MYB.[8] Furthermore, RNA interference in the expression of MYB in the tumors has been shown to significantly decrease cell proliferation.[8]

CHEK2 is a serine/threonine kinase that regulates cell division by interacting with p53, BRCA1, BRCA2, and other tumor proteins in response to DNA damage.[9] Germline mutations in CHEK2 are associated with variants of Li-Fraumeni syndrome and various solid and hematologic malignancies including breast, prostate, renal, colon, and thyroid cancers as well as non-Hodgkin lymphoma.[9] While cylindromas have not been previously described in association with CHEK2 mutations, we hypothesize that our patient's CHEK2 germline mutation made her more prone to developing this lesion. While it

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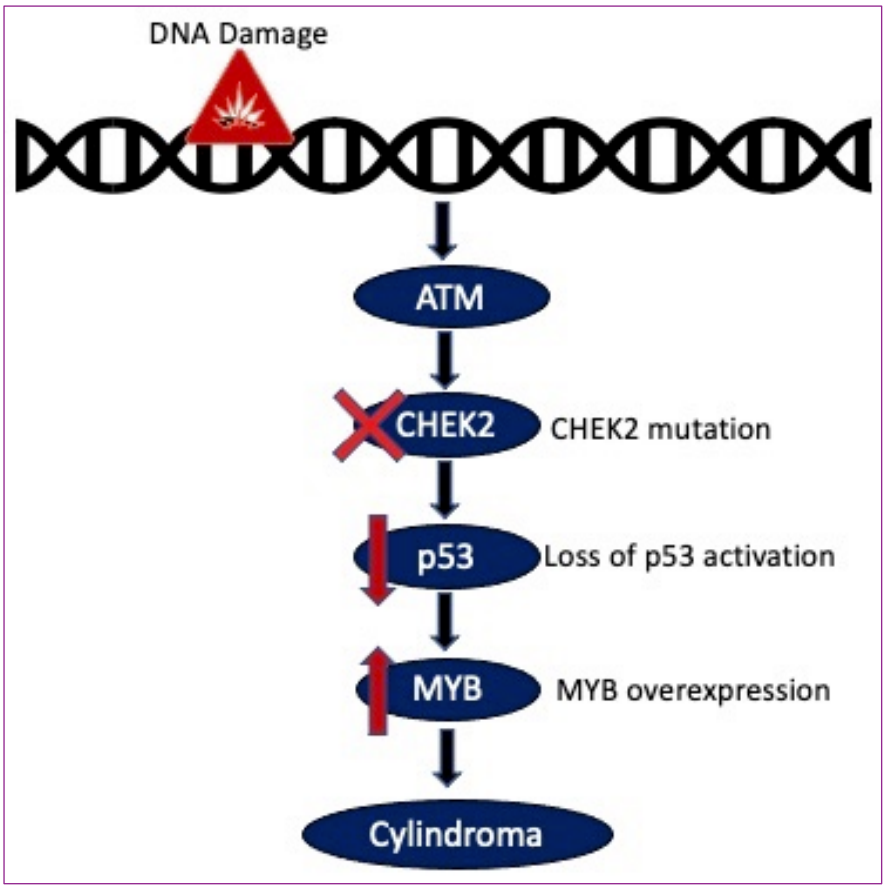

Figure 3. A germline CHEK2 mutation could plausibly lead to the development of cylindromas through the following mechanism: 1) loss-of-function in CHEK2 results in downregulation of the tumor suppressor protein p53; 2) loss of p53 activation decreases inhibition of MYB; 3) MYB upregulation leads to the development of a cylindroma.

is entirely possible that she developed a sporadic cylindroma, these lesions are very rare and tend to affect elderly individuals.[10] While the patient has only developed one cylindroma to date, she will be followed over time for the development of multiple lesions which would further support our hypothesis. A germline CHEK2 mutation could plausibly lead to the development of cylindromas through the following mechanism (**Figure 3**): 1) loss-of-function in CHEK2 results in downregulation of the tumor suppressor protein p53; 2) loss of p53 activation decreases inhibition of MYB; 3) MYB upregulation leads to the development of a cylindroma.[2]

CONCLUSION

We present a case report of a cylindroma developing in a young female patient with a known germline CHEK2 mutation. While it is possible that the patient developed a spontaneous unrelated mutation leading to the development of this lesion, we hypothesize that it could also be related to her underlying CHEK2 germline mutation due to CHEK2's impact on p53 and p53's relationship to MYB, which has been strongly implicated in cylindroma pathogenesis.

Conflict of Interest Disclosures: None

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