Dermatology Practical & Conceptual

Multiple Primary Melanoma in a CHEK2 Mutation Carrier

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Introduction

Checkpoint kinase 2 (CHEK2) gene (22q12.1) encodes the protein CHEK2, a cell cycle checkpoint regulator that acts as a tumor suppressor. CHEK2 is activated by signals from ataxia-telangiectasia, ataxia-telangiectasia mutated and Rad3-related proteins in the setting of double-stranded DNA breaks. Then, it phosphorylates and activates p53 and BRCA1 proteins, inducing cell cycle arrest/apoptosis or DNA repair [1]. Patients with pathogenic mutations affecting CHEK2 may not correctly recognize UV-induced DNA breaks and, therefore, it could be hypothesized that these mutations may increase the risk of melanoma [1,2].

Case Presentation

A 51-year-old woman with more than 150 nevi, a previous history of multiple sunburns and a nevus-associated melanoma in situ, presented with an atypical pigmented lesion on her left lumbar region (Figure 1, A and B). Histopathological examination revealed a non-ulcerated nevus-associated melanoma with a Breslow thickness of 1mm (pT1b). Relevant familial history included a history of breast carcinoma in her mother at the age of 76 years and a possible history of melanoma in her maternal grandmother. Neither the patient brother nor her son had a history of cancer.

Considering her personal and familial history, germline genetic testing for melanoma and breast cancer was offered. Written informed consent was obtained from patient for genetic study of a peripheral blood sample. A c.349A>G (p.Arg117Gly) heterozygous mutation in the CHEK2 gene was identified by Ion Torrent TM Next Generation Sequencing (Thermo Fisher Scientific). No pathogenic variants were found in CDKN2A, CDK4, BAP1, MiTF, BRCA1, BRCA2 or PTEN genes. The same pathogenic mutation was found in her mother.

The patient was included in a surveillance program with total body photography and digital dermatoscopy. Sixteen

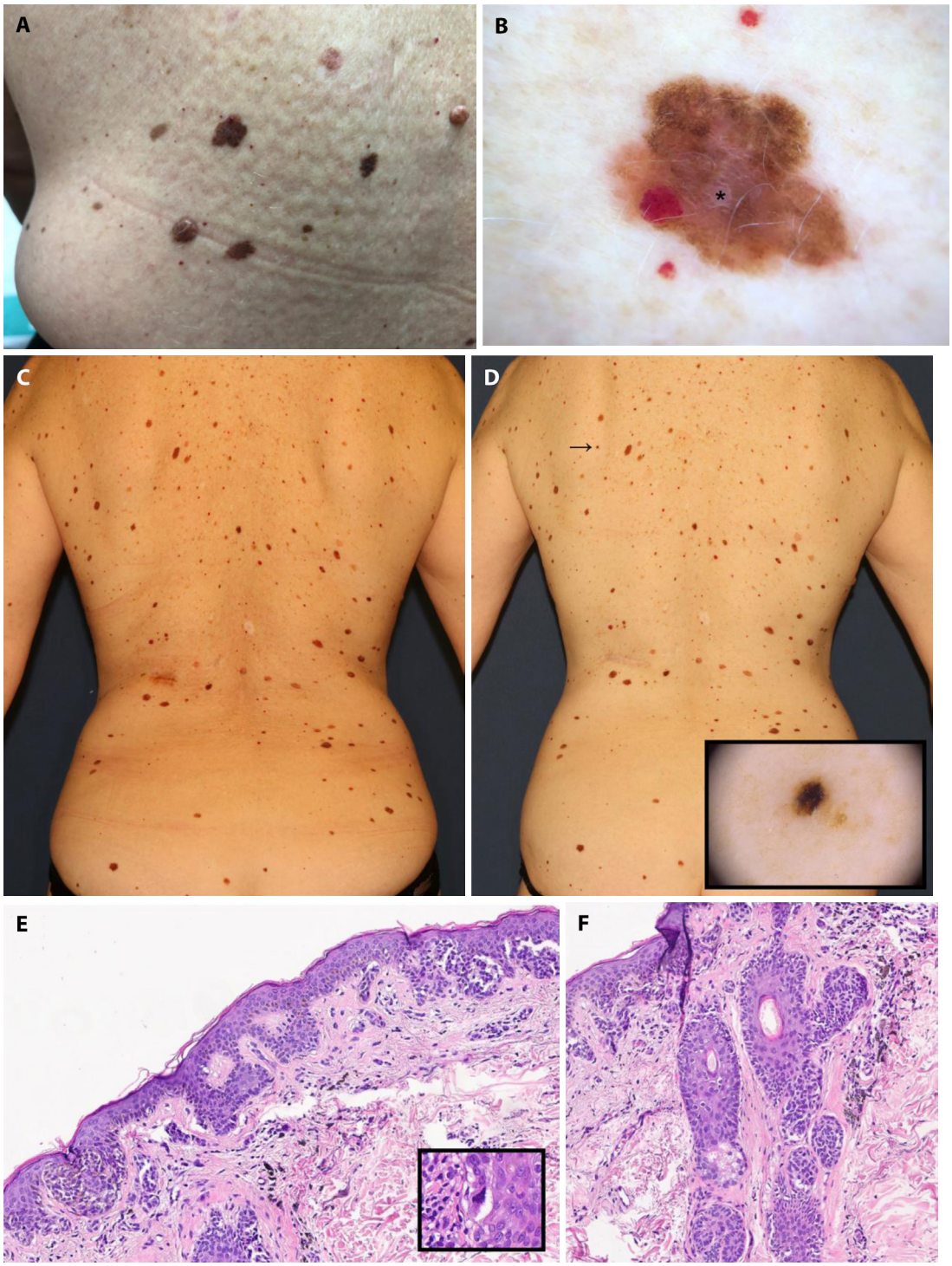

Figure 1. (A) Irregularly pigmented macule on her left lumbar region. (B) Dermatoscopy revealed an atypical pigment network, irregularly distributed brown globules, negative network (asterisk) and dotted vessels. (C) The patient showed more than 150 melanocytic nevi, many of them atypical (baseline total body photograph image). (D) A striking growth and darkening of a previously inconspicuous lesion were notorious (arrow); dermatoscopy showed a homogeneous blue-gray area (FotoFinder Bodyscan ATBM®, x20) (inset). (E) Irregular proliferation of atypical melanocytes within the epidermis, some of them arranged in nests (haematoxylin and eosin, original magnification x 20); an atypical mitosis is observed (inset). (F) Extension of the atypical melanocytes down adnexal structures (H&E, original magnification x 20).

months after the beginning of the follow-up, a striking growth and darkening of a previously inconspicuous lesion was detected (Figure 1, C and D). This lesion was surgically removed, and its histopathologic examination revealed a melanoma with a Breslow thickness of 0,18mm (pT1a) (Figure 1, E and F). One year later, a previous stable lesion on her lower abdomen showed a new pigmented blotch and a blue-gray area (Figure 2, A and B). Histopathologic examination showed a new nevus-associated melanoma in situ (Figure 2, C and D).

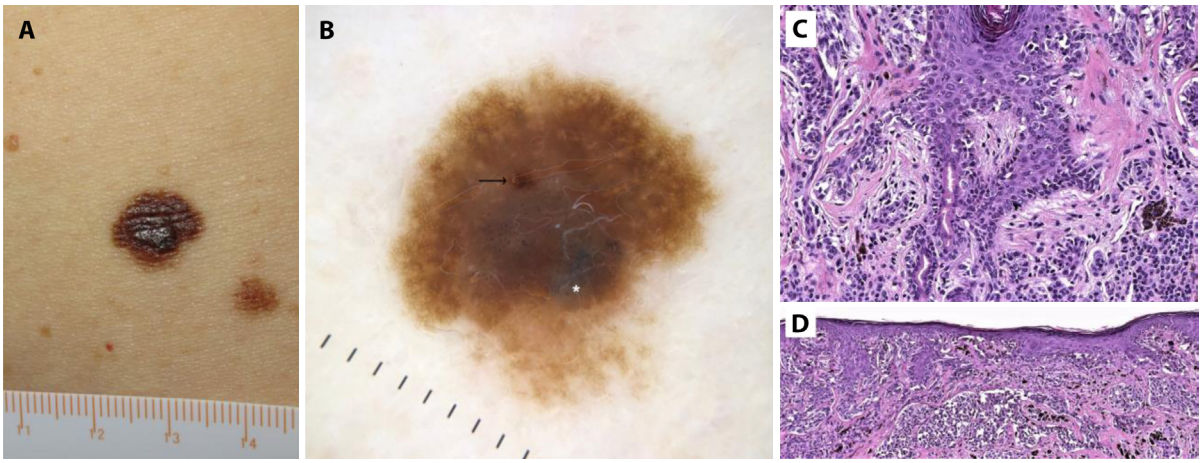

Figure 2. (A) Irregular 12mm-in-diameter pigmented lesion on the lower part of the abdomen. (B) Digital dermatoscopic follow-up showed a new pigmented blotch (arrow) and a blue-gray area (asterisk). (C) The extension of atypical melanocytes to an eccrine duct is easily seen (H&E, original magnification x 20). (D) The melanocytic proliferation is too crowded and with atypical melanocytes above dermal papillae (H&E, original magnification x 10).

Conclusions

When DNA is damaged beyond repair, the activation of p53 induce cell cycle arrest at the G1/S checkpoint or even apoptosis. An in vitro study with nine melanoma cell lines revealed alterations in the p53 pathway, suggesting that p53 inducer and effector genes such as ATM, ATR, CHK1, CHEK2 or Apaf1 represent potential alternative mutational targets in melanoma [3]. Furthermore, a recent in vitro study suggests that alterations in the ATM-CHEK2 signaling pathway may induce genomic instability in melanoma [4].

There is an association between CHEK2 mutations and hereditary breast and colorectal cancer [5]. Nevertheless, there is a lack of studies exploring a possible association with melanoma. A case-control study with 1152 Danish and 752 German patients with melanoma compared with 9142 and 3718 controls, identified a twofold risk of melanoma in CHEK2*1100delC heterozygotes compared with non-carriers. These results were ratified by a meta-analysis [6]. CHEK2 c.349A>G (p.Arg117Gly) is a rare missense variant, which affects an important domain for protein function and there is evidence of its association with breast cancer. Currently, there is no strong evidence supporting an increased risk of melanoma in CHEK2 mutation carriers. Nevertheless, the implication of the CHEK2 pathway in melanoma pathogenesis is plausible. Until more evidence is available, patients with CHEK2 mutations may benefit from sun protection measures and periodic dermatologic examinations.

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