Primary Cutaneous Melanoma Arising in Agminated Melanocytic Nevi: \textit{CDKN2A} and \textit{CDK4} Mutation Screening

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Agminated nevi is an entity characterized by grouped melanocytic lesions that are circumscribed and confined to a localized area of the body. Unlike nevi spilus, which is the main differential diagnosis, agminated nevi lack any clinically visible background pigmentation and commonly appear during puberty. Pigmented lesions that have been described as agminated include common melanocytic nevi, congenital melanocytic nevi, Spitz nevi, blue nevi and multiple lentigines (1, 2). Reports of atypical nevi and malignant transformation within these lesions are rare. Only a few previous reports have documented the occurrence of cutaneous melanoma arising from agminated nevi (3). Patients with more than one primary melanoma are considered candidates for genetic testing of \textit{CDKN2A} and \textit{CDK4}, irrespective of family history. These are the main genes involved in melanoma predisposition (4).

CASE REPORT

A 32-year-old white male presented with a pigmented lesion on his right thigh. Excisional biopsy revealed a cutaneous melanoma with a thickness of 3.5 mm and Clark level III. The sentinel lymph node biopsy was negative. He had no family history of melanoma. Based on total body mapping and digital dermoscopy, the patient had more than 60 disseminated moles, a few of which appeared clinically atypical. A cluster of almost 50 melanocytic lesions was also detected in a 12.0 × 5.0 cm diameter region on his left chest without background café au lait pigmentation (Fig. 1A). He first noticed the cluster of moles during his teenage years. Some of the nevi within the cluster had the clinical appearance of atypical moles. Dermoscopy findings for most of the lesions included a broadened and hyperpigmented network, structureless areas, and irregularly distributed brown dots and globules that corresponded to compound and atypical nevi. In addition, one lesion also presented irregularly distributed black dots and was diagnosed as \textit{in situ} cutaneous melanoma (Fig. 1B). The whole area of agminated nevi was excised and the histopathological findings revealed numerous isolated melanocytic lesions, which were diagnosed as follows: junctional nevi, intradermal nevi, compound nevi (of which 2 had congenital features), junctional nevi with severe melanocytic atypia and one \textit{in situ} melanoma in a pre-existing nevus. The \textit{in situ} melanoma was overlying a compound nevus and had a lentiginous atypical melanocytic hyperplasia along the basal cell layer and a few isolated cells in a pagetoid spread (Fig. 2). The junctional nevus with severe atypia had lentiginous melanocytic hyperplasia, confined to the dermal-epidermal junction. All other lesions had usual and typical histopathological features of melanocytic nevi. There was no lentiginous component within these lesions.

CDKN2A and CDK4 mutation screening

Because of his history of multiple melanomas and atypical mole syndrome, the patient was genetically tested for mutations in the \textit{CDKN2A} and \textit{CDK4} genes. The sequences were matched to DNA reference sequence from a primary sequence database (NCBI GenBank using RefSeq NM_000077.3 and NM_058195.2.1 for \textit{p16} and \textit{p14}, respectively). No \textit{CDKN2A} or \textit{CDK4} germline mutations were detected.

DISCUSSION

The term “agminated” is derived from the Latin “\textit{agmen}”, which means an aggregation, and the term “agminated lesions” refers to a clustering or a circumscribed grouping of lesions confined to a localized area of the body (2, 5). Bragg et al. (2) emphasized that agminated lesions should be distinguished from other forms of segmental distribution that lack a definitive clustering pattern and described five cases of agminated acquired melanocytic

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**Fig. 1.** (A) Agminated atypical nevi on the anterior left chest and multiple melanocytic nevi on the anterior chest and abdomen. The red arrow indicates the \textit{in situ} melanoma within the agminated atypical nevi. (B) Dermoscopic images showing a broadened and hyperpigmented network, structureless areas, and an irregular distribution of brown dots and globules (original magnification \times 10).
nevus of the common and atypical type. In our case, the histopathological description confirms the clinical diagnosis of common, congenital and atypical agminated nevi.

Pigmented lesions that have been described as agminated include blue nevi, multiple lentigines, Spitz nevi, congenital melanocytic nevi, acquired common and atypical melanocytic nevi and lesions within nevi spili (1, 2, 6, 7). The main differential diagnosis of agminated nevi is that nevi spili (speckled lentiginous nevi) lacking a clinically tan background pigmentation (2).

Sterry & Christophers reported a number of aggregates of lentigines, which are commonly acquired nevi and atypical nevi, confined to the upper left quadrant of the body, and two cutaneous melanomas at different stages of progression in this quadrant (8). Similarly, Misago et al. (7) described a case of unilateral atypical nevi associated with cutaneous melanoma. A case of common and atypical agminated nevi associated with atypical mole syndrome has been published by Marghoob and co-workers (1, 2). A few cases of malignant transformation within an agminated nevi have been reported, by Corradin et al. (3).

Germline CDKN2A mutations are detected in 8–17% of patients with multiple primary melanomas (4). In a clinical syndrome called familial melanoma, a higher rate of mutations occurs in patients who have an additional first- or second-degree family member with melanoma. Atypical moles are a common finding in these patients. In Europe, North America and Australia, the mutations usually affect exon 2, which is common to both the p16 and p14 transcripts (9). In Brazilian familial melanoma and multiple primary melanoma patients, mutations affect every part of the gene equally, including the promoter and intron 2 (unpublished data). CDKN2A gene testing is frequently used in early diagnosis of at-risk family members with familial melanoma, but is also applied to patients with multiple primary melanoma and a negative family history (10).

Germline CDK4 mutations also contribute to melanoma predisposition, and all mutations found affect codon 24, with arginine being substituted by a histidine or a cysteine (6). This mutation confers an extremely high risk on a patient of developing melanoma (11).

We believe that further studies examining moderate and low-penetrance genes are needed in this case.

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REFERENCES


Fig. 2. (A) In situ melanoma overlying a compound nevi (haematoxylin and eosin (H&E) × 100). (B) Detail of the in situ melanoma with lentiginous atypical melanocytic hyperplasia along the basal cell layer and a few isolated cells in a pagetoid spread (H&E × 400).