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CASE REPORT

Agminated blue nevus with a GNAQ mutation: A case report and review of the literature

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Agminated blue nevi are dermal melanocytic proliferations that classically present as dark blue macules or papules in a grouped, linear, or blaschkoid distribution. In their more common sporadic form, blue nevi manifest in young adulthood as solitary blue papules or macules on the scalp, face, hands, or feet. By contrast, agminated blue nevi tend to manifest earlier in life, and are distributed more evenly across anatomic sites. Recent studies have identified mutations in sporadic blue nevi in the genes encoding G Protein subunit alpha Q and G protein subunit alpha 11 (GNAQ and GNA11). It is unknown whether agminated blue nevi share the same genetic changes. In the present paper, we present a case of agminated blue nevus on the wrist, and identify an activating mutation (c.626A > T, p.Glu209Leu) in *GNAQ*. We hypothesize that *GNAQ/GNA11* activating mutations arising earlier during development may trigger agminated blue nevi, explaining the broader field of involvement in these cutaneous lesions.

1 | INTRODUCTION

Blue nevi (BN) are dermal melanocytic proliferations that generally present as solitary and small (1-5 mm) dark blue macules or dome-shaped papules. They appear commonly in young adulthood and most frequently manifest on the scalp, face, hands, or feet. When grouped, linear, or in a blaschkoid distribution, BN are referred to as agminated. Activating mutations in *GNAQ* or the paralogue *GNA11*[1,2] have been identified in sporadic blue nevi. It is unknown whether these mutations are also associated with the agminated form. Here, we describe a case of agminated blue nevus with discussion of clinical presentation, histopathology, and genetics, and provide a comparison of similar cases in the literature to date.

2 | CASE REPORT

A 71-year-old woman with no personal or family history of melanoma presented with a cobblestoned 7 × 4.5 cm plaque, consisting of clustered 2 to 4 mm dark brown-to-blue papules on the left wrist (Figure 1A). The lesions were present from birth and enlarged gradually with age, but had not changed in recent years. Dermoscopic examination revealed multiple, grouped, homogeneous brown, and blue-black pigmented structures (Figure 1B). Histopathological examination showed intradermal ovoid and dendritic melanocytes associated with melanophages. Dendritic melanocytes were in parallel orientation with elastotic fibers. No atypical nuclei or mitotic figures were present (Figure 1C). Massive parallel sequencing of the biopsy specimen identified a nonsynonymous mutation (c.626A > T, p.Glu209Leu) in *GNAQ*. Given the clinical presentation, histopathology, and genetics, the patient was diagnosed with an agminated blue nevus. The patient has been managed by periodic observation over time, with no significant interval changes in her presentation.

3 | DISCUSSION

Agminated blue nevi were first described in 1947 by Upshaw.[3] Since then, over 30 cases have been reported in the literature (Supporting Information Table S1).[4–23] Unlike sporadic or common BN, which have a clinical predilection for certain anatomic sites, agminated BN present equally on the trunk, extremities, and head/neck. A review of the 31 cases published since 1990 showed that 9 were present on the extremities, 10 on the head and neck, 10 on the trunk, and 2 on the genitals (Supporting Information Table S1). Agminated BN can present in a blaschkoid or linear distribution as a putative clonal outgrowth from a single cell, and often have an earlier age of onset than sporadic BN. In reviewed cases, 14 were noted at birth and 7 were present

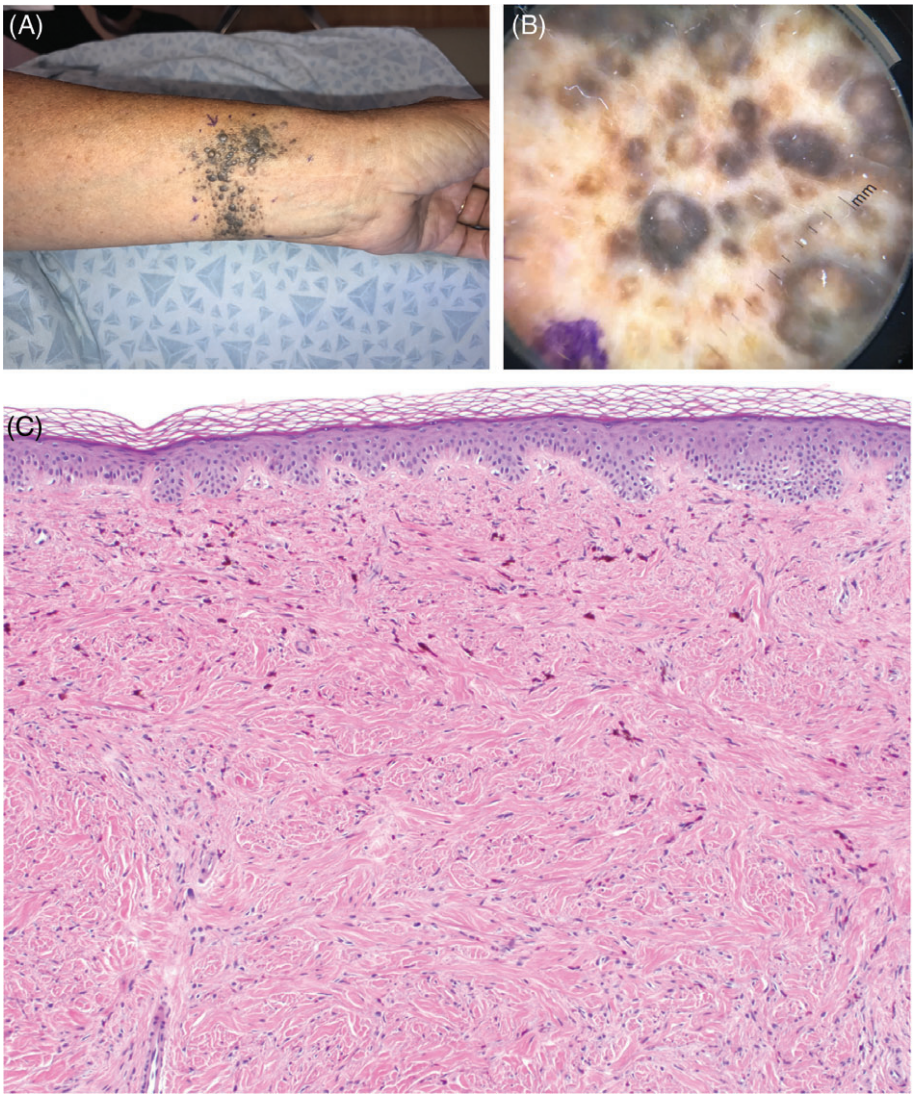

FIGURE 1 A, A cobblestoned 7 × 4.5 cm plaque, consisting of clustered 2 to 4 mm dark brown-to-blue papules in clusters on the left wrist. B, Dermoscopic evaluation shows multiple, grouped, homogeneous brown, and blue-black pigmented structures. C, Hematoxylin and eosin staining shows intradermal ovoid and dendritic melanocytes associated with melanophages. Dendritic melanocytes were in parallel orientation with elastotic fibers. No atypical nuclei or mitotic figures are present. Magnification = 100×

from teenage years. The mean age of presentation was 40 with an equal male-to-female distribution (16 females and 15 males). Six cases have been reported in conjunction with nevus spilus and three cases with melanoma. Interestingly, one case highlighted a superficial spreading melanoma (tumor thickness 1.8 mm, pT2aN0M0, stage IB) developing in conjunction with acquired dermal melanocytosis on a nevus spilus.[24] Agminated BN have also been described in conjunction with EMO syndrome/Carney complex (caused by mutations in *PRKAR1A*),[25] dermatomyositis,[26] and Darier disease.[27]

Blue nevi are triggered by constitutive activating mutations in *GNAQ* or *GNA11*, the protein products of which signal through the mitogen-activated protein kinases (MAPK) pathway. The most commonly observed mutations are GNAQ p.Q209L and GNA11 p.Q209L,[1,2] representing a mutational hotspot in the genes encoding these proteins. Interestingly, this same *GNAQ* mutation was also found in our patient. During development, this mutation increases the number of neural crest cells that differentiate into normal, dermal melanoblasts.[28] *GNAQ* and *GNA11* mutations have been found in more than 83% and 7% of BN, respectively. While similar mutations in *GNAQ* and *GNA11* mutations have been found in uveal melanoma (46% and 33% of cases, respectively)[1,2]; such mutations are not sufficient to cause melanoma, which suggests that a second hit may be the rate-limiting step to malignancy. An example of this can be seen in cases of large plaque-type blue nevus with subcutaneous nodules, which also show an underlying GNAQ p.Q209L activating mutation but have concomitant chromosomal copy number variations characteristic of melanomas; these features have led investigators to view these forms of BN with caution for potentially more aggressive behavior.[29,30]

To date, only three cases of agminated BN have reported genetic data,[25,31–33] but none have identified a probably causative mutation. This case is the first to identify an association between *GNAQ* mutations and agminated blue nevus. Interestingly, other agminated cutaneous tumors also result from mutations affecting the MAPK pathway. In agminated Spitz nevi arising in a nevus spilus, clonal activating point mutations (c.37G > C, p.Gly13Arg) in *HRAS* were

identified. The authors hypothesized that these Spitz nevi arose in an agminated fashion from a common postzygotic clone of melanocytes, likely demarcated by the nevus spilus and with the additional development of a second "hit" mutation.[34] Similarly, an analysis of agminated intradermal nevi with congenital patterns showed a BRAF p.V600E mutation, which was absent in the nonsegmental nevus and in the germline DNA from the patient's blood.[35]

These studies demonstrate that cutaneous neoplasms arising in grouped, segmental or blaschkoid forms are caused by post-zygotic mutations leading to genetic mosaicism. Mutations arising earlier in development correlate to more extensive cutaneous involvement. In cases where mutations arise early enough to affect pluripotent progenitors, the "collision" of different lesions can result, as has been shown for phacomatosis pigmentovascularis, a co-occurrence of dermal melanocytosis and capillary malformation.[36] Further confirming this paradigm, a study examining phacomatosis pigmentokeratotica, a rare epidermal nevus syndrome characterized by the collision of a sebaceous nevus and a speckled lentiginous nevus, identified heterozygous mutations (c.37G > C, p. Gly13Arg) and (c.182A > G, p.Gln61Arg) in *HRAS*, that were present in the sebaceous and melanocytic nevus, but absent from nonlesional skin.[37]

In this context, we speculate that agminated BN arise from earlier post-zygotic mutations in *GNAQ/GNA11*, thereby affecting a broader field of melanocytes and resulting in the characteristic grouped or linear appearance of this uncommon nevus. Further studies will allow us to better comprehend the genetic underpinnings of these complex mosaic cutaneous lesions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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