

## Agminated blue nevus: *GNAQ* mutations and beyond<sup>☆</sup>



### Nevus azul agminado, mutaciones en *GNAQ* y más allá

To the Editor:

We read with interest the Case and Research letter by Sardoy et al,<sup>1</sup> and believe that it can be complemented by our interesting findings on genetic alterations in blue nevi. There are multiple clinical and histological variants of blue nevus, one of the less common of which is agminated blue nevus, which is characterized by the grouping of multiple well-defined bluish lesions.<sup>2</sup>

We describe the case of a 52-year-old patient with no personal or dermatological history of interest who consulted for evaluation of asymptomatic pigmented lesions in the right mandibular region that had appeared 10 years earlier and had increased in number (Fig. 1A and B). En bloc resection was performed for histological analysis (Fig. 2). Additional immunohistochemical staining showed that the sample was negative for preferentially expressed antigen in melanoma (PRAME). Ki-67 immunostaining revealed a low proliferation index. A complete sequencing study of exon 5 of *GNAQ* showed no alterations.

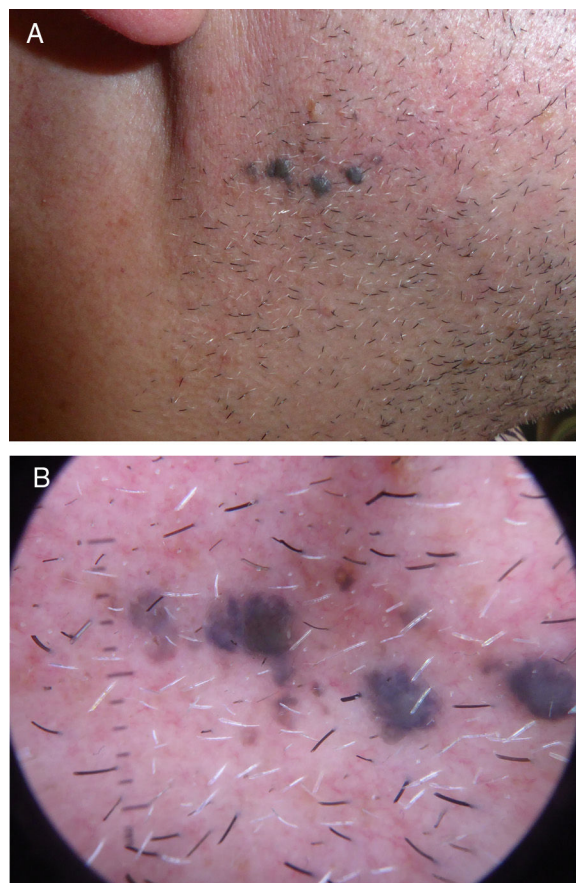
Based on these clinical and histological data, diagnosis of agminate blue nevus was established.

This infrequent presentation of blue nevus is of interest given the potential for clinical diagnostic confusion with melanoma metastasis. Genetic alterations potentially shared with uveal melanoma, nevus of Ota, and nevus of Ito are of particular interest.<sup>3-7</sup>

In blue nevus the most frequently described genetic mutation, which is found in up to 83% of cases and considered a driver mutation, is a somatic mutation in *GNAQ* and *GNA11* (which encode the alpha subunits of heterotrimeric G proteins involved in G-protein-coupled receptor-mediated signaling). This mutation causes the affected genes to act as oncogenes, as it results in constitutive activation of these proteins and continuous activation of the Ras signaling pathway, which is involved in regulation of the cell cycle and proliferation.<sup>3</sup> Consequently, in blue nevi with this mutation there is an increase in the activity of mitogen-activated protein kinase 1 (ERK2), which is activated by RAS/RAF/MAP kinase kinase (MEK).

There is only 1 published report of agminate blue nevus with a proven mutation, located at c.626A > T (p.Glu209Leu) in *GNAQ*.<sup>8</sup>

In some reported cases, including ours, in which no *GNAQ* mutation is detected, activating mutations have been detected in cysteinyl leukotriene receptor 2 (*CYSLTR2*), which is involved in a signaling pathway analogous to that of *GNAQ* and ultimately activates the same intracellular



**Figure 1** A, Four bluish papules (3–4 mm in diameter) surrounded by minute satellite lesions. B, Dermoscopy image showing a homogeneous blue pattern.

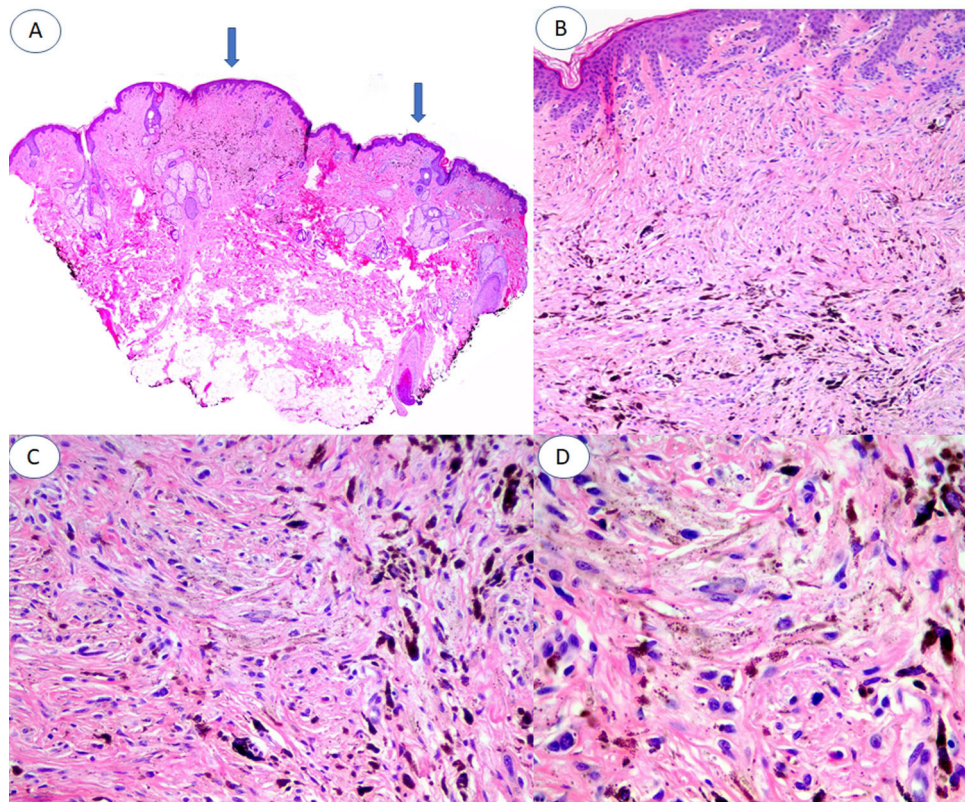
processes. This is yet another driver mutation, mutually exclusive from *GNAQ*.<sup>6</sup>

Driver mutations affecting *GNAQ/GNA11* and *CYSLTR2* can be accompanied by additional mutations in different cellular pathways that favor the progression and malignant transformation of the lesions.<sup>4-7</sup> The most widely known mutation is in the BRCA1-associated protein 1 gene (*BAP1*). *BAP1* acts as a tumor suppressor and is involved in DNA repair processes, the ubiquitin-proteasome system, regulation of transcription, and chromatin modulation.<sup>5</sup> Inactivation of this protein, either by partial deletion of the *BAP1* locus on chromosome 3 or alteration in the phosphorylation or ubiquitination of its protein chain, results in accelerated progression of cell proliferation that can trigger malignant transformation of blue nevus.<sup>5</sup>

Furthermore, these alterations described for blue nevus and for blue-nevus-like melanoma closely resemble those found in other pathological processes such as uveal melanoma. For example, the *GNAQ* mutation has been described in 46% of uveal melanomas, where it also acts as a driver mutation and can be associated with other mutations affecting *BAP1* or other pathways involved in chromosomal instability.<sup>5</sup>

Knowledge of genetic alterations and intracellular signaling pathways in these lesions is not only of diagnostic value, but may also have therapeutic implications. For example,

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**Figure 2** A, Panoramic image of the lesion in which 2 areas of blue nevus are evident (arrows), one of about 3 mm and the other of about 1 mm. B, Compact nests of spindle-shaped melanocytes located in the papillary and superficial reticular dermis without the presence of nests at the dermoepidermal junction (hematoxylin-eosin [HE], original magnification  $\times 4$ ). C, Detail of melanin distribution, with denser granules visible in the deepest part of the lesion (HE, original magnification  $\times 10$ ). D, Detail of melanocytes, showing monomorphic nuclei and the absence of mitosis and necrosis (HE, original magnification  $\times 20$ ).

the use of MEK inhibitors, with or without phosphatidylinositol 3 kinase (PI3K) or mammalian target of rapamycin (mTOR) inhibitors, has been proposed for the treatment of uveal melanoma and could also prove useful for the treatment of blue nevi with progression to melanoma.<sup>4</sup>

Finally, PRAME immunostaining has been recently proposed as a diagnostically useful marker to distinguish between nevi and melanoma, and is a biomarker of metastatic risk in uveal melanoma.<sup>9,10</sup> In our case, the negative PRAME immunostaining is in line with the other histological findings that support a diagnosis of blue nevus in our patient. To our knowledge, this is the first report of PRAME staining of agminate blue nevus.

Given the potential diagnostic and therapeutic implications of blue nevus with an atypical clinical presentation, as in the present case of agminate blue nevus, knowledge of the underlying genetics is important. PRAME immunohistochemistry and genetic analyses can increase diagnostic specificity in cases of atypical melanocytic lesions.

### Conflicts of interest

Dr. Llamas has acted as a speaker and consultant for Janssen-Cilag, AbbVie, Celgene, Pfizer, Novartis, Lilly, Almirall, and Leo-Pharma, and has participated in clinical trials. The remaining authors have no conflicts of interest to declare.

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P. Rodríguez-Jiménez,<sup>a,b,\*</sup> F. Mayor-Sanabria,<sup>a</sup> A. Rütten,<sup>c</sup> J. Fraga,<sup>d</sup> M. Llamas-Velasco<sup>a,e</sup>

<sup>a</sup> Departamento de Dermatología, Hospital Universitario de La Princesa, Madrid, Spain

<sup>b</sup> Clínica Dermatológica Internacional, Madrid, Spain

<sup>c</sup> Friedrichshafen Dermatopathologie, Friedrichshafen, Alemania

<sup>d</sup> Departamento de Anatomía Patológica, Hospital Universitario de La Princesa, Madrid, Spain

<sup>e</sup> Centro Médico Voth, Madrid, Spain

\* Corresponding author.

E-mail address: [pedro.rodriquez.jimenez90@gmail.com](mailto:pedro.rodriquez.jimenez90@gmail.com) (P. Rodríguez-Jiménez).

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## Morbidity Associated With the Timing of Lymphadenectomy for Sentinel Lymph Node Metastasis in Melanoma: A Clarification Concerning the Available Evidence<sup>☆</sup>



### Morbilidad relacionada con el momento de la linfadenectomía por afectación del ganglio centinela en el melanoma: Una puntualización a su evidencia

To the Editor:

I recently read with interest the special article published in your journal by Moreno-Ramírez et al<sup>1</sup> on the proposed management of patients with melanoma and metastasis of the sentinel lymph node. I could agree more with the majority of the proposals, and I congratulate the authors on their efforts to put order on a controversial and continually changing topic. However, I disagree with the authors on at least one of the points supporting their proposal. Table 3 of the article states that the “Frequency of surgical morbidity is greater in patients who undergo immediate lymph node dissection than in those who enter follow-up with therapeutic dissection”, a statement the authors claim is supported by level 1b evidence.

This statement is surprising because the corresponding citation refers the reader to the MSLT-II study, in which no specific analysis was performed, nor any conclusion drawn, on the association between surgical morbidity and the moment at which lymphadenectomy is performed.<sup>2</sup> In fact, discussion of adverse effects in the Results section

of the cited article only mentions that “Adverse events were more common among patients after completion of lymph-node dissection than among patients in the observation group”, and makes no mention of “follow-up with therapeutic dissection”, suggesting that the findings of this study do not support the authors’ statement.

It is possible that Moreno-Ramírez et al are actually referring to the MSLT-I study,<sup>3</sup> which shares the same first author with the MSLT-II study and compares morbidity associated with immediate versus delayed lymphadenectomy. However, if this is indeed the case, the conclusion is the opposite to that presented. The MSLT-I study<sup>3</sup> concludes that there is no higher incidence of dysesthesias in the immediate lymphadenectomy group, and that lymphedema is significantly more frequent in the delayed versus the immediate lymphadenectomy group (20.4% and 12.4%, respectively;  $p=0.04$ ). These findings are in direct contrast to the statement in the aforementioned Table 3.<sup>1</sup> In fact, in the MSLT-I study multivariate analysis to identify risk factors for lymphedema revealed that body mass index and delayed lymphadenectomy were the only factors for which a trend towards an association was observed, irrespective of the location (axillary or inguinal) of the lymphadenectomy.

It should be taken into account that the MSLT-I study included cases of melanoma in which sentinel node biopsy was indicated, while the MSLT-II study included patients with sentinel lymph node involvement. This difference should not alter the conclusions about the time point at which lymphadenectomy is performed, nor the corresponding level of evidence (given the design of the study).

In conclusion, without detracting from the article’s conclusions or the proposed decision-making algorithm, it would be prudent, and would better support the authors’ argument, to properly qualify and correct this point.

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