HMB45 protein expression and the immunohistochemical maturation in common blue nevi: a reappraisal

Dear Editor,

Common blue nevi, first described by Jadassohn-Tièche in 1906, are melanocytic proliferations composed of pigment cells reminiscent of the embryonal neural crest-derived dendritic melanocytic precursors. They commonly occur on the dorsal aspects of extremities, scalp, and buttocks of children and young adults. Histologically, blue nevi are composed of stage II or symmetrical circular melanocytes, arranged in a neurotized, spindle-shaped melanocytic dermal plexus. The melanocytic cells in the dermis, capable of differentiating into blue nevi. The human homolog of the mouse silver protein (gp100 and Pmel17) is a melanocyte-specific type I membrane protein. It is important for the formation of melanosomal fibrils that help the maturation of stage I pre-melanosomes to stage II. The HMB45 antibody was developed from an extract of a lymph-node metastasis of melanoma. It specifically reacts with the glycosylated form of gp100 restricted to the fibrillar melanosome, which is responsible for the binding of the antibody to the melanosome. The melanocytic cells that react with HMB45 are derived from neural crest, possibly initiated by dermal inflammation or other stimuli. These nevi may arise from mutated precursor stem cells in the dermis, capable of differentiating into blue nevi. The melanocytic precursor cells, which express HMB45, are derived from neural crest, possibly initiated by dermal inflammation or other stimuli. These nevi may arise from mutated precursor stem cells in the dermis, capable of differentiating into blue nevi.

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In this study, the preserved HMB45 protein expression in both superficial and deep portions of the lesions implies the lack of immunohistochemical maturation in blue nevi. This preserved HMB45 protein expression in these nevus cells is indicative of their activated phenotype with active melanosome formation. Although mechanisms underlying this activated phenotype in common blue nevi are unknown, it may be reasoned to the release of melanocytic growth factors such as hepatocyte growth factor, endothelin-1, and α-melanocyte-stimulating hormone. These factors can alter the HMB45 protein glycosylation during various pathogenic states of melanocytes, help activate melanogenesis, and stimulate the motility and proliferation of the normal resting residual cells at the dermal melanocyte pools. It is possible that the cells of the common blue nevi directly arise from the activated extracellular dermal melanocyte stem cells. The latter persist after birth in the superficial nerve sheath of peripheral nerves. These cells can proliferate, giving rise to migratory melanocyte precursors with activated phenotype and HMB45 protein expression.
Figure 1  Immunohistological features of common blue nevi with HMB45 protein expression (diffuse or patchy staining patterns). (A, B and C), A case of 59-years old lady presented with 0.5 cm hyperpigmented glistening macule on the skin of the right arm. Histologically, the lesion is composed of a proliferation of spindle-shaped and dendritic melanocytes, admixed with pigment-laden macrophages ("melanophages"). Mitotic figures and junctional melanocytic activity are absent. Histologic maturation is seen at the peripheral and deep parts of the lesion, where the spindle-shaped cells insinuate themselves singly among the thickened collagen fibers of the reticular dermis. A sparse perivascular lymphocytic infiltrate is also seen. There is no individual cell necrosis or cells in mitosis. (D), Further immunohistochemical evaluation was performed with the proper positive and negative controls that revealed strong diffuse Melan-A staining. (E, F, G and H), The tumor cells show HMB45 protein expression throughout the entire lesion (diffuse pattern of staining). (I, J, K and L), A case of a 63-year-old lady with a 0.4 cm hyperpigmented macule on the chest wall. Sections show an admixture of the dendritic epithelioid melanocytes, melanophages in the mid reticular dermis amidst collagen bundles. (L), There is no mitosis or individual cell necrosis or inflammatory cell infiltrate. Further immunohistochemical evaluation was performed with the proper positive and negative controls that revealed strong diffuse Melan-A staining. (M, N, O and P), The tumor cells show diffuse HMB45 protein expression throughout the entire lesion.
**Figure 2** Immunohistological features of common blue nevi with HMB45 protein expression (patchy or individual cell staining patterns). (A, B and C), A case of a 56-year-old lady with a hyperpigmented macule, 0.2 cm, over the upper mid-back. Histologically, there is a well-circumscribed, symmetric dermal growth composed of elongated, finely branching melanocytes insinuated between the collagen fibers of the upper and mid dermis. The melanocytes are admixed with some melanophages. There is periadnexal (perifollicular) aggregation of the melanocytes. (D), Further immunohistochemical evaluation was performed with the proper positive and negative controls that revealed strong diffuse Melan-A staining throughout the entire lesion. (E, F, G and H), Some groups of HMB45 positive dermal melanocytes are noted (patchy pattern of staining). (I, J, K and L), A case of a 49-year-old lady with a smooth, gray-tan lesion, 0.7 cm in size, over the skin of the left buttoc. Histological sections show alteration of the dermis by a symmetric growth consisting of a variable admixture of dendritic melanocytes, some melanophages, and fibrosis. There is no apparent cytologic atypia, cell necrosis, or mitotic activity. Further immunohistochemical evaluation was performed with the proper positive and negative controls that revealed strong diffuse Melan-A staining throughout the entire lesion. (M, N, O and P), Occasional HMB45 positive dermal nevic cells are noted (individual-cell pattern of staining).

This study reported HMB45 protein expression in the dermal melanocytes of the common blue nevi, indicative of their activated phenotype. The underlying mechanisms of this activated phenotype, such as the role of growth factors, are open for further investigations.

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**Authors’ contributions**

Mahmoud Rezk Abbelwahed Hussein fully and solely contributed to the followings: Approval of the final version of the manuscript; critical literature review; data collection, analysis, and interpretation; effective participation in research orientation; intellectual participation in propaedeutic and/or therapeutic; management of studied cases; manuscript critical review; preparation and writing.
Prevalence of recurrent oral ulcers and association with ABO/Rh group systems in a Lebanese sample

Dear Editor,

Recurrent oral ulcers present a group of diseases characterized by repeated episodes of benign, contagious, or non-contagious and spontaneously-healing ulcerations in otherwise healthy individuals. These can range from traumatic, infective, aphthous, ulceration related to oral dermatoses, drug-induced, and ulceration as a manifestation of systemic disease. It is important that an experienced clinician examines oral ulcers and performs the necessary investigations with individuals suffering from recurrent lesions.

Usually, diagnosis is mainly based on the patient’s clinical history. In most cases, ulcers appear 3 to 6 times per year and last 7 to 10 days. However, the most common recurrent ulcerative condition of the oral cavity is by far recurrent aphthous stomatitis (RAS).

Several authors have studied the correlation between blood group antigens of recurrent oral ulcers, mainly RAS. However, to our knowledge, there are no studies on recurrent oral ulcers in the Lebanese population to date. Consequently, this study aims to assess the possible correlation between the ABO blood group and such lesions. Additionally, we report on the prevalence and distribution of recurrent oral ulcers in a sample of the general Lebanese population.

This was a cross-sectional survey study conducted between December 2019 till March 2020 in Lebanon. The survey questionnaire was constructed by a panel of oral medicine professionals. The questionnaire consisted of demographic questions in addition to 15, predominantly close-ended, questions on the participant’s history of oral ulcerations, frequency, period, blood group, and other associated factors. This study was reviewed and approved by the ethical committee of Baabda Governmental University Hospital.

The survey was conducted online and distributed via a participation link that points to the survey. Participants had the option to choose between English and Arabic. The survey was totally voluntary and anonymous. The only inclusion criterion was age older than or equal to 18 years old.

Data was then transferred into and analyzed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics were reported for all variables. The Chi-Square tests and Fischer’s exact test were used to assess statistically significant differences between categorical variables. Significance was interpreted at p < 0.05.

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Study conducted at Observe Clinical Research Group.