RIC

CARTA AL EDITOR

BRAF mutations among patients from the Northeast of México with malignant melanoma

Óscar R. Fajardo-Ramírez,* Julio C. Salas-Alanis,** Eduardo Guzmán-Huerta,* Ubaldo Martínez,* Álvaro Barbosa,*** Sean-Patrick Scott,* José A. Hernández-Hernández,* Luis M. Villela*

* Hematology and Cancer Cathedra, Escuela de Medicina y Ciencias de la Salud, Tecnológico de Monterrey. Centro Médico San José de Tec Salud.
** Departamento de Ciencias Básicas. Universidad de Monterrey.
*** Servicio de Patología, Escuela de Medicina y Ciencias de la Salud, Tecnológico de Monterrey, Centro Médico San José de Tec Salud.

According to the American Cancer Society, metastatic melanoma represents only 5% of all dermatology malignancies in the skin,[1] but it is responsible for 80% of all deaths. Due to a delay in diagnosis, it is estimated that only 14% of patients survive 5 years after diagnosis.[2] BRAF mutation has been reported in multiples types of cancer but there is currently no information on the prevalence of the BRAF mutation among Latin-Americans, especially in Mexican population. The most frequent mutation in this oncogen (BRAF V600) represents the 90% of cases,[3] therefore the objective of the study is to determine the prevalence of the BRAF mutation among a sample of patients with melanoma from the Northeast of México and correlate it to clinical characteristics.

Thirty-eight melanoma samples collected between 2001 and 2011 were selected from two different pathology labs located in Monterrey, México; one of them was a private Hospital (Centro Médico San José) and the other one from private clinic (MD Julio C. Salas-Alanis). A total of 38 samples were selected, but for technical reasons (DNA quality), just 33 included in this study (Table 1). Inclusion criteria were: pathological diagnosis of melanoma between 2001 and 2011, Mexican Hispanics, and a biopsy specimen embedded in paraffin with good quality. Exclusion criteria were others kind of skin cancer, fine needle biopsy, incomplete sample, and metastases into the skin from other primary tumor different from melanoma. Approvals by the Ethics and Research Committees of the School of Medicine Tecnológico de Monterrey were obtained. Clinical variables included sex, age at diagnosis, and anatomic site of the tumor. The anatomic site of the tumor was determined by the skin biopsy sent to the pathology laboratory, and was classified into five different categories:

- Head, face, or neck.
- Trunk.
- Arms.
- Legs, and
- Mucosa.

After appropriate pathologic confirmation of the diagnosis of melanoma of every sample, tumor samples were tested for BRAF V600E using a kit based on the PCR/hybridization method. DNA extraction was performed using the QIAamp DNA FFPE Tissue kit (Qiagen) following the manufacturer's instructions. The BRAF mutation was detected using the ViennaLab BRAF StripAssay® kit (ViennaLab Diagnostics GmbH, Vienna, Austria) according to the manufacturer's instructions. For the purpose of this study, the mutation of BRAF V600 was considered positive if it was found in the PCR analysis. Determination of the BRAF V600 mutation was considered a dependent variable. MINITAB 16 and Microsoft Excel 2007 were used to analyze the diffe-

Table 1. Demographics and Clinical Characteristics of the Studied Sample.

	Total (n=33, 100%) Frequency	BRAF+ (n=24, 73%) Frequency	Prevalence	95% CI	BRAF- (n = 9, 27%) Frequency	Prevalence	95% CI	P-value
Sex								
Male	21	15	71%	50-86%	6	29%	14-50%	1.00
Female	12	9	75%	46-91%	3	25%	9-54%	
Anatomic site of tumor								
Head/Face/Neck	8	5	63%	30-86%	3	37%	14-70%	0.22
Trunk	10	8	80%	48-95%	2	20%	5-52%	
Upper Extremity	5	4	80%	36 - 97%	1	20%	3- 64%	
Lower extremity	8	7	88%	51-99%	1	12%	1-49%	
Mucosa	1	0	0%	NA	1	100%	NA	
Unknown	1	0	0%	NA	1	100%	NA	
Clinical diagnosis								
Nodular melanoma	12	11	92%	62-100%	1	8%	0-38%	0.39
Acral lentiginous melanoma	1	1	100%	NA	0	0%	NA	
Superficial spreading melanoma (superficial + *in situ*)	7	5	71%	35-92%	2	29%	8-65%	
Spitz Nevi	1	0	0%	NA	1	100%	NA	
Metastasic melanoma	3	3	100%	NA	0	0%	NA	
Malignant melanoma not otherwise specified (*melanoma maligno*)	9	4	44%	19-73%	5	56%	27-81%	

Data as frequencies and percentages. P-Value calculated with c^2 test. NA: Not available. Confidence interval based on normal distribution with small sample correction.

rences between BRAF positive and BRAF negative groups. The results were expressed as frequencies or as percentage (%), the association between the clinical characteristics and the BRAF status was made using the χ^2 test, all tests were interpreted based on two-tailed hypothesis. The significance level was set at ≤ 0.05 in all cases. The BRAF V600E mutation was found in 24 patients (73%), while 9 patients were negative for this mutation (27%).The sex distribution among the total patients was 21 men (64%) and 12 women (36%); BRAF V600E mutation was positive in 15 men (71%) and 9 women (75%) with no statistical difference. The tumor localization were head and neck in 8 (24%); trunk in 10 (30%); arms in 5 (15%); legs in 8 (24%); on mucosa (0.3%), and indeterminable (0.3%), the BRAF status did not influence the localization.

With respect to the clinical diagnosis and the BRAF status, there was also not only dependence between them, but there was also an association specifically between the nodular melanoma and BRAF, been more often present the mutated allele in this subtype than in the wild type, as can be observed that 92% of the patients (11 cases) diagnosed as nodular melanoma harbor the mutated allele; whereas the wild type allele was present in only 8% of the patients (1 case). This is the first study of Mexican patients diagnosed with melanoma in the Northeast of the country, knowing BRAF V600E mutation status, and the correlation of it with their clinical features. Clinical implications of this type of studies are related to the evidence of improving the melanoma treatment with BRAF inhibitors. Several studies have been carried out to evaluate the prevalence of BRAF mutations in melanoma patients, regarding this; Si, *et al.*,[4] reported a 25.5% of melanoma cases with BRAF mutations in Chinese population. Another report by Lang, *et al.*[5] showed 25% of mutations in exon 15 of the BRAF gene from samples of melanoma patients from Glasgow, Scotland. In our study we found a higher prevalence of BRAF mutation, 73% of Mexican patients with melanoma harbor the V600E mutation. This study permits us to determine BRAF mutation status in northeastern population of México. In a previous study, Flaherty, *et al.*[3] reported that the prevalence of BRAF mutation in melanoma ranged from 40-60%. Therefore, as our data show, BRAF mutation prevalence among Mexicans is higher than in other populations, meaning that a considerable number of patients will

benefit with BRAF kinase inhibitors therapy. In summary, we provide a description of the BRAF status in patients diagnosed with melanoma; these findings suggest a new option for Mexicans from the Northeast with a diagnosis of melanoma carrying the BRAF mutation to benefit from new treatments.

REFERENCES

1. Miller AJ, Mihm MC. Melanoma. *N Engl J Med* 2006; 355: 51-65.
2. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J. Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation. *N Engl J Med* 2011; 30; 364(26): 2507-16.
3. Flaherty KT, McArthur G. BRAF, a Target in Melanoma. *Cancer* 2012; 116: 4902-13.
4. Si L, Kong Y, Xu X, Flaherty KT, Sheng X, Cui C, et al. Prevalence of BRAF V600E mutation in Chinese melanoma patients: large scale analysis of BRAF and NRAS mutations in a 432-case cohort. *Eur J Cancer* 2012; 48(1): 94-100.
5. Lang J, MacKie RM. Prevalence of exon 15 BRAF mutations in primary melanoma of the superficial spreading, nodular, acral, and lentigomaligna subtypes. *J Invest Dermatol* 2005; 125(3): 575-9.

Reimpresos:

Julio C. Salas-Alanis M.D.
Profesor e investigador de dermatología
Universidad de Monterrey
Correo electrónico: drjuliosalas@gmail.com

Recibido el 21 de marzo de 2014.
Aceptado el 14 de mayo de 2014.