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Comparing BRAF mutation status in corresponding primary and metastatic cutaneous melanomas: Implications on optimized targeted therapy

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Background: Selective oral BRAF inhibitors show promising results in the treatment of metastatic melanomas. Consequently, this mandates checking the concordance of BRAF status in primary (PM) and metastatic (MM) melanomas to optimize individual targeted therapy.

Design: Extended BRAF testing for 9 mutations on 95 lesions from 40 patients (men/women: 27/13; age= 59 13 years) including 40 PM with their corresponding MM (n=42), recurrences (n=9) and second primaries (n=4) was performed. Multiple metastatic sites were present in 9 patients [2 sites (n=6), 3 sites (n=2) and 4 sites (n=1)].

Results: BRAF mutation status was obtained for 85/95 (89.5%) lesions. V600E was the only identified mutation type documented in 35.4% of PM vs. 18.9% of MM. The overall PM-MM BRAF status discordance rate was 32.3% (11/34), and this was significantly more frequent in PM with mutant BRAF (8/12; 67%) versus PM with wild-type BRAF (3/22; 14%, p=0.005). Patients with metastasis to lymph nodes (3/20; 15%) were less likely to be discordant compared to those with metastasis to other sites (8/14; 57.1%, p=0.023). Females (7/13; 53.8%) were more likely to have discordant PM-MM BRAF status than males (4/21; 19%, p=0.06). Patient age was similar in patients with concordant and discordant BRAF status (58 13 vs. 62 14 years; p=0.41). PM anatomic location (p=0.23) and time-to-metastasis (p=0.55) were also unrelated to PM-MM BRAF mutation discordance. Discordant BRAF mutation status was predicted by multivariate binary logistic regression: 1) the presence of a mutant BRAF in PM [OR (95% C.I.) = 23.4 (2.4-229.7)] and 2) male gender [OR = 0.094 (0.01-0.93)]. MM-MM BRAF concordance was available for 6 possible comparisons and displayed a 100% concordance rate.

Conclusion: A high discordant rate implies the need for re-testing of the MM before initiation of BRAF targeted therapy. High MM-MM concordance advocates that testing the most accessible metastatic site is sufficient to obtain accurate BRAF mutation status.

Recent Publications:

1. Zgheib E, Habib R, Moukarbel R and Khalifeh I (2016) Old world leishmaniasis: an ancient disease with nonstandardized microscopic and clinical classifications. *J Cutan Pathol.* 43(10):815–20.
2. Alam E, Abbas O, Moukarbel R and Khalifeh I (2016) Cutaneous leishmaniasis: an overlooked etiology of midfacial destructive lesions. *PLoS Negl Trop Dis.* 10(2):e0004426.
3. Saroufim M, Charafeddine K, Issa G, Khalifeh H, Habib R, et al. (2014) Ongoing epidemic of cutaneous leishmaniasis among Syrian refugees, Lebanon. *Emerging Infectious Diseases* 20(10).
4. Antar A, El Hajj H, Jabbour M, Khalifeh I, El-Merhi F, et al. (2014) Primary effusion lymphoma in an elderly patient effectively treated by lenalidomide: case report and review of literature. *Blood Cancer Journal* 4(3).
5. El Khoury J, Khalifeh I, Kibbi A G and Abbas O (2013) Cutaneous metastasis: clinicopathological study of patients from a tertiary care center in Lebanon. *Int J Dermatol.* doi: 10.1111/j.1365-4632.2012.05650.x.

Biography

Ibrahim Khalifeh After earning his MD from Damascus Medical School in 1999, completed a surgery internship (2000-2001) and pathology residency (2001-2002) at American University of Beirut Medical Center. In 2002, he left for the USA where he did four years of training in Pathology and Laboratory Medicine at Wayne State University in Detroit (2002-2006), Oncologic Pathology and Cytopathology fellowships at MD Anderson Cancer Center (2006-2008) then he joined the University of Alabama where he completed one year of fellowship in Dermatopathology (2008-2009). Dr. Khalifeh is a diplomat of the American Board of Anatomic and Clinical Pathology, Cytopathology and Dermatopathology. He joined the Department of Pathology and Laboratory medicine at AUBMC in 2009 as assistant professor. He has been involved in multiple projects related to cutaneous leishmania, melanoma, dysplastic nevi and BRAF.

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