Microsatellite Instability Predicts Response to Anti-PD1 Immunotherapy in Metastatic Melanoma

Dear Editor,

Immune-checkpoint blockade is a type of passive immunotherapy aimed at enhancing preexisting anti-tumor responses of the organism, blocking self-tolerance molecular interactions between T-lymphocytes and neoplastic cells (1,2). Despite a significant increase in progression-free survival, a large proportion of patients affected by metastatic melanoma do not show durable responses even after appropriate diagnostic categorization and shared therapeutic choices (3-9). Therefore, predictive biomarkers of clinical response are urgently needed, and predictive immunohistochemistry (IHC) meets these requirements. Strong evidence suggests that DNA mismatch repair (MMR) deficiency is a frequent condition in malignant melanoma, as well as in other tumors (10). As is known, DNA MMR is a safeguard system for the detection and repair of DNA errors, which can randomly occur in the phase of DNA replication inside

Figure 1. Subungual primary melanoma with metastatic spreading to the brain and ileum in a middle-aged female patient treated with significant benefit by pembrolizumab: when compared with Mlh1, Pms2 and Msh2 status, the exclusive loss of IHC expression for Msh6 protein has been established. The ileal metastasis, here illustrated, and the one in the brain show the same IHC profile of the primary melanoma; they are in fact characterized by an exclusive loss of IHC expression for Msh6 protein, if compared with Mlh1, Pms2, and Msh2 status (hematoxylin and eosin; Mlh1: clone M1, Ventana; Pms2: clone EPR3947, Ventana; Msh2: clone G219-1129, Ventana; Msh6: clone 44, Ventana; chromogen: 3,3′ diaminobenzidine tetrahydrochloride hydrate; original magnification: ×10).

the cell. In humans, seven DNA MMR proteins (Mlh1, Mlh3, Msh2, Msh3, Msh6, Pms1, and Pms2) work in a coordinated and sequential manner to repair DNA mismatches. When this system is defective, the cell accumulates a series of replication errors in terms of new microsatellites; therefore, a condition of genetic hypermutability and microsatellite instability (MSI) takes place inside the cell itself (11). For this reason, my working group has started to search for MMR protein deficiency in melanoma biopsies from patients of both sexes and of all ages with metastatic spread, correlating the data with the response to pembrolizumab, the well-known anti-programmed cell death protein 1 (PD1) human monoclonal immunoglobulin G4, capable of blocking the interaction between PD1, the surface receptor of activated T-lymphocytes, and its ligand, the programmed death-ligand 1 (PD-L1), favoring melanoma cell attack by T-lymphocytes (1) rather than its depression (12). PD-L1 is highly expressed in about half of all melanomas and thus the role of PD1 in melanoma immune evasion is now well established (13). Surprisingly, the best therapeutic results to pembrolizumab, in terms of progression-free survival and overall survival, occur precisely in those patients, approximately 7% in my database, affected by deficient MMR (dMMR) melanomas. In particular, the most important benefits to pembrolizumab-based treatment have occurred in a female patient, who developed a subungual melanoma in the second finger of the left hand at the age of 41 years, together with lymph node metastases to ipsilateral axilla at the onset. The patient was promptly submitted to amputation of the first phalanx and emptying of the axillary cable. The primary tumor was a vertical growth phase melanoma with a Breslow's depth of 1.4 mm; three mitotic figures for 1 mm^2 were ascertained. There was no evidence of ulceration, regression, microsatellitosis, or lymphocytic infiltration; moreover, the surgical margins tested free of disease. Further molecular analyses did not show rearrangements in B-RAF and C-KIT genes. After four years, metastases appeared in the brain and ileum; however, at present the patient is still alive and in complete pembrolizumab response with progression-free survival and overall survival of 956 days and 2546 days, respectively. The tumor was afterwards identified as a dMMR melanoma for an exclusive loss of Msh6 expression on IHC (Figure 1). This finding is in line with the fact that the *U.S. Food and Drug Administration* has approved the use of pembrolizumab in 2017 for unresectable or metastatic solid tumors with MMR deficiency (14). In conclusion, dMMR melanoma seems to be a particular subset of disease that can be identified with high sensibility and specificity by predictive IHC as a complete loss of one or more DNA MMR proteins and that deserves targeted therapy.

References:

1. Najem A, Krayem M, Perdrix A, Kerger J, Awada A, Journe F, *et al.* New drug combination strategies in melanoma: current status and future directions. Anticancer Res. 2017;37:5941-53.
2. Roncati L, Barbolini G, Piacentini F, Piscioli F, Pusiol T, Maiorana A. Prognostic factors for breast cancer: an immunomorphological update. Pathol Oncol Res. 2016;22:449-52.
3. Piscioli F, Pusiol T, Roncati L. Nowadays a histological sub-typing of thin melanoma is demanded for a proper patient management. J Plast Reconstr Aesthet Surg. 2016;69:1563-4.
4. Piscioli F, Pusiol T, Roncati L. Wisely choosing thin melanomas for sentinel lymph node biopsy. J Am Acad Dermatol. 2017;76:25.
5. Piscioli F, Pusiol T, Roncati L. Diagnostic disputes regarding atypical melanocytic lesions can be solved by using the term MELTUMP. Turk Patoloji Derg. 2016;32:63-4.
6. Roncati L, Piscioli F, Pusiol T. Surgical outcomes reflect the histological types of cutaneous malignant melanoma. J Eur Acad Dermatol Venereol. 2017;31:279-80.
7. Piscioli F, Pusiol T, Roncati L. Higher predictive value of sentinel lymph node biopsy in patients with histological subcategorization of thin melanoma. Int J Dermatol. 2017;56:93-4.
8. Piscioli F, Pusiol T, Roncati L. Thin melanoma subtyping fits well with the American Joint Committee on Cancer staging system. Melanoma Res. 2016;26:636.
9. Roncati L, Piscioli F, Pusiol T. Current controversies on sentinel node biopsy in thin and thick cutaneous melanoma. Eur J Surg Oncol. 2017;43:506-7.
10. Iyer RR, Pluciennik A, Burdett V, Modrich PL. DNA mismatch repair: functions and mechanisms. Chem Rev. 2006;106:302-23.
11. Ellegren H. Microsatellites: simple sequences with complex evolution. Nat Rev Genet. 2004;5:435-45.

12. Roncati L, Barbolini G, Scacchetti AT, Busani S, Maiorana A. Unexpected death: anaphylactic intraoperative death due to Thymoglobulin carbohydrate excipient. Forensic Sci Int. 2013;228:28-32.
13. Wang X, Teng F, Kong L, Yu J. PD-L1 expression in human cancers and its association with clinical outcomes. Onco Targets Ther. 2016;9:5023-39.
14. U.S. Food & Drug Administration. FDA approves first cancer treatment for any solid tumor with a specific genetic feature. FDA News Release; May 23, 2017 (available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm560167.htm).

Luca Roncati, MD, PhD

Department of Medical and Surgical Sciences, University Hospital of Modena, Modena, Italy

Corresponding author:
Dr. Luca Roncati, MD, PhD
Department of Medical and Surgical Sciences
Institute of Pathology
University Hospital of Modena
Policlinico
I-41124 Modena (MO)
Italy
emailmedical@gmail.com

Received: March 11, 2018
Accepted: November 5, 2018