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A rare BRAF V600E mutation detected by next-generation sequencing in a superficial spreading melanoma: case report and potential diagnostic implications

Dear Editor,

Increased biological and therapeutic understanding in melanoma is drastically changing the mortality rate in advanced stages. According to the COSMIC database (Catalogue Of Somatic Mutations In Cancer, April 2019[1]), 41% of the melanomas harbour BRAF oncogene mutations and approximately 97% of BRAF mutations are situated in codon 600. The most common mutation (80–90%) is represented by a substitution of valine to glutamic acid (V600E), followed by valine to lysine (V600K; 5–12%).[1] These mutations enhance BRAF activity, leading to increased phosphorylation of MAPK/ERK pathway downstream molecules, especially MEK, resulting in cell uncontrolled

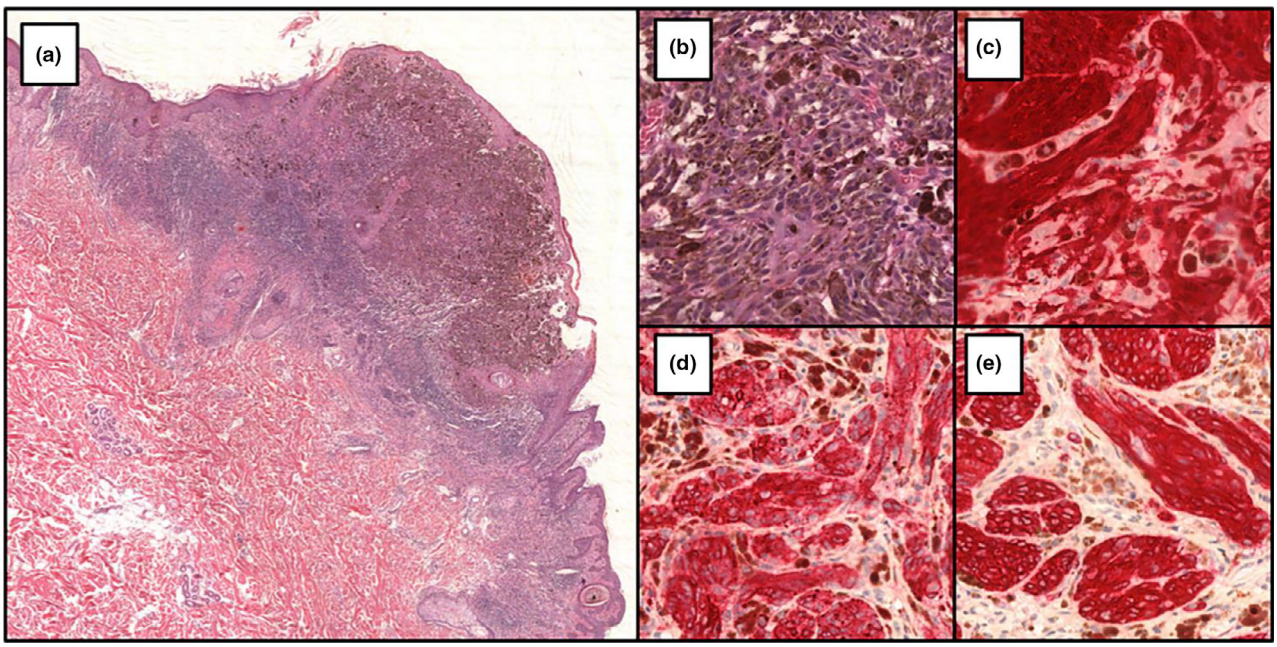

Figure 1 (a) Low-power photomicrograph showing asymmetric, lentiginous and continuous melanocytic proliferation, organized in cords and solid the dermo-epidermal junction and papillary and reticular dermis (magnification 4×); (b) high-power photomicrograph showing atypical melanocytes with a fused appearance, altered ratio nucleus/cytoplasm, evident eosinophilic nucleolus and large, weakly eosinophilic cytoplasm, often with granules of melanotic pigment (H&E magnification 40×); the cells showed immunoreactivity for S-100 (c), Melan-A (d) and HMB-45 (e) (magnification 40×).

proliferation.[2] We describe here a case of a 68-year-old female presenting with melanoma harbouring a rare BRAF V600E 1799_1800 TG>AA mutation.

Dermoscopic findings included irregular pigmented network, regression, irregular dots and ulceration. Histopathological examination of the lesion reported a superficial spreading melanoma of 1.6 mm Breslow thickness, Clark level III, 1 mitosis/mm^2 (Fig. 1a). Tumour cells expressed S-100, MART1 and HMB45 (Fig. 1c–e).

Staging CT scan revealed multiple pulmonary metastases in the middle lobe, anterior segment of the right lower lobe (RLL) and posterior segment of the left lower lobe (LLL) (Fig. 2a). Mutational analysis of BRAF with Real-Time PCR Kit Easy BRAF™ (DIATECH) was performed, and no mutation was detected in the BRAF gene. A nivolumab immunotherapy was immediately started, but a 4-month follow-up full-body CT scan revealed pulmonary disease progression (Fig. 2b). In consideration of the inoperable condition of the metastasis, the general status of the patient and the radiologic disease progression, we decided to repeat the BRAF mutation analysis using NGS testing with Actionable Tumor Panel UMI Kit (Qiagen, Milano, Italy) and a BRAF V600E 1799_1800 TG>AA mutation was detected. Consequently, the patient could start dabrafenib and trametinib combination treatment resulting in complete disease remission after 2 months of therapy (Fig. 2c). Currently, the patient has no signs of disease.

Metastatic melanoma is a disease of increasing incidence all over the world. Mutation in BRAF oncogene constitutes an important factor to direct proper treatment through targeted therapy.

Normally V600E mutation occurs when thymine is substituted with adenine at nucleotide 1799 (1799 T>A). Occasionally (89 on 302211 cases 0.029% reported on COSMIC[1]), this mutation can be associated with another substitution (adenine replaces guanine) taking place at nucleotide 1800 ('complex' mutation 1799_1800 TG>AA). Unfortunately, this mutation is not detected by the common BRAF Real-Time PCR kits, whilst it can be easily spotted by next-generation sequencing (NGS) method.

Indeed, BRAF V600E 'false negative' patients could be missing a life-saving therapeutic option such as BRAF and MEK inhibitors. In support of our hypothesis, a recent study by Zhu *et al.*[4] showed that out of 24 cases with negative BRAF V600E mutation analysed by allele-specific PCR, 16 (66%) harboured an actionable (FDA-approved therapy or available clinical trial) mutation detected by targeted NGS testing.

In addition, another study from Wheler *et al.*[5] reported how NGS might identify potentially actionable DNA alterations that could account for target therapy–resistance, paving the way for a precision-medicine approach in melanoma treatment.

In the near future, NGS will replace all established methods for molecular diagnostic, like PCR, for its high sensitivity and multiplexing options, allowing to generate a molecular profile of each analysed tumour sample.[3]

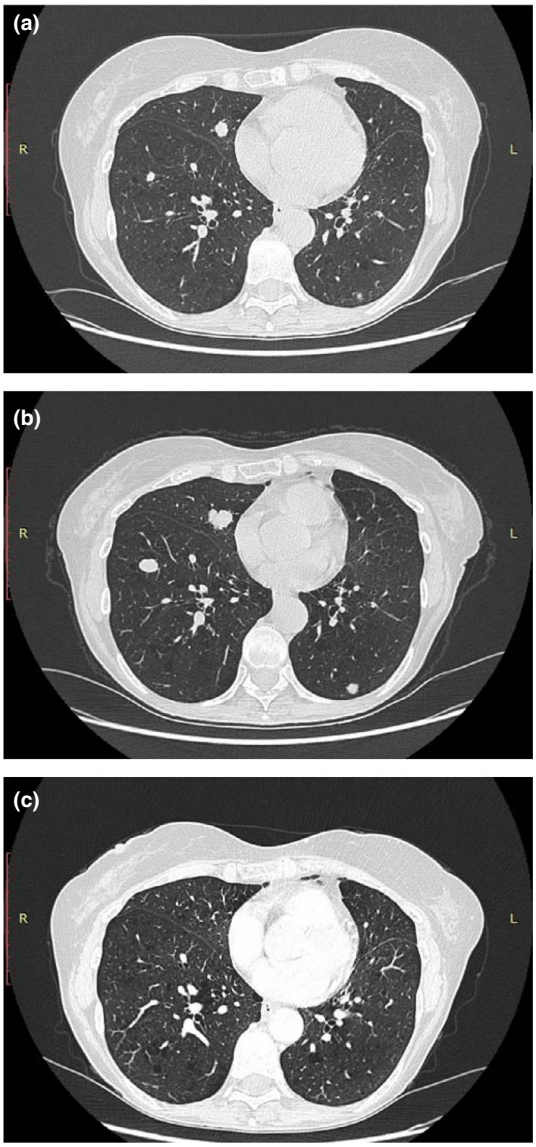

Figure 2 (a) Staging CT scan showing the presence of three nodular formations related to metastasis in the RLL, LLL and MLL of about 5–10 mm in diameter. (b) CT scan 4 months after metastasis appearance shows disease progression due to volumetric doubling of the three known repetitive lesions placed in the MLL, anterior segment of the RLL and posterior segment of the LLL. (c) CT scan 2 months after combo target therapy (Dabrafenib + Trametinib): complete remission of the nodular elements previously located at the pulmonary bases.

Further hypotheses and clinical studies could examine if tumour cells, harbouring a BRAF V600E 1799_1800 TG>AA mutation, are more or less responsive to immunotherapy agents as suggested by our case.

In the light of this, NGS would be especially valuable for clinicians in order to personalize the management of patients with

metastatic melanoma.[6] Our case highlights the importance of NGS assay as a mandatory tool for BRAF mutational status in melanoma.

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Kyrle disease associated with hidradenitis suppurativa successfully treated with tumour necrosis factor inhibition

Editor

A 41-year-old woman with a diagnosis of Kyrle disease (KD) and multitherapy-resistant hidradenitis suppurativa (HS) was referred for evaluation after having been unsuccessfully treated with oral retinoids (isotretinoin 0.5 mg/Kg/die for 6 months) and several cycles of antibiotics (clindamycin, rifampin and tetracycline). She had KD and HS since the age of 38 and 35 years, respectively, was a heavy tobacco smoker (20 cigarettes daily) and had a medical history of acne and rheumatoid arthritis (Charlson comorbidity index, CCI, score 0). An eventual familiarity for HS was not referred. The clinical examination showed numerous hyperpigmented, itchy, follicular keratotic papulonodular lesions on her upper and lower limbs related to the KD (Fig. 1a,b,c). Painful abscesses (pain visual analog scale score 90) and hypertrophic scars were observed at the inguinal regions and buttocks and were classified as HS Hurley II stage of severity with an Autoinflammatory Disease Damage Index (ADDI) of 3 (Fig. 2a,b). Her quality of life was severely hampered by disability and social discomfort (DLQI 27).

Adalimumab therapy was administered at the recommended dose for HS therapy (160 mg on day 1, 80 mg on day 15 and a single 40-mg injection every week from week 4 onwards). A marked and rapid improvement of HS skin lesions (pain visual analog scale score 0) with concomitant notable clinical remission of KD was observed after 24 weeks of treatment (Figs 1d,e,f; 2c, d). An improvement of overall quality of life was also referred (DLQI 2). The effect was durable over the 54 weeks of treatment, and adalimumab was well tolerated. In particular, we performed routine laboratory tests at baseline before starting adalimumab and every 3 months during the treatment and, auspiciously, we did not find any alteration in liver function tests, renal parameters or glycemia.

Kyrle disease is a rare subtype of acquired perforating dermatosis, characterized by hyperkeratotic and ulcerated nodules and papules which may coalesce to form circinate plaques, and usually involves the extensor surface of upper and lower limbs, and the trunk.[1] KD has been seen in association with multiple disorders, including diabetes mellitus, renal and liver diseases, congestive heart failure, hyperlipidaemia, infective diseases and abnormal metabolism of vitamin A.[2] To date, our case reports for the first time the association between KD and HS and the successful response to adalimumab therapy. Treatment options for KD commonly include topical corticosteroids and retinoids, keratolytic agents, nb-UVB and PUVA phototherapy, doxycycline and acitretin [1]. Discontinuation of these therapies often results in recurrence of skin lesions; hence, treatment of KD is frequently unsatisfactory and needs new molecules options.

Adalimumab is a highly specific tumour necrosis factor (TNF)-alpha inhibitor, binding to both soluble and membrane-bound TNF-alpha. TNF-alpha is a proinflammatory cytokine with a pathogenetic role in several immune-mediated diseases such as HS, psoriasis and pyoderma gangrenosum. The efficacy and safety of adalimumab in treating HS are largely demonstrated, whereas no evidence of its off-label use in treating KD has been reported.[3,4]