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## **Delayed oral toxicity from long term Vemurafenib therapy**

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Dear Editor,

We read with interest the article by Vigarios *et al.*<sup>1</sup> describing eight patients treated with a variety of BRAF inhibitors who developed asymptomatic hyperkeratotic oral mucosal lesions. These were frequently multifocal and presented following a mean onset of three months of treatment with a BRAF inhibitor. In one patient, one such lesion rapidly developed into oral squamous cell carcinoma requiring excision. We would like to highlight delayed oral toxicity in a long-term responder to a BRAF inhibitor.

We report a 70-year-old male who was commenced on vemurafenib therapy in March 2012 for BRAF mutant-positive metastatic melanoma. Within the first six months of treatment, he developed multiple cutaneous squamoproliferative lesions including four cutaneous squamous cell carcinomas. He has tolerated continuous treatment with vemurafenib 960mg twice daily, reporting only photosensitivity and plantar hyperkeratosis as adverse effects. In October 2014, after 32 cycles of vemurafenib, the patient complained of oral discomfort. Examination revealed extensive hyperplastic changes along the gingival margins (Fig.1a) with indurated hyperplastic ulcerated mucosa along the right buccal alveolus associated with the molar teeth (Fig.1b). There was associated plaque accumulation and similar, less severely affected areas along the left upper and left lower buccal aspect of the gingivae associated with the lower first and second molar teeth. The differential diagnoses we considered included a lichenoid reaction including lichen planus, infection with human papilloma virus, fixed drug eruption and malignancy. There was no response to potent topical fluticasone propionate 400mcg and chlorhexidine 0.2% mouthrinse. Multiple biopsies from the oral cavity demonstrated severe chronic inflammatory infiltrate and hyperplastic, severely inflamed squamous epithelium (Fig.2). Reactive nuclear atypia consistent with underlying inflammation was present. There was no dysplasia or invasive carcinoma. Although his symptoms improved with regular use of fluticasone mouthwashes, his oral lesions persist. He has continued on full dose vemurafenib and the latest staging CT scan at 3.5 years demonstrates no measurable disease. He continues treatment whilst being closely monitored by oncology, dermatology and oral medicine physicians.

We report the first case, to our knowledge, of a patient with metastatic melanoma responding to vemurafenib who developed multiple hyperplastic inflammatory oral mucosal lesions after two years and eight months, which have now been followed up for one year without malignant transformation. The time course of the oral mucosal lesions and their clinical appearance in our

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patient is quite different to those described by Vigarios *et al.*<sup>1</sup> Similarly, Mangold *et al.* described a patient who developed severely symptomatic gingival hyperplasia three months after commencing vemurafenib therapy which only resolved after treatment was discontinued due to disease progression.<sup>2</sup> Although no convincing evidence of dysplasia or invasive carcinoma was noted in our patient's oral biopsies, oral malignancy associated with BRAF inhibition has been reported.<sup>3</sup> Increased RAS signalling may contribute to the development of hyperplastic oral lesions as is thought to be the case for cutaneous squamous cell carcinomas arising in this context.<sup>4</sup> Reporting of adverse effects in long-term responders may help us to determine the mechanisms underlying these changes.

Oral mucosal lesions associated with BRAF inhibitor therapy may be under-reported as a systematic oral examination is not routinely performed. We agree with Vigarios *et al.* supporting the need for regular oral mucosal examinations in individuals with metastatic melanoma responding to BRAF inhibition, to identify lesions that may predispose to secondary oral malignancy.

## References

- <sup>1</sup> Vigarios E, Lamant L, Delord JP *et al.* Oral squamous cell carcinoma and hyperkeratotic lesions with BRAF inhibitors. *Br J Dermatol.* 2015;172(6):1680-2.
- <sup>2</sup> Mangold AR, Bryce A, Sekulic A. Vemurafenib-associated gingival hyperplasia in patient with metastatic melanoma. *J Am Acad Dermatol.* 2014;71(5):205-6.
- <sup>3</sup> Larkin J, Del Vecchio M, Ascierto PA *et al.* Vemurafenib in patients with BRAF (V600) mutated metastatic melanoma: an open label, multicentre, safety study. *Lancet Oncol.* 2014;15(4):436-44.
- <sup>4</sup> Su F, Viros A, Milagre C *et al.* RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. *N Engl J Med.* 2012;366:207-15.

## Figure legends

Fig. 1a – Examination revealed extensive hyperplastic changes along the gingival margins.

Fig. 1b – There was indurated hyperplastic ulcerated mucosa along the right buccal alveolus associated with the molar teeth.

Fig. 2a – Histological analysis of the abnormal areas showed severe chronic inflammation and hyperplastic, severely inflamed squamous epithelium (haematoxylin and eosin, x2 original magnification of lesion from right buccal alveolus).

Fig. 2b – There was underlying dense lymphoplasmacytic inflammation as well as epithelial nuclear atypia related to inflammation but no dysplasia (haematoxylin and eosin, x10 original magnification of lesion from right buccal alveolus).



