Multiple milia are superficial epidermal inclusion cysts (epidermoid cysts) that seldom cause discomfort unless they have ruptured internally, causing a foreign body reaction and consecutive abscess formation. Milia are most often found on the face and scalp and are associated with mild mechanical trauma or burning (1).

We report here a further case of multiple milia as a possible adverse effect of vemurafenib therapy. Vemurafenib is a B-Raf enzyme inhibitor approved for the treatment of late-stage melanoma harbouring a BRAF V600E mutation.

CASE REPORT
A male patient in his fifties presented with an asymptomatic skin eruption that had developed over the last 3 weeks. The patient suffered from malignant melanoma with distant metastases at the time of examination. First diagnosis of melanoma was 3 years ago with an ulcerated anal malignant melanoma measuring 6 mm in vertical diameter (pT4b). The patient refused any adjuvant therapy and remained free of progression for over one year until detection of bipulmonal and cerebral metastases. Stereotactic radiation was applied to the brain metastases. As mutation analysis of the primary melanoma revealed a V600E BRAF mutation systemic treatment with vemurafenib was advised but refused by the patient. Following chemotherapy with dacarbazine and due to further progression the patient received ipilimumab. As the metastatic disease progressed further the patient changed his mind on vemurafenib treatment and started with 920 mg twice daily orally. The patient denied any previous illness or infection and had not received any kinase inhibitor treatment in the past. Clinical examination 7 weeks after starting vemurafenib revealed multiple white, globular, follicular-bound, superficial keratinous cysts located on the cheeks as well as on chest and upper back varying in size between 2–10 mm in diameter and partly surmounted by a visible pore (Fig. 1a and b). The lesions had developed within 7 weeks after starting vemurafenib. At that time there were no signs of malignant skin lesions and no abnormalities on his hands and feet. A punch biopsy of the right cheek was performed (Fig. 1c). Microscopic examination revealed externally ruptured, non-inflammatory infundibular cysts containing walls of stratified squamous epithelium several layers thick with a granular cell layer resembling the infundibular portion of hair follicles (Fig. 1c).

Fig. 1. Clinical presentation with multiple white, asymptomatic, globular, follicular-bound, superficial keratinous cysts located on the cheeks (a) as well as on chest (b) and upper back varying in size between 2–10 mm in diameter and partly surmounted by a visible pore. Microscopic analysis (c) revealed externally ruptured, non-inflammatory infundibular cysts containing walls of stratified squamous epithelium that were several layers thick with a granular cell layer resembling the infundibular portion of a hair follicle (H&E staining).

As all possible therapeutic approaches for these lesions were refused by the patient the skin lesions persisted over the entire course of vemurafenib treatment. Beginning at 10 weeks after starting vemurafenib the patient also developed several keratoacanthomata as well as squamous carcinomata in sun-exposed areas such as his lower eye-lid, his chest and his left shoulder. As revealed later by the patient’s wife the patient stopped taking vemurafenib 8 months after start of the treatment; most interestingly, the cystic lesions disappeared afterwards to some extent. The patient passed away 2 months later due to a massive cerebral haemorrhage of his multiple brain metastases.

DISCUSSION
In our patient the multiplicity and the onset of appearance within 7 weeks after starting vemurafenib as well as the regression after stopping the treatment lead us to assume that these multiple epidermal cysts were indeed adverse skin reactions to vemurafenib. The use of vemurafenib significantly increases progression-free survival and overall survival in this population of patients, but is associated with numerous adverse skin reactions (2–6). According to the literature, almost all patients receiving vemurafenib presented with at least one adverse skin reaction (2, 4–6). The
most common cutaneous side-effects observed in around 50% of patients are verrucous papillomata and hand–foot skin reaction. Other common toxic effects of the skin are a diffuse hyperkeratotic perifollicular rash, photosensitivity and alopecia. Epidermoid cysts were observed in 33% of the patients as well as eruptive naevi, and malignant skin tumours such as squamous cell carcinoma and primary malignant melanoma were also reported (2–6).

It is noteworthy that multiple milia are known to appear predominantly on sun-exposed areas of the integument implying effects of UV-mediated DNA damage (1). Our patient reported extensive sun exposure due to garden work over several decades and appeared with chronically sun-damaged skin of his face, chest and upper back prior to vemurafenib treatment. To date, cystic lesions presenting as milia cysts on the face in melanoma patients treated with vemurafenib were observed in 13 patients (31%) in a single-centre report and occurred after a mean time to onset of 48 days (5). Most interestingly, multiple milia are described similarly but less frequently among patients undergoing treatment with sorafenib, a pan-RAF inhibitor (7, 8) suggesting a RAF-specific effect in the development of benign skin lesions such as multiple milia.

Multiple milia are a self-limiting disease and treatment is only necessary for cosmetic reasons or for relief of rare clinical symptoms such as inflammation due to internal rupture. The most effective treatment is evacuation using a sterile needle and applying tangential pressure. Moreover, effective treatment options for multiple lesions include topical retinoids and electrocautery (1). Without any treatment, secondary milia may resolve spontaneously but tend to persist (1).

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REFERENCES