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Current Perspective

Oncogene status as a diagnostic tool in ocular and cutaneous melanoma

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Abstract The majority of human tumours can be easily and correctly diagnosed based on clinical information and pathological assessment. In some cases however, correct diagnosis can prove difficult. In such cases, molecular approaches can be of significant diagnostic value. In recent years, the understanding of genetic alterations has greatly increased. In cutaneous melanoma, it is now well recognised, that 70–80% of tumours harbour *BRAF* and *NRAS* mutations. These mutations never occur in uveal melanoma. On the other hand activating *GNAQ* and *GNA11* mutations are found in ~90% of uveal melanomas, and are exceptionally rare in other melanomas (<1%).

Here, we demonstrate a number of melanoma cases, where distinguishing if a tumour was of cutaneous or ocular origin was not possible based on clinical and pathological assessment. In these cases there was either atypical clinical presentation or metastasis of unclear primary. Histological distinction between uveal and cutaneous melanomas, especially at the stage of metastasis, is not reliable as they can be morphologically very similar.

In all cases we present, a simple genetic assessment of oncogene mutation status was able to clearly define the melanoma type. This type of genetic assessment is of great diagnostic value

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and due to its simplicity could be performed in routine clinical practice even in smaller institutions.

1. Introduction

The majority of melanomas, both ocular and cutaneous, are easily and accurately diagnosed based solely on clinical and pathological assessment. In select cases however, correctly diagnosing melanocytic tumours with these criteria alone can be difficult. This can be due to tumours presenting atypically (i.e. at unusual locations or with unusual morphology, immunohistochemical [IHC] marker expression, etc.). Another scenario where proper diagnosis can be challenging is when patients present with malignant melanocytic proliferations at more than one site. Here the question can arise if the tumours are related or alternatively have developed independently of each other. In these cases, making distinctions based purely on morphology and IHC markers can prove difficult, in particular as these parameters are prone to evolve and change when tumours metastasise.

The last few decades have led to a detailed understanding of the genetic underpinnings of melanoma. This has brought the realisation that most melanomas harbour one of a few commonly occurring activating oncogene mutations. For cutaneous melanomas the majority harbour *BRAF* (50–60%) [1,2] or *NRAS* (15–30%) [3,4] mutations. Melanomas from acral, mucosal, and chronically sun damaged skin can also harbour *KIT* mutations or copy number gains [5].

Ocular melanomas consist of uveal and conjunctival melanomas. Uveal melanomas have been found to harbour activating *GNAQ* and *GNA11* mutations in 80–90% of tumours [6,7]. In contrast, conjunctival melanomas frequently harbour *NRAS* and *BRAF* mutations, similar to cutaneous melanoma [8].

Aside from determining oncogene status for classification and diagnostic purposes, it can also have considerable clinical consequences regarding both follow-up as well as therapy. The introduction of targeted therapies i.e. for mutated BRAF or downstream molecules of the MEK-ERK-pathway has dramatically improved the therapeutic options – but are only effective in patients with the relevant mutations [9–11].

Here we present select cases from our clinic, which highlight how determining oncogene status can be extremely helpful in correctly diagnosing either the melanoma type or the relationship between different melanocytic lesions.

1.1. Case 1

A 71-year-old patient developed a melanocytic tumour of the right eye (Fig. 1A), which clinically appeared to be of conjunctival origin. Pathology reported a melanoma affecting the conjunctiva with considerable intrabulbar involvement. Based on the clinical and pathological findings (Fig. 1A–D), the tumour was classified as a conjunctival melanoma. Local treatment consisted of ruthenium-106 brachytherapy. Four months later the patient developed liver metastasis (CT image, Fig. 1E). Whole body CT staging did not demonstrate other metastasis or further ocular involvement. One of the liver metastases was biopsied and the *NRAS* and *BRAF* mutation status determined, finding both to be wild type. Both the mutational status and the course of disease were not typical for conjunctival melanoma, but reminiscent of uveal melanoma. We sequenced *GNAQ* and *GNA11* and identified a *GNA11* Q209L (c.626A>T) mutation (Fig. 1F). The diagnosis was changed to uveal melanoma, most likely having originated from the ciliary body.

1.2. Case 2

A 74-year-old patient presented with a melanocytic lesion of the conjunctiva (Fig. 2A). The tumour was surgically removed and the diagnosis of a conjunctival melanoma made. Two months later, a uveal melanoma of the ipsilateral eye with periscleral and optical nerve invasion was identified. The patient received an enucleation.

A subsequent genetic analysis of the conjunctival melanocytic lesion demonstrated a *GNA11* Q209L (c.626A>T) mutation (Fig. 2B) and a complete loss of chromosome 3 in copy number analysis. The conjunctival tumour was therefore re-diagnosed as a metastasis of the uveal melanoma.

1.3. Case 3

A 55-year-old female presented with a swollen lymph node, which was extirpated and on pathological review diagnosed as a metastasis of a malignant melanoma. No primary cutaneous lesion was identified and the patient received inguinal lymph node dissection. At the same time, the patient described a worsening of vision of the right eye. Fundoscopy revealed a melanocytic choroidal