Program III: Molecular and genetic properties of changing naevi
Patient: Female, 39 years old

Lesion: Central Mid Back

Lesion: Chest
Dynamic Changes in Nevi of a Patient With Melanoma Treated With Vemurafenib

Importance of Sequential Dermoscopy

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Background: Therapy with vemurafenib, an inhibitor of mutated BRAF, yields a response rate of approximately 50% in patients with metastatic melanoma harboring a BRAF V600E mutation. As an adverse effect of vemurafenib, proliferative disorders of keratinocytes, including squamous cell carcinoma, have been described. Low concentration of vemurafenib as present in the epidermis were found to activate wild-type RAF, which, in combination with a preexisting RAS mutation, can promote keratinocyte proliferation. While activating BRAF mutations occur in approximately 50% of melanomas, they are even more frequently observed in melanocytic nevi.

Observation: We present the case of a patient with dynamic changes of melanocytic nevi well documented by sequential digital dermoscopy during vemurafenib therapy. A variety of dermoscopic changes were observed. First, nevi involuted, and all of these originally showed a centrally elevated papillomatous and predominant globular pattern. Second, preexisting nevi increased in size, and pigmentation that rendered them atypical. Such lesions were flat and showed a predominant reticular pattern at baseline. Third, multiple new nevi occurred. One example of each of the latter 2 categories was excised and showed wild-type BRAF.

Conclusion: Our findings of changing nevi in a patient treated with vemurafenib highlight the need for sequential skin examinations, including dermoscopy.

BRAF<sup>V600E</sup> mutation status in involuting and stable nevi upon BRAF± MEK treatment

McClenahan P et al.
JAMA Dermatology 2014
A: Before BRAF inhibitor

B: Eruptive Nevi 5 months after initiation of BRAF inhibition

C: Involution of nevi 14 months after combined BRAF and MEK inhibition
Melanocytic nevi excised during B-Raf proto-oncogene (BRAF) inhibitor therapy: A study of 19 lesions from 10 patients

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Background: There are limited descriptions of histopathology and immune profiles of new or changing melanocytic nevi in the setting of B-Raf proto-oncogene (BRAF) inhibitor therapy.

Objective: We sought to identify their distinctive features.

Methods: Clinical charts and histologic review, neuroblastoma RAS viral (v-ras) oncogene homolog genotyping, and immunohistochemistry for HMB-45, BRAFV600E, phosphorylated extracellular signal-regulated kinase (pERK), phosphorylated protein kinase B, CD4, and CD8 were performed on 19 melanocytic nevi from 10 patients and 23 control nevi.

Results: BRAF inhibitors were administered for metastatic melanoma (7), colonic adenocarcinoma (2), and papillary thyroid carcinoma (1). The average duration of BRAF inhibition before lesion excision was 8 months. Frequently associated histologic features included pigmentation of the stratum corneum, hyperpigmented keratinocytes, dermal melanophages, and deep HMB-45 expression. The lesions were BRAFV600E and neuroblastoma RAS viral (v-ras) oncogene homolog wild-type, expressed diffuse weak-moderate pERK, and possessed a predominance of CD8+ in comparison with CD4+ T lymphocytes within the dermal infiltrates.

Limitation: This is a retrospective study of a small and heterogeneous group.

19 melanocytic nevi from 10 patients and 23 control nevi diffuse weak moderate pERK a predominance of CD8+ in comparison with CD4+ T lymphocytes within the dermal infiltrates in BRAFwt lesions
Questions

1. How rapidly are naevi changing in Stage III and IV melanoma patients undergoing targeted therapies and/or immunotherapies and which germline genotype and molecular naevi characteristics predict these changes?

2. Are involuting and/or growing naevi clinical markers of response to targeted therapies and/or immunotherapies?

3. What differences in the somatic genotype of naevi are characterizing changeable naevi?

4. What defines distinct epigenetic profiles attributable to changeable naevi and how this relates to dermoscopic and histopathologic naevus types?

5. Differences in lymphocytic infiltration?

6. Differences in MAPK pathway signalling?
Key characteristics

- Observational prospective clinical study
- Cohort 1: 120 (including 20 patients as part of a pilot study) melanoma patients with stage III and IV will be recruited over a period of 18 months with a follow-up of two years
- Cohort 2: 50 high risk cohort, recruited from already existing pool of patients with: personal history of melanoma; family history of melanoma; atypical mole syndrome
- 3-D total body photography and dermoscopy imaging of all naevi larger > 5mm
- Baseline demographic data
- Germline DNA from saliva
- Blood to obtain serum or plasma and for biomarker
- Follow up: for BRAF/MEK 1xmonth on site; PD-1: Nivolumab 14 days; Pembrolizumab 21 days – initially from our side every 4th month, if necessary adjusted
- average of up to 3 naevi per patient (both cohorts), including one stable naevus
- Microbiopsies
- DNA, RNA, microRNA, and protein (QIAGEN Allprep kit)
- WES, SNP arrays, RNA-seq, miRNA-seq
- Methylation arrays (DNA methylation), Histone methylation
- Tissue slides: IHC for T cell infiltrate, lymphocytic infiltration, signalling pathways
Outcomes

• Define genetic and molecular changes in rapidly changing naevi in advanced melanoma patients compared to high risk individuals.
• Define whether distinct epigenetic changes are representative of changing naevi in metastatic melanoma patients versus high risk individuals
• Define treatment specific characteristic lymphocytic subpopulations (immune responses)
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