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Research letters

Acquired resistance to the Hedgehog pathway inhibitor vismodegib due to smoothened mutations in treatment of locally advanced basal cell carcinoma

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To the Editor: Sporadic basal cell carcinoma (BCC) is the most frequent malignancy in Caucasians. It mostly behaves indolently; however, when neglected, it can become destructive (locally advanced BCC).[1] Upregulation of Hedgehog (Hh) signaling is crucial in the development of almost all BCCs.[2] Vismodegib is a synthetic Smoothened (SMO) antagonist that inhibits the Hh pathway, with response rates up to 47.6% in locally advanced BCC.[3]

We saw a 68-year-old woman with a 15-cm wide deeply ulcerating infiltrative BCC on her left shoulder, which initially started as a small asymptomatic red papule that was neglected for 20 years (Fig 1, *A*). Magnetic resonance imaging (MRI) confirmed widespread tumor invasion of the shoulder girdle muscles but no evidence of lymphogenic or visceral metastasis. Because curative surgery and radiation therapy would impair shoulder function and enhance the risk of lymphedema of the arm, we treated our patient with vismodegib 150 mg once daily. Treatment resulted in dramatic clinical tumor regression within 8 weeks with complete regression and scar tissue remaining after 16 weeks (Fig 1, *B*). After 20 weeks of continuous treatment, multiple nodules became visible in the former tumor area (Fig 1, *C*). MRI showed multifocal tumor recurrence in the skin and underlying muscles. Biopsies of two of the skin nodules revealed infiltrative BCC (histology in Fig 1, *D-F*). Because of this progressive disease, vismodegib was discontinued and complete surgical excision was performed (week 27).

To unravel the mechanism of resistance, we performed mutation analysis on pretreatment tumor tissue, and on both responding tissue and recurrent tumor nodules (obtained at the time of surgical excision). With genomic DNA analysis of the PTCH1 coding exons (GenBank RefSeq NM_000264.3) a presumably heterozygous c.1728_1728+1delinsAA (Fig 2, *A*) mutation was found together with loss of heterozygosity in the primary BCC and in the recurrent tumor nodules, indicating that cells from the original tumor had survived. This mutation was not present in DNA isolated from buccal mucosa (saliva) or responding tissue.

Because vismodegib resistance in medulloblastoma is caused by acquired mutations in SMO,[4] we reasoned that similar mutations might explain resistance in BCCs. We therefore sequenced SMO (GenBank RefSeq NM_005631.4) in two recurrent BCCs and detected two different, novel heterozygous missense SMO mutations (c.842G>T (p.Trp281Leu) in exon 4 and c.961G>A (p.Val321Met) in exon 5) (Fig 2, *B*). These SMO mutations were not found in pretreatment tumor tissue, responding tissue, or buccal mucosa swab (not shown). The presence of 2 different mutations precludes a clonal origin of the resistant BCC nests, supporting tumor heterogeneity, even though they arose from the same clonal primary tumor. Possibly, even more SMO mutations might underlie tumor regrowth in this case, because not all new tumor nodules were biopsied. Our observation suggests that BCC can acquire resistance to vismodegib via different types of SMO mutations.

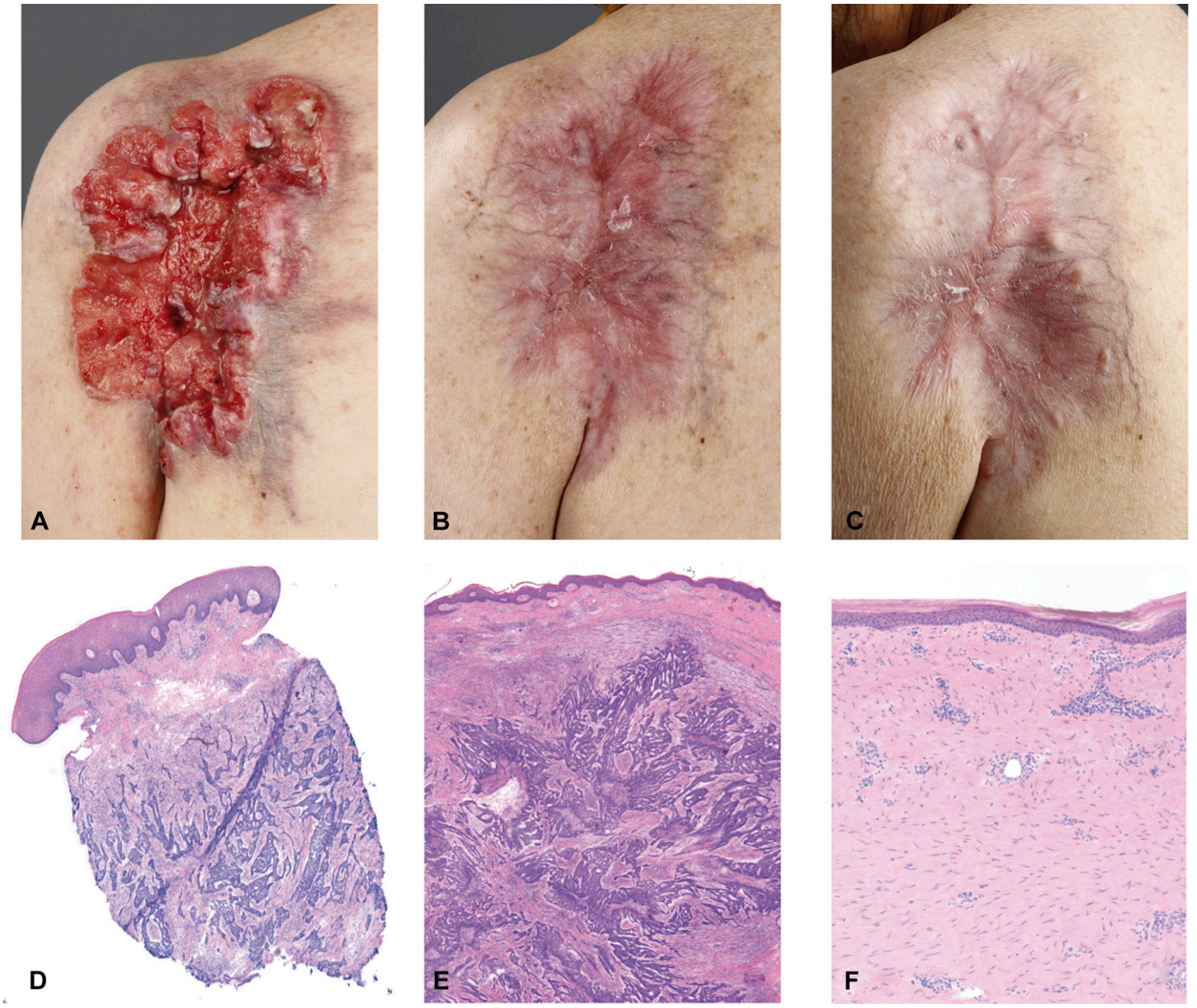

Fig 1. Clinical pictures and histologic examination on pretreatment and posttreatment tissue. **A**, Basal cell carcinoma (BCC) before treatment with vismodegib. **B**, Complete clinical response 16 weeks after start of treatment. **C**, Newly developed tumor nodules, 27 weeks after start of treatment. **D**, Tumor biopsy before treatment with vismodegib, showing infiltrative palisading basaloid cells reaching into the reticular dermis fitting the diagnosis of BCC. **E**, Biopsy from newly developed tumor nodule after 27 weeks of treatment with vismodegib, showing infiltrative basal cell carcinoma. **F**, Biopsy of responding tissue after 27 weeks of vismodegib, showing extensive fibrosis with an increased number of fibroblasts, neovascularization, a sparse lymphocytic infiltrate, but no residual BCC. (**D-F**, Hematoxylin-eosin stain; original magnification ×2.5).

Tumor resistance is a challenge in targeted treatment of BCC. Possible approaches to overcome tumor resistance are combination therapy with different small molecule inhibitors, sequential or rotational therapy with nontreatment periods, or alternating different small molecule inhibitors. These approaches may lead to synergistic therapeutic effects, a lower application dosage, and even prevention of (acquired) tumor resistance. Experience with targeted therapy for melanoma has already shown that combination of different agents leads to a delay in development of tumor resistance.[5] In vismodegib treated BCC, other SMO inhibitors, such as itraconazole and arsenic trioxide, are possible drug candidates for this strategy. In the future, mutational analysis on pretreatment and recurrent tumor tissue may contribute to anticipating the type of resistance, in order to proactively alter therapy and customize treatment of both patient and tumor characteristics.

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