Vismodegib treatment in a case of locally advanced basal cell carcinoma resulted in tumor destruction and complete wound healing through granulation tissue

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OBJECTIVES

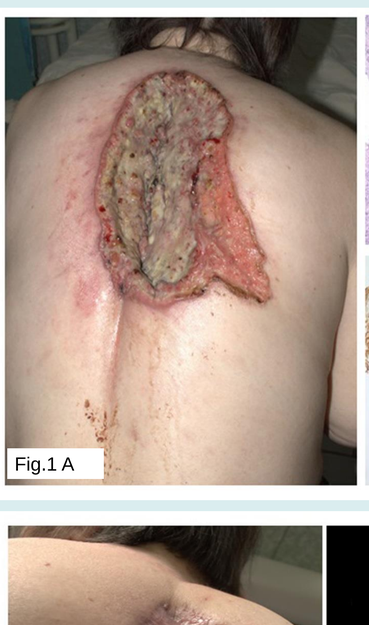
The role of Hedgehog (Hh) signaling pathway is well recognized during embryonic development. There is sufficient data that it is active in adults, promoting tissue repair by activation of stem cells. Alterations in the Hh signaling pathway are found to lead to development of several types of cancer, including basal cell carcinoma (BCC) (1-5).

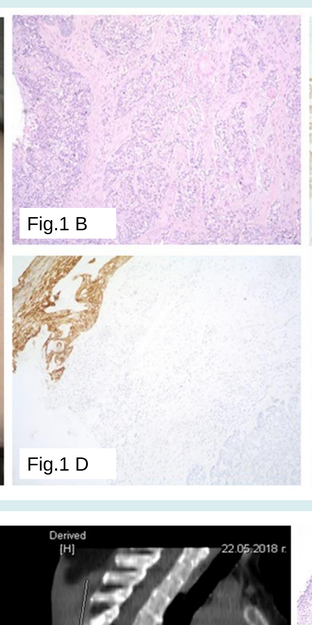
Hedgehog inhibitor vismodegib is therapy of choice for patients with locally advanced or metastatic BCC, not suitable for surgical treatment and radiotherapy (6). Vismodegib is a Hh inhibitor that binds to and inhibits Smo, which is involved in Hh signaling pathway (6). In addition to the classical activation of the Hh signaling pathway, alternative mechanisms of stimulation (non canonical) are known to exist (7-8) . Reviewed data from contemporary literature demonstrates that Smo is involved in both canonical and non-canonical Hh signaling pathways. Based on literature, it was further hypothesized that antagonists of one Smo dependent pathway may simultaneously be agonists of other Smo dependent pathway (5).

Aim of the current report is to describe the observed clinical and morphological anti-cancer effects in a patient with locally advanced BCC, under vismodegib treatment (150mg daily), to describe and analyze the clinical and morphological findings in the process of simultaneous tumor destruction and wound repair trough granulation tissue. We were intrigued by the fact that the tumor destruction did not result in a chronic wound rather was accompanied by substitution of the affected muscle, subcutaneous tissue and skin by granulation tissue.

PATIENT AND METHODS

A 56 year old, female patient with ulcerated locally advanced BCC affecting one third of the middle upper part of her back, reaching to the depth of vertebral processes, histologically verified as keratotic variant (Fig. 1) was under treatment for 12 months with vismodegib (150mg per day). Objective response were estimated by two control biopsies, two radiological examinations and four photo documentation files.





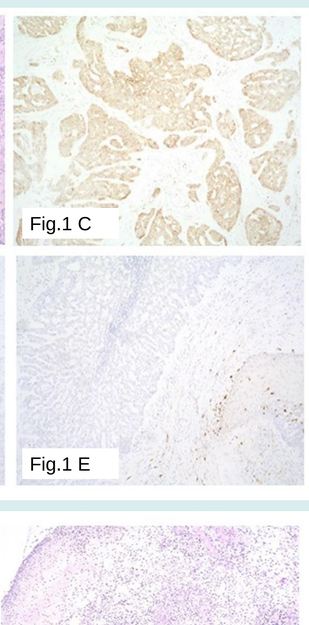


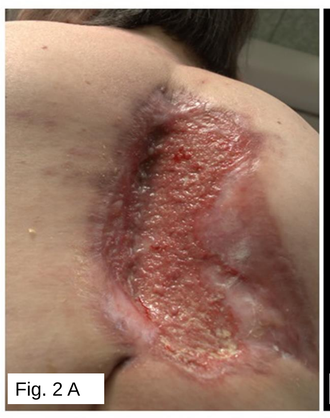
Fig 1A - Ulcerated, defect of the skin;

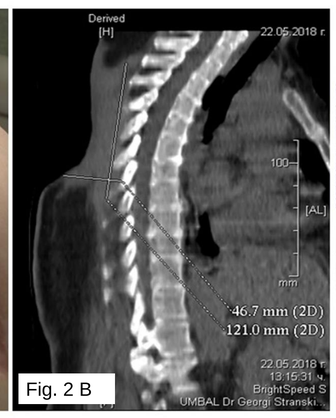
Fig 1B - Diagnostic biopsy revealed basal cell carcinoma keratotic variant with ulceration of the overlying skin (H&E, 100x);

Fig 1C - The tumor cells were immunopositive for Bcl-2 (Bcl-2, 100x);

Fig 1D - Negative staining for EMA (EMA, 100x);

Fig 1E - Negative staining for S100 (S100, 100x)





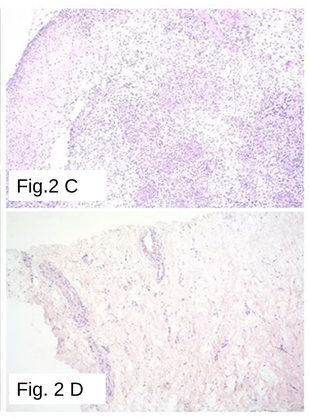
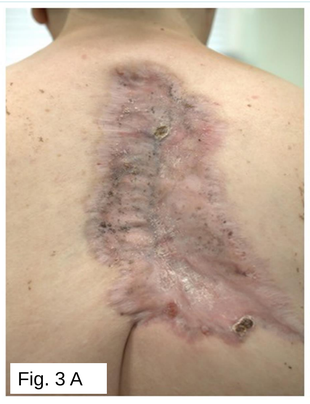
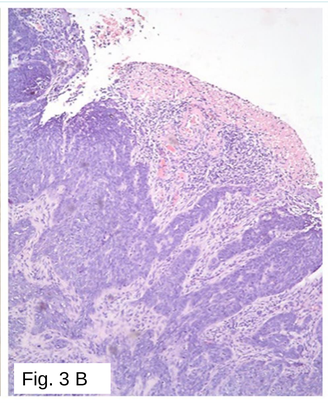


Fig 2A.Partly healing ulcerated, defect of the skin;

2B CT scan demonstrated soft tissue lesion affecting the median posterior and paravertebral area from Th3 to Th9, reaching in depth supraspinal ligament; Fig. 2C Biopsy demonstrated granulation tissue and mixed inflammatory infiltrate background (H&E, 200x);

Fig. 2D Core biopsy from the tumor site demonstrated morphological appearance of fibrotic scar (H&E, 200x)





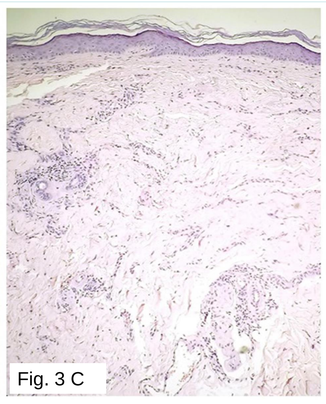


Fig 3A. Almost completely healed skin defect with limited ulcerated areas;

3B Biopsy demonstrated ulcerated skin with underlying infiltration from BCC (nodular variant) (H&E, 200x);

3C Non-ulcerated skin demonstrated morphological changes significant for scar. No skin appendages were evident (H&E, 200x)

RESULTS

For the twelve months of treatment, no further progression of the lesion was observed. The ulceration resolved completely and >30% reduction in the sum of the longest diameter (according to external visible dimensions) was observed. Local immunity was sufficient to prevent spread of bacterial infection. CT scan demonstrated substitution of the defects with fibrosis. First control biopsy demonstrated granulation tissue and mixed inflammatory infiltrate in the background with focal giant "foreign body“ cells. Deep core needle biopsy from the tumor site demonstrated morphological appearance of a fibrotic scar (Fig. 2). Second control biopsy from limited superficial ulceration demonstrated persistent tumor cells (Fig. 3). Partial response to treatment was observed. The patient is still currently under treatment.

Discussion

The result from vismodegib application in the described case showed simultaneous tumor destruction and replacement of the tissue defect by granulation. So far, several reports emphasize on the extensive granulation tissue growth in the context of vismodegib treated BCC (9-10). The current case elucidates three vital aspects: chronic wound due to BCC and normal tissue interaction, vismodegib induced BCC destruction and tissue repair by granulation tissue.

Chronic wounds can not heal due to multiple factors, including diabetes, infection and underlying tumor growth (11). In our case, the inhibitory role of tumor cells on the process of wound healing and repair is successfully overcome by vismodegib, which demonstrated considerable antitumor effect. Vismodegib is known to inhibit SMO and thus acts as an antagonist of the canonical Hh pathway, leading to inhibition of tumor cells proliferation and apoptosis (12). After commencement of vismodegib treatment, rapi development of granulation tissue occurrs suggesting that it may be more than just an antagonist of cancer growth but also acts as an activator of non-canonical Smo dependent Hh pathway in progenitor cells in the affected tissues as well as in bone marrow mesenchyme progenitor cells. Such possible double effect was suggested for other molecules affecting Smo (5). Mesenchyme progenitor cells are known to attenuate inflammatory responses thus preventing a wound to become chronic and secrete growth factors, promoting angiogenesis, fibroblast proliferation and deposition of collagen (13). Potential progenitor cell activation by vismodegib could be suggested as an explanation for our observations and could explain the resolution of the wound formation after the destruction of the BCC. The Hh signaling pathway is one of the many complex cell signaling pathways, known to coordinate inflammatory response and control tissue repair (14). The role of MMPs (including MMP-2 and -9) in the context of Hh signaling and inhibition should also be considered (15-16).

Despite the fact, that the exact mediators and pathways of tissue repair in the present case are uncertain, there is ample histological evidence of simultaneous tumor destruction and ongoing tissue repair with surprisingly good local control of bacterial infection of the wound in the context of Hh signaling pathway antagonist vismodegib.

We believe that pharmacological modulation of tissue repair signaling could be the way to achieve wound healing by scar formation or even complete structural and functional recovery of the skin.

CONCLUSIONS

- We observed a clinically meaningful benefit from vismodegib treatment in locally advanced BCC patient and efficient substitution of missing tissues with granulation tissue and wound healing.
- The observed tumor response and subdued chronic inflammation led to efficient tissue repair that made further reconstructive surgical procedures unnecessary.
- The detailed understanding of the interaction between vismodegib, BCC cells and normal tissue, leading to complete wound healing through granulation tissue will allow better planning of treatment and would make outcome predictable.
- *Take home message:* Vismodegib treatment achieves antitumor effect in BCC that is observed to be accompanied by efficient and rapid wound healing.
- *Take home question:* Could a Hh signaling pathway antagonist (like vismodegib) promote accelerated chronic wound healing as a Hh signaling pathway agonist?

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