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Case Report

A neglected basal cell carcinoma in a young patient: successful treatment with immunocryosurgery

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ABSTRACT

Patients with neglected basal cell carcinomas (BCC) still represent in many cases a therapeutic challenge. When feasible, surgery is the preferable approach; however, surgical treatment of large tumors may require extensive reconstruction, occasionally with substantial functional and aesthetic sequels. Currently, non-surgical modalities are intensively evaluated for BCC. In one of authors' departments the combination of cryosurgery during continuous daily imiquimod (immunocryosurgery) has been established as an effective, office-compatible tissue sparing treatment for all BCC <2cm in maximal diameter, including tumor relapses, and selected cases of larger tumors. Herein we exemplary demonstrate this modality by presenting the remarkable case of a young female patient with a giant (6x5 cm) BCC at her right temporal region that was successfully treated with immunocryosurgery: Complete clearance was achieved after five treatment courses, with corresponding treatment pauses, over a period of 11 months; the tumor remains relapse-free after 24 months follow up. Socioeconomic reasons and failure to pursue adequate health-care facilities may have contributed to neglect in the present patient. In conclusion, neglected, not complicated BCC in young patients can be successfully treated with non-surgical modalities, like immunocryosurgery.

Keywords: Basal cell carcinoma, Neglect, Imiquimod, Cryosurgery, Immunocryosurgery, Non-surgical treatment

INTRODUCTION

Basal cell carcinoma (BCC) is the most common cancer in individuals of European descent and it is typically diagnosed in the elderly.[1,2] When feasible, surgery is the most preferable therapeutic approach;[3,4] yet surgical treatment of large tumors may require extensive reconstruction measures, occasionally with substantial aesthetic and functional, sometimes mutilating sequels. For the aforementioned reasons, the search for efficacious, cost-effective, non-surgical treatment modalities for this frequent neoplasm is currently a promising active clinical research field. In one of authors' departments the combination of cryosurgery during continuous daily imiquimod (immunocryosurgery) has been established as an efficient, office-compatible, tissue sparing treatment for BCC <2 cm in maximal diameter, including tumor relapses.[5,6] Meanwhile this protocol has been adapted to treat certain cases of larger (quite >2 cm), invasive tumors.[7,8] Herein we present the case a

young female patient with a giant, neglected BCC that was successfully treated with a course of five immunocryosurgery cycles.

CASE REPORT

A 29-year old female patient presented with a solitary, slightly pruritic lesion of the right temporal area. She reported that two small adjacent nodules (the patient describes them as 'warts') had preexisted at this site since birth. During the last 10 years the present lesion grew out of them, slowly expanding to the currently 6x5 cm large pigmented, focally erosive, freely movable over the underlying structures plaque by progressive laterally expansion and substitution of the adjacent superficial skin structures (Figure 1A). Her rest medical history was unremarkable and she had given birth to two healthy children. Relevant laboratory examinations, including a CT scan of the skull, were within normal limits. A 4 mm punch biopsy showed basaloid tumor cell aggregations with peripheral palisading and occasional peripheral clefting embedded in a mucinous stroma. Tumor nests were partially connected to the epidermis. Histologic criteria in favor of a trichoblastoma / trichoepithelioma were not evident in the available material, particularly papillary mesenchymal bodies could not be recognized (Figure 2A).

We diagnosed a pigmented BCC that, in accordance to the history, might have developed out of a preexisting *nevus sebaceous*. The patient was concerned about the aesthetic sequels of the proposed surgery, and it was decided to commence immunocryosurgery. Figure 3 displays tumor size in the course of the treatment, along with the extent of the surrounding area of inflamed skin. In order to quantify the kinetics of tumor response to therapy, tumor and inflamed skin area around it were measured from serial digital clinical images as a function of time since the onset of treatment. Spatial scale in cm was set in baseline image (Figure 1A) using the size of the major axis of the tumor. To enable comparison the acquired images were spatially registered to the same coordinate system[9,10] and the surface areas of the structures of interest in the picture were planimetrically determined in cm^2. Complete clearance was achieved after five immunocryosurgery cycles with corresponding treatment pauses over a period of approximately 11 months (Figure 1B-1D). For each 5-week treatment cycle the patient applied a sachet of the commercially available 5% imiquimod cream (Aldara®, MEDA Hellas) every night on the entire lesion. A session of mild cryosurgery (liquid nitrogen, open spray, 2 freeze-thaw cycles, 15 sec of effective freezing time each) was performed at day 14 of each cycle to the lesional skin area, in appropriate surface sections (for detailed description of treatment protocol see: Supplementary Material in[7]). A treatment pause was instituted in-between the succeeding cycles (one-month pause intervals until cycle 3, more prolonged breaks thereafter; Figure 3). The clinically observed persistence of tumor rests was confirmed with a biopsy prior to the 4th treatment cycle (Figure 2B-2C and Figure 3). Therapy was generally well tolerated; however, during the 4th cycle the patient experienced a flu-like syndrome with headache, ipsilateral neck lymphadenopathy and low-grade fever (37.4°C), which peaked after the cryosurgery session. This was accompanied by a disproportionate induction of local inflammation at the site of treatment (Figure 3). The BCC cleared completely after the 5th treatment cycle and the patient remains disease free for 24 months thereafter.

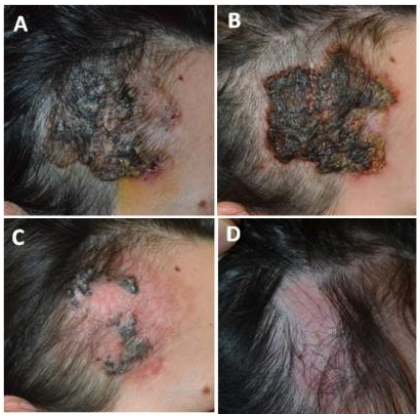

Figure 1: Panel A. Tumor at baseline. Panel B. Tumor at the end of the 1st immunocryosurgery treatment cycle. Panel C. Tumor remnants just prior to the 4th immunocryosurgery cycle at the day of the second follow-up biopsy. Panel D. The tumor area 18 months after the end of treatment.

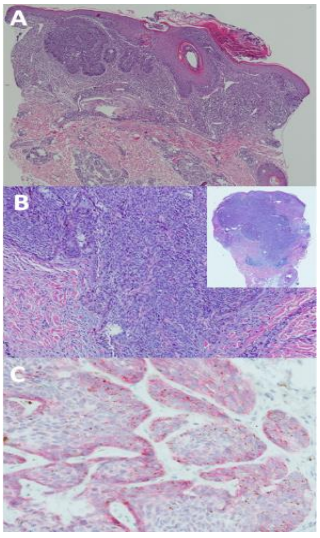

Figure 2: Panel A. Pretreatment: Superficial basaloid tumor nests with peripheral palisading (Haematoxylin-Eosin, original magnification: x4). Panel B. Representative histology of residual tumor after 3 immuno-cryosurgery treatment cycles ('2nd biopsy', Figure 3): Basaloid tumor cells nests with peripheral palisading and pigmentation (Haematoxylin-Eosin, x10). Insert: Basaloid tumor with partly vertical orientation but missing trichoblastomatous differentiation (Haematoxylin-Eosiv, x2). Panel C. Immunostaining with Ber EP4 (CD 326). Tumor cells are posi-tive and this is enhanced towards the peripheral areas of the aggregations (Tumor from 2nd biopsy: APAAP, x20).

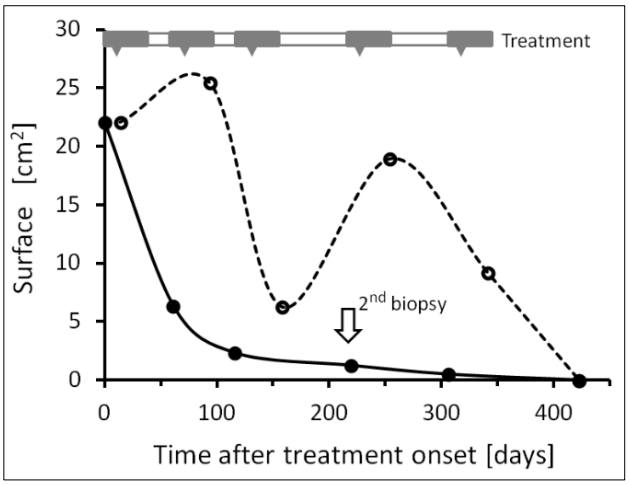

Figure 3: Diagram of treatment: course of tumor size (solid symbols; in cm^2) and the size of the accompanying inflammation (open symbols; in cm^2) in relation to the immunocryosurgery treatment cycles (shadowed periods correspond to imiquimod application; arrowheads indicate time-points of cryosurgery sessions within each immunocryosurgery cycle).

DISCUSSION

Basal cell carcinoma is a tumor of elderly individuals, e.g. being among females <30 years old about 60 times less frequent compared to individuals aged >85 years.[11] However, a BCC arising on a nevus sebaceous, although a comparatively seldom event, comprises one of the most prevalent subgroups of BCC by pathogenesis category seen in younger individuals.[12,13] In the present case we did not confirm the development of the BCC from a nevus sebaceous since we did not find any consistent remnants in the biopsied material. Based on the anamnesis information we still regard this tumor as a BCC that may have originated from a rather small nevus sebaceous, which was meanwhile completely substituted by the growing neoplasm. In the clinical-histopathological differential diagnosis of this case we also considered trichoepithelioma/trichoblastoma and basaloid follicular hamartoma (BFH).[14] A linear unilateral BFH[15] would be the most relevant latter diagnosis for this patient as it presents as a solitary plaque in a limited, mosaic pattern on the scalp and face.[16] Additionally the diagnosis of BFH was not supported by the histology (Figure 2); the basaloid tumor cell nests in this case extended relatively deeply into the interfollicular dermis and were not confined to the superficial dermis layers as is typical for BFH.[17] Notably, although a very uncommon event, we cannot completely exclude the possibility that the present BCC arose out of a preexisting, meanwhile completely ablated BFH lesion.[17] On the other hand regarding the differentiation from trichoblastoma / trichoepithelioma it is worth noting that this latter tumor is the most frequently arisen neoplasm in a nevus sebaceous.[13,18] A trichoepithelioma, a benign adnexal neoplasm, usually presents as a small, slowly growing plaque that shares many histopathological features with BCC and occasionally with the quite more aggressive microcystic adnexal carcinoma, a diagnostic challenge, particularly if only small and superficial biopsy probes are available.[19] Also the diffusely positive immunhisto-chemical staining pattern with the Ber-EP4 antibody (Figure 2C) although a sensitive marker for BCC is a feature shared also with trichoepitheliomas.[20] However, the observation of peripheral nest clefting - although limited in the present case- together with the mucinous stroma and the absence of papillary mesenchymal bodies are all in favor of the histopathological diagnosis of a BCC in our patient.[21] Last but not least, from the clinical point of view, BCC diagnosis is more fitting for this tumor. A giant solitary trichoepithelioma, consistent with the present lesion, is mostly a very rare polypoid lesion of the trunk. Conclusively, the most reasonable diagnosis in the present case is that of a BCC that may have originated in a nevus sebaceous and could be successfully treated with immunocryosurgery.

Another interesting observation during the treatment of this patient is the paradoxical excacerbation of the inflammatory reaction during the 4th immunocryosurgery treatment cycle, which was accompanied by treatment-associated systemic side effects and cannot be explained by the clinically evident tumor burden which was constantly decreasing (Figure 3). Since standard immuno-cryosurgery without any deviations was also applied during this cycle we suggest that still poorly understood immunopathological phenomena may have triggered the observed peak of inflammation. Significant perturbations in the numbers of circulating inflammatory cell subpopulations are found in parallel to local tumor tissue alteration during immunocryosurgery.[22] In particular, we have demonstrated that during the treatment of BCC with a standard 5 week immunocryosurgery cycle the number of Tregs that express the skin homing Cutaneous Lymphocyte Antigen ($CLA^+T_{reg}s$) initially increases to a maximum in the middle of the treatment cycle and subsequently decreases to normal levels again towards the end of the treatment period in parallel to diminishing tumor burden and intensity of the accompanying inflammatory tissue reaction. Since $T_{reg}s$ are well known to effect the damping of inflammatory responses[23,24] we suppose that their induction in the middle of the treatment cycle may be related to and contribute to the control of the inflammatory tissue reaction in the late phase of an immunocryosurgery cycle. Although lymphocyte subpopulation were not determined in the presented case - as they are not a routing study in our setting - we suppose that the preceding three repetitive treatment cycles might have induced inflammatory cell homeostasis perturbations that subsequently favored excess inflammatory response during the 4th cycle. We report this observation, because we are not aware of a similar outcome during immunocryosurgery for BCC; however, on the other hand our experience with repetitive treatment cycles is limited since we rarely need to apply more than two cycles to treat a BCC.[5-8]

Finally, large BCC are typically seen in elderly males,[25] and a giant neglected tumor in a young female is rather an exception. The pathogenesis of neglected BCC is complex and besides advanced age, psychiatric comorbidities play an important role.[26] However, the present case corresponds to an economic emigrant from another Balkan country, otherwise a healthy and active person. Socioeconomic reasons and inadequate locally available health-care facilities may have contributed to neglect. In conclusion, neglected, not complicated BCC in young patients can be successfully treated with non-surgical modalities, as is the proposed immunocryo-surgery. Meanwhile, vismodegib has been approved as the first-in-group hedgehog inhibitor for the treatment of advanced BCC with promising therapeutic activity for neglected tumors[27,28] and is available in some countries. However, the use of vismodegib must be used with particular caution in young female in reproductive age, like the present patient.[29,30] In the future, individualized treatment plans with targeted combination of modalities and close monitoring of ongoing response are essential in order to optimize minimally invasive treatment schedules for advanced BCC.

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