Case report

rare tumors

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Giant morphea-form basal cell carcinoma of the umbilicus: Successful debulking with vismodegib

Mariana Orduz Robledo[1], Eve Lebas[1], Marie-Annick Reginster[2], Mahmoud Baghaie[3], Sabine Groves[4] and Arjen F Nikkels[1,5,6]

Abstract

Basal cell carcinoma of the umbilicus is very rare. The nodular subtype is the main representative. Giant basal cell carcinomas represent around 1% of all basal cell carcinomas. The hedgehog pathway inhibitor vismodegib is indicated for advanced basal cell carcinoma and CD56-negative immunostaining seems indicative for successful treatment. A 54-year-old man presented a 10 cm × 14 cm large and 4.5 cm deep morphea-form basal cell carcinoma with faint immunohistochemical CD56 expression arising from the umbilicus. A sequential treatment was initiated with debulking using vismodegib 150 mg per day for 4 months, followed by reconstructive surgery. To the best of our knowledge, this is the first report of a giant basal cell carcinoma of the morphea-form type of the umbilicus. The sequential treatment plan reduces the duration of vismodegib inherent adverse effects and significantly reduces the tumor mass prior to surgery. Besides increasing adherence to vismodegib treatment, this approach facilitates the surgical technique and improves cosmetic outcome.

Keywords

Morphea-form basal cell carcinoma, vismodegib, umbilicus, neuroendocrine differentiation

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Introduction

Basal cell carcinoma (BCC) is the most common form of cancer in general and the most common type of skin cancer. BCCs are preferentially localized on photo-exposed areas, particularly the face and the scalp, although BCCs may be observed on non-photo-exposed areas. The most common subtype of BCC is nodular BCC (>60%), followed by superficial BCC (30%). The more invasive and aggressive forms, such as metatypic, plexiform, and morphea-form BCCs, are rare and more difficult to diagnose on clinical grounds only. This latter group has a poorer prognosis, a higher rate of recurrence, and may lead to locally advanced and/or metastatic BCC.

[1]Department of Dermatology, Liège University Hospital (CHU), Liège, Belgium
[2]Department of Dermatopathology, Liège University Hospital (CHU), Liège, Belgium
[3]Department of Radiodiagnostics, Liège University Hospital (CHU), Liège, Belgium
[4]Private Practitioner, Liège University Hospital (CHU), Liège, Belgium
[5]Skin Cancer Center, University de Liège, Liège, Belgium
[6]Department of Dermatology, CHU du Sart Tilman, University de Liège, Liège, Belgium

Corresponding author:
Arjen F Nikkels, Department of Dermatology, CHU du Sart Tilman, University de Liège, B-4000 Liège, Belgium.
Email: af.nikkels@chu.ulg.ac.be

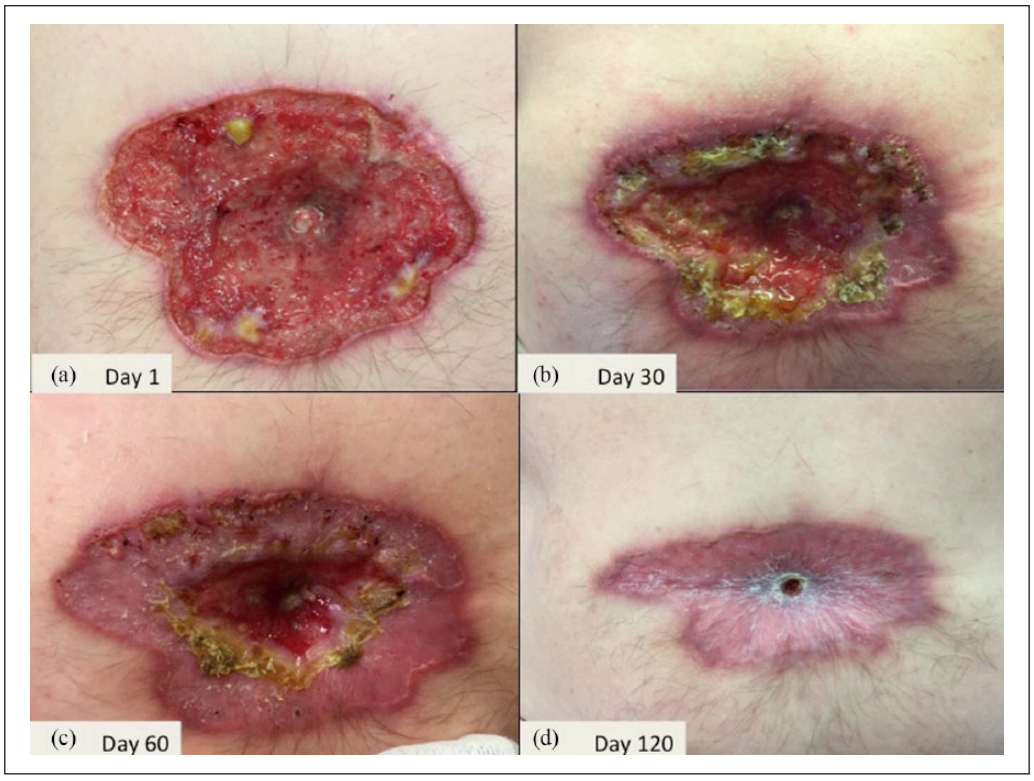

Figure 1. Clinical evolution of the giant morphea-form BCC after: (a) 1 day, (b) 30 days, (c) 60 days and (d) 120 days.

BCCs of the umbilical region are extremely rare and only 17 cases have been published until now.[1–4] Most of the reported umbilical BCCs were of the nodular subtype and accessorily of the superficial subtype.[1] Their mean size was around 1–1.5 cm in diameter.[1]

Giant BCCs (>5 cm in diameter) represent around 1% of all BCCs. Supergiant BCCs are even more exceptional and are defined by a lesion size exceeding 20 cm. Both types present extensive superficial spreading and deep ingrowth.[5–11]

Vismodegib and sonidegib are hedgehog pathway inhibitors (HPIs) indicated as oral treatment for locally advanced and/or metastatic BCC.[12,13] The HPIs significantly reduce the BCC tumor mass. Unfortunately, it is not uncommon to observe tumor regrowth following the interruption of HPI treatment. Furthermore, HPI-associated adverse effects, including muscle cramps, fatigue, loss of taste, and hair loss, may be difficult to tolerate for the patient on a long-term base. Hence, HPIs are more and more favored as debulking agents prior to surgery.[14]

To the best of our knowledge, this case is the first report of a giant morphea-form BCC of the umbilicus. This case illustrates the place of vismodegib as oral debulking agent in the treatment plan before surgery.

Case report

A 54-year-old male patient presented a 14 cm × 10 cm large and 4.5 cm deep ulcerated wound with infiltrated nodular borders centered on the umbilicus (Figure 1(a)). The borders were sharply delineated. The patient had no particular medical or surgical history. He did not take any medication but was a heavy smoker (more than 30 cigarettes per day since the age of 18). The lesion appeared about 8 years ago as a small and easily bleeding fleshy tumor of the umbilicus. The patient did not seek medical attention as the lesion was not painful and because he thought that what had appeared spontaneously would also disappear spontaneously. There was no history of chronic umbilical inflammation, prior radiotherapy, or traumatism to the lesion site. On clinical examination, the lesion did not adhere to the underlying fascia or muscle plans. There were no locoregional lymphadenopathies. There were no signs of a basal cell nevus syndrome or Gorlin syndrome. A clinical differential diagnosis of pyoderma gangrenosum, verrucous carcinoma, eroded spindle cell carcinoma (SCC), or eroded BCC was suggested. A 4-mm punch biopsy obtained under local anesthesia was suggestive for SCC (Figure 2(a)). Due to the clinical-pathological incoherence, a large excisional biopsy was performed revealing deep infiltrating morphea-form BCC (Figures 2(b) and 3(a)). Immunohistochemical studies revealed strong positive stainings for BerEp4 and chromogranin A, but CD56 expression was only marginal (Figure 3(b)). Ki67 immunostaining revealed numerous positive cells. Keratin 20 immunostaining was negative. The final histological diagnosis was an infiltrating morphea-form BCC with

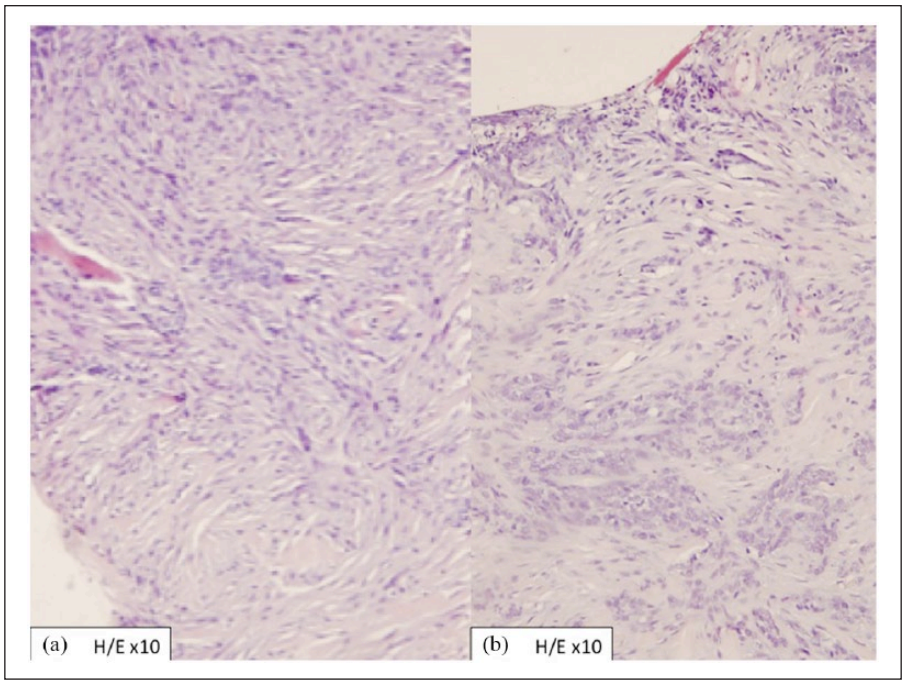

Figure 2. (a) Histopathologic suspicion of squamous cell carcinoma on the initial 4-mm punch biopsy, (b) Deep infiltrating morphea-form BCC on the excisionnal biopsy.

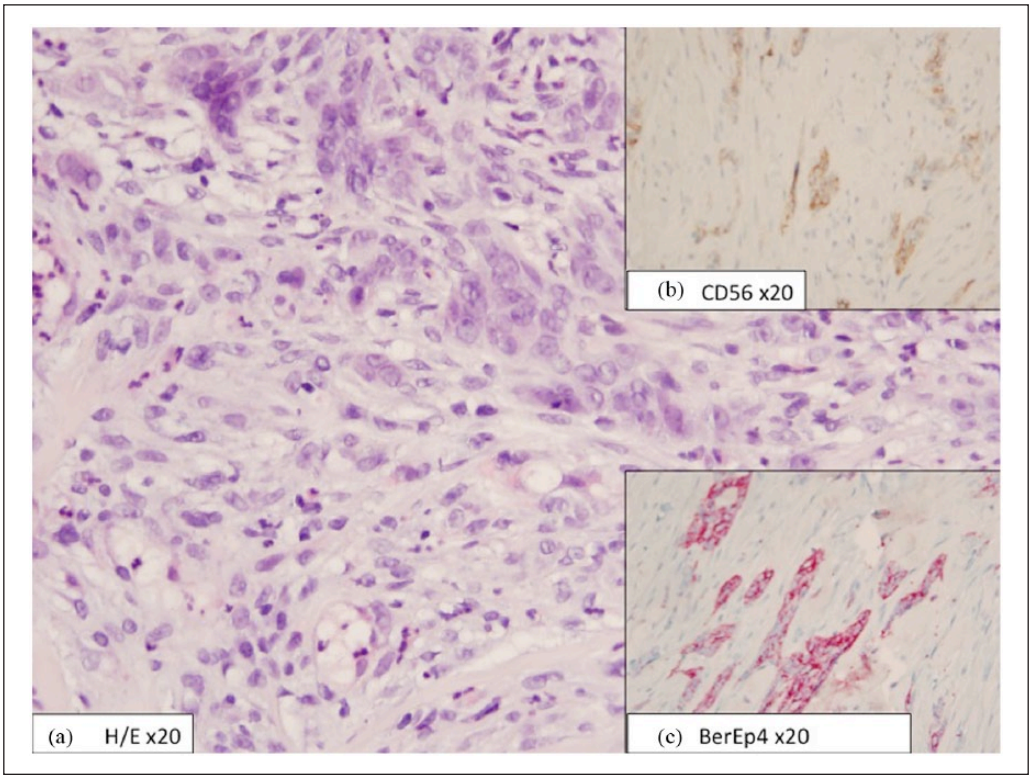

Figure 3. (a) H/E staining illustrating the sclerodermiform BCC, (b) faint CD56 immunostaining, and (c) strong immunohistochemical BerEp4 expression.

neuroendocrine differentiation. Blood screening revealed no abnormalities. Magnetic resonance imaging (MRI) revealed a deep tumor infiltration until the muscular fascia (Figure 4(a) and (b)). Ultrasound and computed tomography (CT) scan did not detect any further involvement of the loco-regional lymphatic ganglia.

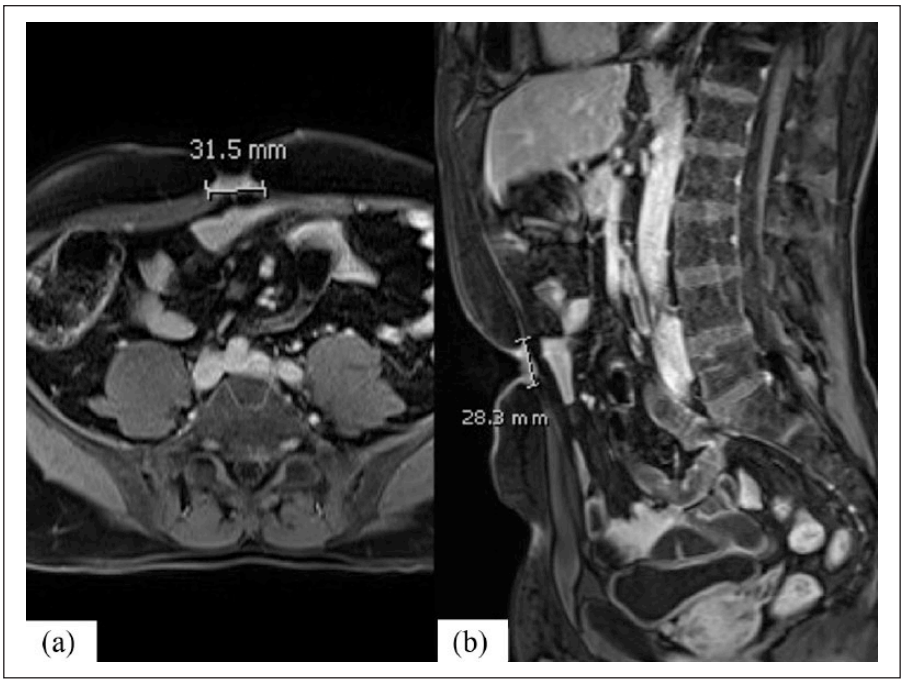

Figure 4. MRI illustrating the tumoral invasion until the abdominal fascia, (a) transversal view, (b) sagittal view.

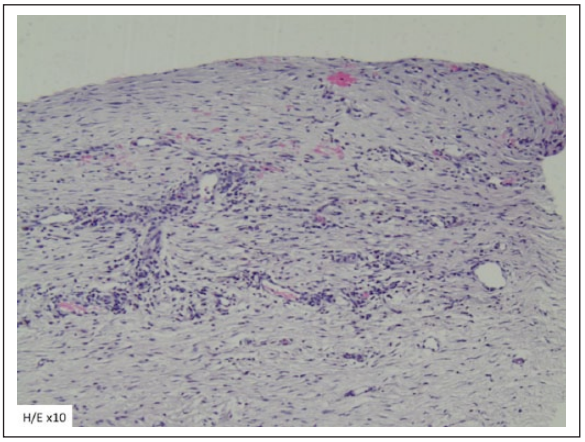

Figure 5. Histologic aspect of the skin after 4 months of vismodegib therapy, showing cicatricial tissue without residual tumor tissue.

The cutaneous tumor board decided, in accordance with the patient and his general practitioner (GP), for a two-stage sequential treatment plan, starting with a 3- to 4-month course of vismodegib 150 mg per day aiming at the reduction of the tumor mass followed by a new feasibility assessment for surgery. The common vismodegib-related adverse effects were observed in the form of alopecia, muscle cramps, and dysgeusia and later ageusia. The patient suffered most from the ageusia but accepted relatively well the other adverse events. Four months later, the lesion was significantly reduced in depth and extension and was not oozing or bleeding anymore (Figure 1(d)). The skin aspect was atrophic and cicatricial, not adhering to underlying structures. Ultrasound examination did not reveal any deep tumor infiltration. This significant shrinkage both in size and depth (Figure 1(a)–(d)) finally allowed plastic surgery, respecting a 0.5 cm surgical margin. Histology only revealed cicatricial scar tissue without any sign of residual BCC, particularly at the borders of the lesion (Figure 5). Until today, the follow-up is 6 months, and there are no clinical signs of BCC recurrence and ultrasound examination was unremarkable.

Discussion

BCC is the most frequent cutaneous malignancy in the light-skinned population worldwide and the most common cancer among all other cancers. Risk factors are long-term, cumulative ultraviolet (UV) light exposure, chronic inflammation, environmental exposure to carcinogens, including chemical agents and arsenic, immunosuppression, and genetic syndromes such as xeroderma pigmentosum and Gorlin, Bazex-Dupré-Christol, and Rombo syndromes.[15] Furthermore, smoking also seems to increase the risk for acquiring BCC.

The umbilicus is a fibrous scar with adherent overlying skin caused by the ligation of the umbilical vessels and urachus at birth. The umbilicus may present primary and secondary tumors. The first group includes cutaneous endometriosis, congenital polyps, benign nevi, papillomas, and adenocarcinomas. Secondary lesions are of metastatic origin and include, among others, the Sister Joseph's nodule, originating from gastrointestinal or ovarian cancer.[16]

BCCs arising in the umbilicus are exceptional. A recent review reports a total of 17 cases. Of 14 cases, histology was available and nodular BCC was observed in 9/14 cases, superficial BCC in 3 cases, and 2 cases were identified as Pinkus fibroepithelioma.[1] Women were more often involved.[1] The maximum size observed was 6.5 cm × 4.5 cm, but the gross majority of lesions were <2 cm.[1] Hence, typical umbilical BCC is not considered as a giant BCC. Median time to diagnosis was 24 months.[1]

BCCs may present several differentiation patterns such as squamous, sebaceous, apocrine, eccrine, pilar, and endocrine differentiation. Neuroendocrine differentiation of BCC, identified by chromogranin A and synaptophysin expression, was shown in 72.2% and 9.09% of BCCs.[17] Whether the neuroendocrine pattern in our case of umbilical BCC is related to the umbilical site remains unclear. Molecular profiling evaluating the Sonic Hedgehog/Patched/Gli axis mutations as well as mutational burden and other cooperating mutations could lead to a deeper understanding of the origins of this type of rare tumor, but was unfortunately not available.

Giant BCC mostly occurs in elderly male patients, with a peak incidence in the seventh decade of life. Giant BCCs are typically located on the trunk, most commonly the back, followed by the face and upper extremity.[6] It develops as a long-standing tumor with a mean disease duration of 14.5 years. After an initial indolent character, they may present aggressive and rapid growth, deep invasion but remain often painless. The average size at presentation is 14.7 cm in its largest diameter. The presence of metastasis at the time of presentation represents the most significant adverse prognostic factor. Local recurrence or metastasis develops in 38.3% of patients despite optimal therapy.[8] The overall prognosis is poor.[5,7–10] The overall reported cure rate is 61.7% after a mean follow-up of 2 years. In addition, the fear of diagnosis of cancer and a general distrust in traditional medical care seems common among patients with giant BCCs, hence delaying diagnosis and treatment.[5] The origin of giant BCCs seems to be overall neglect by the patient[7,10] or surgical traumatism.[3]

This article also illustrates the difficulty to correctly diagnose giant BCC on a 4-mm punch biopsy, probably related to the morphea-like cellular strands potentially mimicking infiltrating SCC.

The origin of umbilical BCC remains unclear, but several hypotheses may be proposed. A first risk factor is long-term cigarette smoking. Furthermore, BCCs are more prone to develop on cicatricial tissue, including the umbilicus. Third, chronic bacterial colonization and/or infection may create a long-standing inflammatory background, again favorable for the development of BCC.

A recent study evaluating the predictability to a positive response to vismodegib using various immunohistochemical markers (CD56, PDGF-R, CD117, MMP9, TIMP3, CXCR4) on BCC samples identified that a positive CD56 immunostaining was significantly associated with an increased risk of primary failure to vismodegib (odds ratio (OR) = 5.5; 95% confidence interval (CI): 3.4–29.8; $p = 0.0488$).[18] The marginal CD56 expression in our case was indeed correlated with a good clinical response to vismodegib.

Surgery was the preferred treatment option in 13/16 cases of umbilical BCC.[1] Particular care should be taken to a deep excision.[19] A surgical excision down to and including the umbilical attachment to the peritoneum may be needed, and intraoperative margin assessment using Mohs surgery is recommended to avoid the risk of excessive tissue removal or of incomplete excision.[19,20] Treatment recommendation for giant BCCs is wide and deep local excision of the tumor with or without postoperative radio-chemotherapy.[8] Close monitoring and long-term follow-up are mandatory due to the high rate of loco-regional recurrence.[8]

To our best knowledge, this is the first report of a giant BCC of the morphea-form subtype with a neuroendocrine differentiation originating from the umbilicus responding to vismodegib. Short-term use of HPIs is useful for debulking prior to surgery and helps to increase treatment adherence.

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