Rare bone toxicity associated with vismodegib

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INTRODUCTION

Basal cell carcinoma (BCC) is the most common skin cancer in white populations.[1] The majority of BCCs are easy to manage, thanks to a timely diagnosis and effectiveness of treatments in primary lesions, whereas locally advanced and metastatic diseases are still challenging.[1,2]

The introduction of hedgehog pathway inhibitors has radically changed the outcomes of difficult-to-treat BCCs.[2] However, the advantages in terms of disease control rates are obtained at the cost of common nonnegligible toxicities, mostly represented by muscle spasms, alopecia, dysgeusia, weight loss, and asthenia.[2] The duration of vismodegib treatment exposes patients to mild toxicities for a long period, leading to a high rate of discontinuation.[3]

Here we report the case of a 74-year-old woman affected by multiple advanced BCCs with lymph node metastases who experienced a rare bone toxicity during vismodegib treatment.

Abbreviations used:

BCC: basal cell carcinoma
CT: computed tomography

CASE DESCRIPTION

A 74-year-old woman presented in July 2017. Dermatologic examination showed 6 large lesions located on the trunk and upper limbs, with the largest one reaching 13 cm (Fig 1); some of them appeared as bleeding tumors and others as ulcerated plaques. Skin biopsies were performed for all lesions, with the histopathologic diagnosis of multiple BCCs. A total body computed tomographic (CT) scan showed axillary, retroperitoneal, and inguinal lymph-node metastases. The patient was hospitalized to receive blood transfusions because of severe anemia (hemoglobin level 6.1 mg/dL) and the Eastern Cooperative Oncology Group Performance Status score was 2.

Vismodegib treatment (150-mg oral capsules once a day) was started in August 2017. We observed a rapid improvement of the patient's general condition (Eastern Cooperative Oncology Group Performance Status score 1), and remarkable tumor shrinkage was obtained after 6 months of treatment (Fig 2). In October 2017, total-body CT scans showed a consistent reduction of all nodal metastases, although somatic vertebral collapses of T11, T12, L2, L3, and L4 were detected (Fig 3). Dual-energy x-ray absorptiometry bone densitometry of the hip confirmed severe osteoporosis (T score −3.0), and serum vitamin D levels were below normal limits. The patient started supplementation therapy with oral vitamin D (50,000 UI/week for 3 weeks, followed by maintenance therapy of 50,000 UI/month), calcium carbonate (1000 mg/day), and oral alendronate (70 mg/week). In February 2018,

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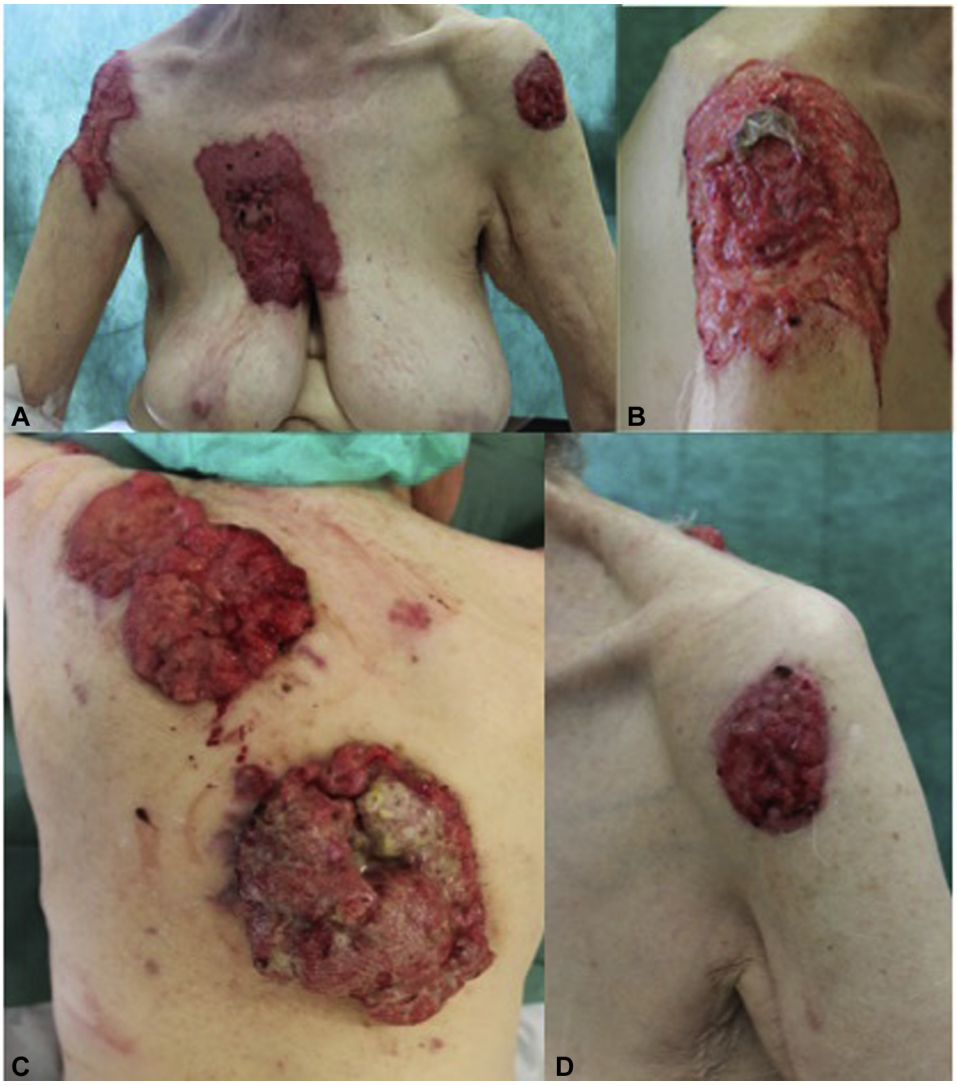

Fig 1. Multiple giant basal cell carcinomas on the trunk (**A, C**) and upper extremities (**B, D**) in a 74-year-old woman.

CT scans showed 2 additional costal fractures (Fig 4, *A*). The patient's clinical condition was progressively worsening (Eastern Cooperative Oncology Group Performance Status score 2), with accentuation of her kyphosis and a significant impairment in her daily activities because of worsening osteoporosis. A whole-body skeletal scintigraphy excluded bone metastases. We thus decreased vismodegib dosage to every other day and prescribed subcutaneous denosumab. A total-body CT scan in May 2018 revealed progression of nodal metastases and no new nontraumatic fractures; therefore, we decided to again increase the vismodegib dosage to a daily administration. In August 2018, CT scan showed lymph node partial response and initial consolidation of costal fractures (Fig 4, *B*). The patient is still receiving vismodegib treatment, maintaining the clinical response of all cutaneous BCCs and nodal metastases. Our patient did not show the common adverse events of vismodegib, with the exception of G3 alopecia according to the National Terminology Criteria for Adverse Events Version 4.0.[4]

DISCUSSION

The hedgehog pathway is an important signaling crossroad involved in proliferation and differentiation of cells and tissues. Its activation is known to play a role in bone homeostasis, affecting osteoblastic differentiation and bone mineralization with increased matrix deposition.[5,6]

The inhibition of bone turnover induced by vismodegib favored the development of nontraumatic fractures, thus leading to an unusual

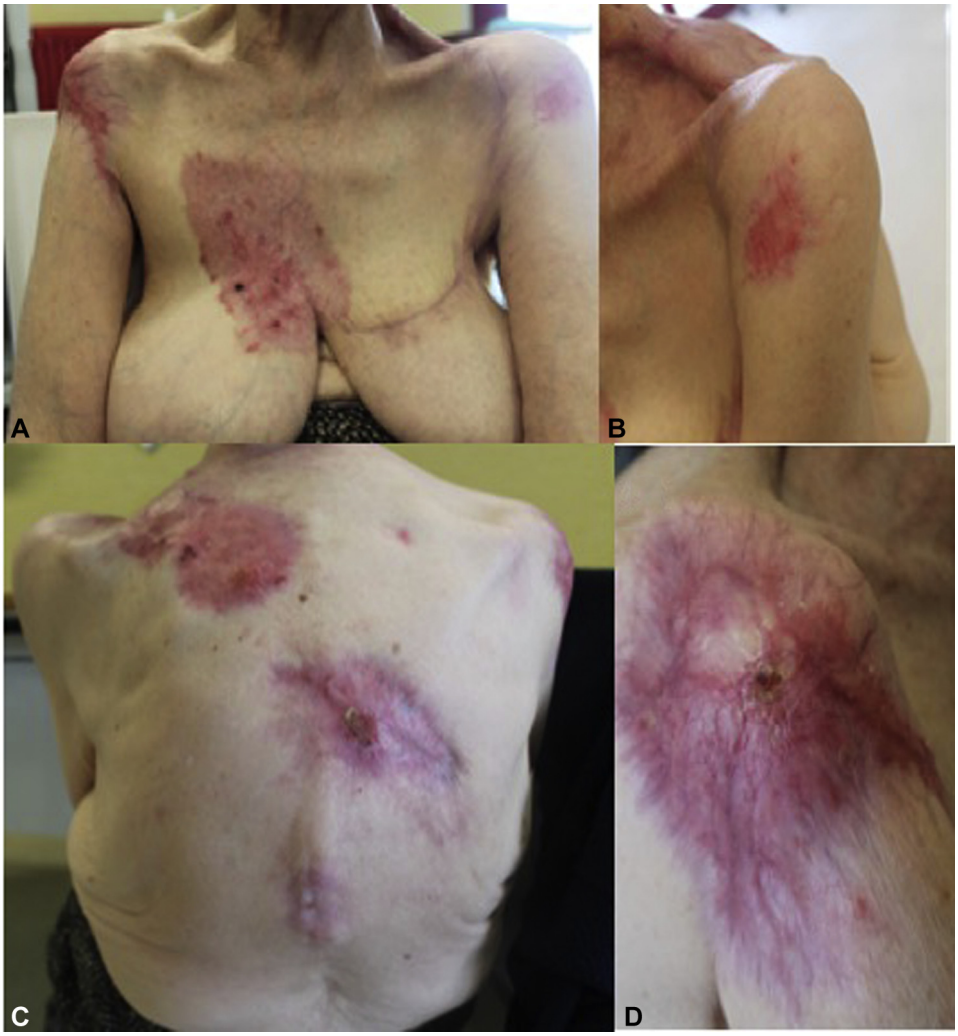

Fig 2. Remarkable resolution of all basal cell carcinomas after 6 months of vismodegib treatment (**A** to **D**).

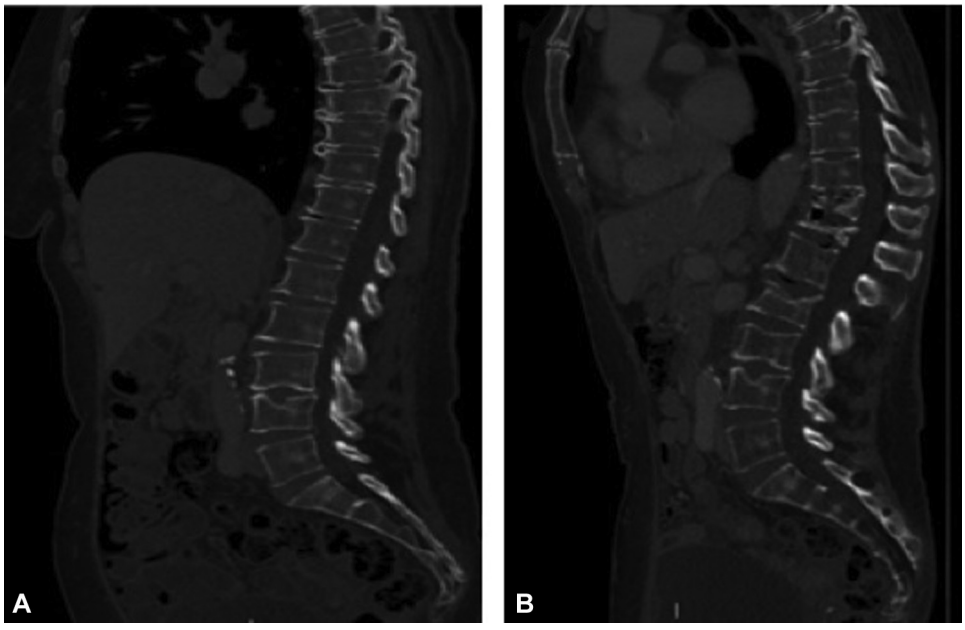

Fig 3. Computed tomographic scans at baseline in August 2017 (**A**) and scans showing somatic vertebral collapses in October 2017 (**B**).

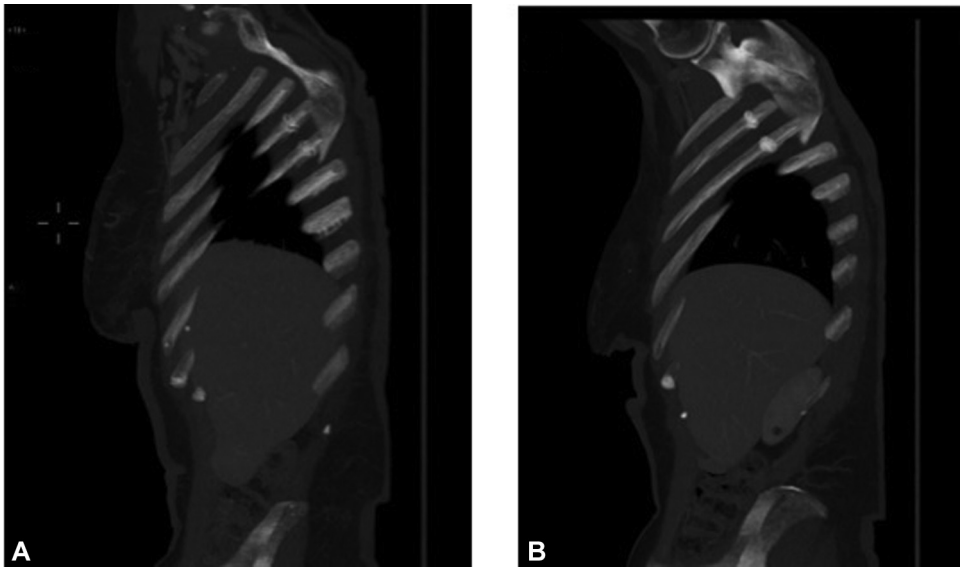

Fig 4. Computed tomographic scans showing costal fractures in February 2018 (**A**) and initial consolidation in August 2018 (**B**).

connective tissue toxicity. Six hip fractures were reported in the STEVIE study.[7] Bone toxicities were observed in preclinical studies in rats, and furthermore, premature fusion of the epiphyses has been reported in pediatric patients exposed to vismodegib.[8,9] To our knowledge, this is the first report of a severe bone toxicity associated with vismodegib. Management of bone toxicity requires a multidisciplinary approach. We emphasize the importance of vitamin D supplementation in frail elderly patients, especially in hypomobile postmenopausal women, before starting treatment with vismodegib because this drug, according to our experience, could worsen preexisting osteoporosis in patients with multiple risk factors. Latest guidelines confirmed the efficacy of alternate schedules, especially in case of cumulative toxicities.[10]

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