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Case Report

A Male Patient with Humoral Hypercalcemia of Malignancy (HHM) with Leukocytosis Caused by Cutaneous Squamous Cell Carcinoma Resulting from Recessive Dystrophic Epidermolysis Bullosa

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Abstract. Recessive dystrophic epidermolysis bullosa (RDEB) is a severe skin disorder. Although the patients are at risk for cutaneous squamous cell carcinoma (SCC), no case of cutaneous SCC derived from RDEB with humoral hypercalcemia of malignancy (HHM) has been reported. We present the first case report of a male patient with HHM with leukocytosis caused by cutaneous SCC resulting from RDEB. A 20-yr-old Japanese male patient with RDEB; the diagnosis was confirmed by electron microscopic examination, suffered an intractable skin ulcer and hypercalcemia and leukocytosis. PTH-rP, SCC antigen and Granulocyte colony-stimulating factor (G-CSF) levels were elevated. The histological diagnosis of the skin lesion was made well-differentiated SCC. Immunohistochemical staining showed the expression of PTH-rP in atypical tumor cells. For the control of hypercalcemia before an amputation, we used zoledronate safely and could control the serum Ca concentration in the normal range. After the amputation of his right leg including SCC, leukocytosis improved immediately and PTH-rP in blood decreased to the normal range. One month after the amputation, local recurrence of cutaneous SCC and multiple lung metastases were observed. PTH-rP increased gradually associated with hypercalcemia. Although the patient reached an unfortunate turning point about 4 mo after the amputation, we propose that zoledronate is an effective and safe treatment for HHM with cardiorenal complications.

Key words: squamous cell carcinoma, hypercalcemia, PTH-rP, G-CSF, recessive dystrophic epidermolysis bullosa, zoledronate

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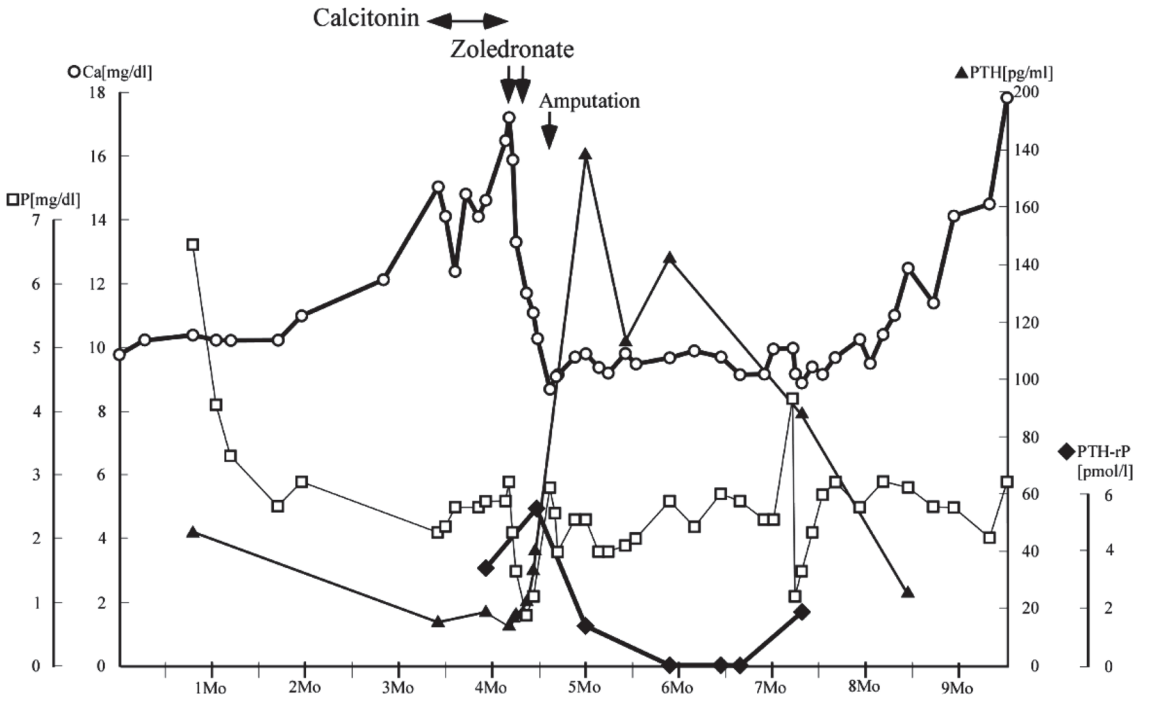

Fig. 1 Clinical course. The time course of Ca, P, PTH, and PTH-rP concentration are shown. The 0 mo is the referral point. The time course of the anti-hypercalcemic therapies using elcatonin and zoledronate and the amputation of the leg are indicated at the top.

Introduction

Epidermolysis bullosa (EB) is a family of genetic blistering skin diseases with dysfunction of cell adhesion molecules in the cutaneous basement membrane zone. Among these, recessive dystrophic EB (RDEB, Hallopeau-Siemens type; OMIM#226600) is caused by genetic mutation of type VII collagen securing the basement membrane to the underlying dermis. RDEB is characterized by trauma-induced blistering beneath the basement membrane, intractable skin ulcers, scarring, milia, and nail dystrophy. Patients with RDEB are at high risk of developing cutaneous squamous cell carcinoma (SCC). In RDEB, the cumulative risk is 76.5% by the age of 60 yr compared with a life-time risk of cutaneous SCC in the general non-EB United States population of 9–14% among men and 4–9% in women (1). Unlike sporadic SCC in the general population, RDEB-associated cutaneous SCC readily metastasizes and has emerged as a prevalent life-threatening complication in these patients.

Hypercalcemia has been reported secondary to various cancers. Parathyroid hormone-related protein (PTH-rP), which has significant homology with human parathyroid hormone (PTH) in the N-terminal region, interacts with a common PTH/PTH-rP receptor in bone and kidney, and causes humoral hypercalcemia of malignancy (HHM). Although lung SCC is sometimes associated with HHM, a little cases of cutaneous SCC have been reported, and no case of cutaneous SCC derived from RDEB with complicating HHM. We present here the first case report of a 20-yr-old Japanese man with both HHM and leukocytosis assumed to be due to the production of G-CSF caused by cutaneous SCC resulting from RDEB.

Case report

A 17-yr-old Japanese man was referred to the pediatric unit of our hospital for chronic cardiorenal failure due to prolonged malnutrition and body fluid loss from skin lesion. His height and weight were 130.0 cm (–7.2 SD) and 25.3 kg (–3.9 SD), respectively. He had a history of generalized trauma-induced blisters and erosions from birth. There was no family history of any similar skin conditions. Electron microscopy of his skin biopsy specimens confirmed the diagnosis of RDEB [Data have not obtained]. At the age of 20 (Fig. 1; 0 mo), he suffered an intractable skin ulcer on his right foot, treated by several ointments, which persisted for about 5 mo and eventually rose up like an exudative tumoral mass. As the ulcer expanded, serum calcium increased gradually and reached 14.6 mg/dl (Fig. 1; 3.5 mo). Dermatologic examination revealed widespread blisters, erosions, and scarring all over the extremities and trunk. There was extensive dystrophic scarring leading to flexion contractures, complete digital fusion and nail loss of the hands and feet and, on the right foot, an exudative verrucous tumor with an irregular margin was observed (Fig. 2A, B). Laboratory examinations showed a white cell count of 39,440 /mm^3 (neutrophils: 92.0%, Ca: 14.6 mg/dl (corrected by serum albumin concentration; Ca measurement+(4-albumin)), iP: 2.6 mg/dl, ALP: 863 U/l (normal value, 134–359), intact PTH: 19.0 pg/ml (10–60), PTH-rP: 3.4 pmol/l (<1.1), SCC antigen: 63 ng/ml (<2.0) and G-CSF: 402 pg/ml (<18.1). Twenty-four hours creatinine clearance was 14.8 ml/min, showing severe renal dysfunction, with preservation of urine volume (Table 1). A skin biopsy taken from the ulcerative tumoral mass showed the proliferation of atypical squamous cells with hyperkeratosis, cancer pearls and dyskeratotic cells, resulting in the histological diagnosis of well-differentiated SCC (Fig. 3A, B). Immunohistochemical staining with anti-PTH-rP polyclonal antibodies showed a positive reaction for atypical tumor cells (Fig. 3C). His leg X-rays revealed thin cortical bones, probably due to malnutrition or immobilization. Computed tomography (CT) scanning of his leg showed tumor mass invasion from his right internal malleolus up to near the knee joint with irregular margins. No evidence of metastasis was detected by whole-body CT, positron emission tomography and bone scintigram. Because diuretics therapy had already been started for chronic heart failure and rehydration was difficult because of cardiorenal complications, he was treated firstly with calcitonin (Elcitonin^R, Asahi KASEI, Japan) (Fig. 1). Serum calcium decreased temporarily,

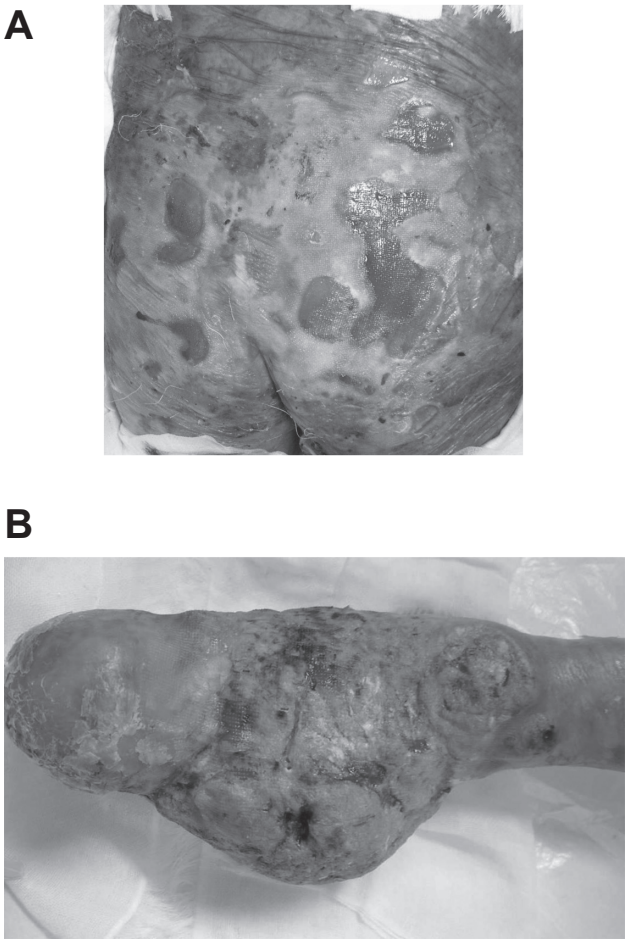

Fig. 2 Photographs of skin lesions. a: Widespread blisters, erosions, and scarring on the hip. b: Exudative verrucous tumor with an irregular margin on the right foot.

Table 1 Laboratory Data (at 3.5 mo in the Fig.1)

[Complete blood count]			
WBC	39,440	/mm^3	
neutrophils	92.0	%	
lymphocytes	4.5	%	
monocytes	3.0	%	
RBC	293 × 10^4	/mm^3	
Hb	9.4	g/dl	
Ht	28.7	%	
Plt	58.2 × 10^4	/mm^3	
[Blood chemistry]			
Na	138	mEq/l	
K	3.8	mEq/l	
Cl	103	mEq/l	
BUN	4	mg/dl	
Cr	0.7	mg/dl	
AST	21	U/l	
ALT	13	U/l	
Ca (corrected)	14.6	mg/dl	
iP	2.6	mg/dl	
ALP	863	U/l	(134–359)
ChE	973	U/l	
T-chol	222	mg/dl	
T.P.	6.4	g/dl	
Alb	2.4	g/dl	
CRP	15.6	mg/dl	
[other values on calcium and phosphate metabolism]			
BAP	68.5	U/l	(13.0–33.9)
NTx	157	mmol BCE/l	
Urine NTx	2,572	mmol BCE/mmol Cr	(<55)
1,25(OH)$_2$D	11.1	pg/ml	(20–60)
Urine Ca/Cr	1.06		
%TRP	73.0	%	
intact PTH	19.0	pg/ml	(10–60)
PTH-rP	3.4	pmol/l	(<1.1)
[Tumor marker]			
SCC antigen	63	ng/ml	(<2)
[Other]			
G-CSF	402	pg/ml	(<18.1)
[Urinalysis]			
Gravity	1.007		
pH	6.5		
Protein	(1+)		
Occult blood	(–)		
24h-Ccr	14.8	ml/min	

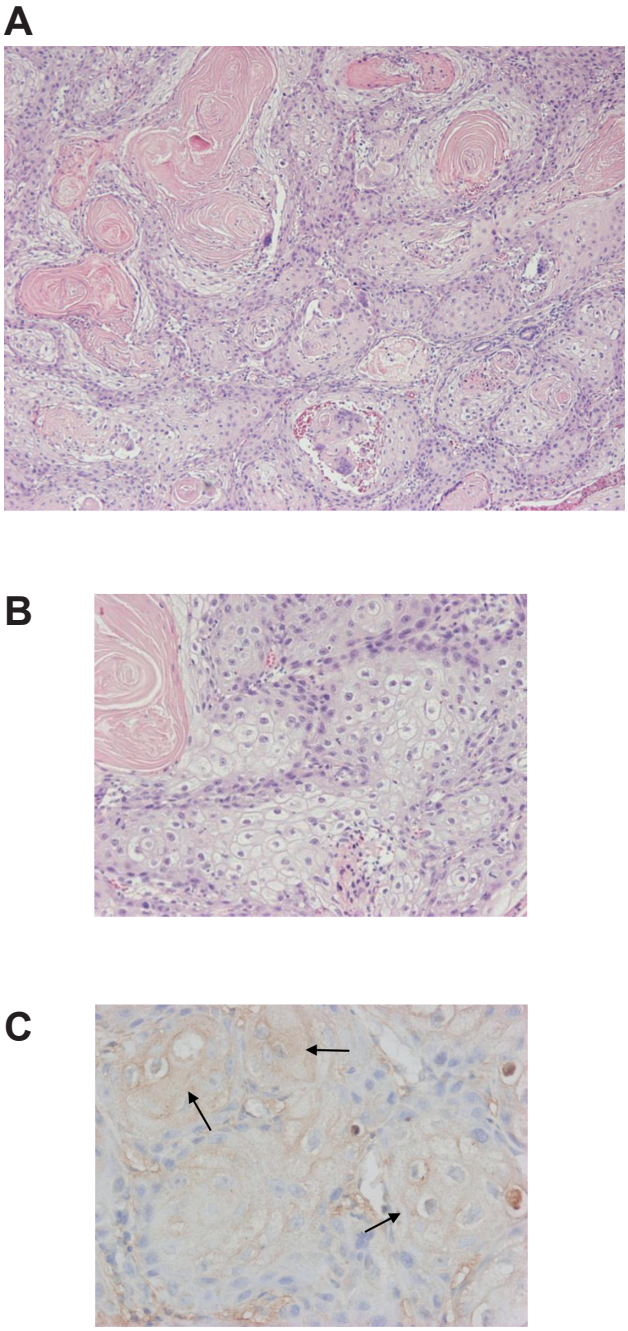

Fig. 3 Light microscopy of the tumor revealed proliferative lobules of atypical epithelium with squamous pearl, invading the subcutaneous fat. a: low power, b: high power (hematoxylin and eosin staining), **c:** Immunohistochemical staining with anti-PTH-rP polyclonal antibodies showed the positive reaction of atypical tumor cells.

but increased again, reaching 17.2 mg/dl in a month. Although he did not present with obvious clinical symptoms for hypercalcemia, intravenous bisphosphonate was administered for two days. We selected zoledronate (Zometa®; Novartis, Japan) (0.5 mg per day × 2 d) because it did not need high-volume administration, in consideration of the cardiorenal complications. The dose of zoledronate was determined according to his body weight and renal function. Although urine volume decreased slightly and serum creatinine increased slightly (max. 0.9 mg/dl), no other zoledronate complication was observed. Serum calcium decreased immediately and normalized 8 d after zoledronate administration, and his right leg was amputated below the knee out. The surgical margins were free of tumor macroscopically (Fig. 4A). After the operation, leukocytosis and G-CSF improved to the normal range immediately. Serum calcium remained within the normal range and intact PTH increased; consequently $1,25(OH)_2D$ increased and PTH-rP decreased to the normal range. Postoperative chemotherapy and radiation therapy were not performed because of his poor general condition. One month after the amputation, an ulcer around the operation scar spread and grew like a tumor mass (Fig. 4B). When local recurrence of cutaneous SCC was observed, multiple lung metastases were detected by CT. PTH-rP increased gradually, worsening hypercalcemia to 17.8 mg/dl. Lung metastasis complicated his dyspnea gradually and he died about 4 mo after the amputation. No attempts were made to resuscitate or to perform extraordinary therapeutic measures. An autopsy was refused by his family.

Discussion

A wide range of cancers produces PTH-rP and causes paraneoplasmic syndrome called HHM. PTH-rP has high affinity for PTH/PTH-rP receptors similar to PTH and increases serum calcium when its blood level is raised. Although

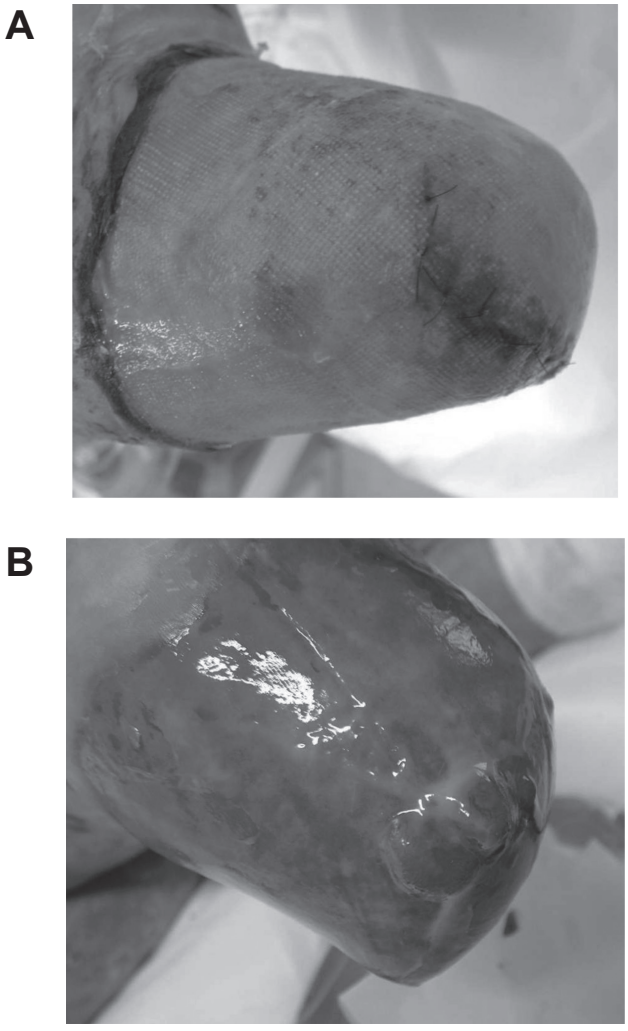

Fig. 4 Photographs of skin lesions at the amputation site. a: Surgical margins were free from tumor macroscopically. b: One month after amputation, an ulcer around the operation scar spread and grew like a tumor mass.

more than half of HHM is caused by SCC among the many kinds of cancer cells including lung and oral cavity; for no clear reason, there are not many cases derived from cutaneous SCC (2–8). The present patient showed severe hypercalcemia and leukocytosis as well as elevated serum PTH-rP and G-CSF levels. Furthermore, a positive cytoplasmic reaction to antibodies against PTH-rP was shown in cutaneous SCC at biopsy, followed by normalization of hypercalcemia, leukocytosis, PTH-rP and G-CSF after surgical excision of the tumor. And reflecting a hungry bone syndrome, PTH and I,25$(OH)_2$D were increased. Kato *et al.* (3) reported a patient with cutaneous SCC accompanied with marked hypercalcemia and leukocytosis; however, our literature search revealed no case reports of cutaneous SCC resulting from RDEB, producing both PTH-rP and G-CSF.

Management of HHM is aimed at the control of serum calcium, preferably by removal of the tumor, but alternatively by pharmacological means, including forced diuresis and agents such as bisphosphonates, glucocorticoids, mithramycin, calcitonin, and gallium nitrate (9). Calcitonin shows rapid reduction of serum calcium levels (maximal response to rapid reduction of serum Ca levels occurs within 12–24 h) and has fewer side effects than other agents (9). This was administered first in our patient, but the reduction was small and transient, so its value was questionable. On the other hand, bisphosphonates are effective for hypercalcemia, and approximately 60–90% of patients have normal serum calcium levels within 4–7 d, and the responses last for 1–3 wk. Thus, bisphosphonate therapy should be considered as the first-line treatment for hypercalcemia. Among many bisphosphonate agents, such as pamidronate and alendronate, are used in pediatric patients. Since these bisphosphonates need a high volume of infusion for administration, more attention is required for patients with cardiorenal complications. As our patient showed relatively severe renal dysfunction, we decided to use zoledronate, which does not require high-volume administration. Although the urine volume decreased slightly and serum creatinine increased slightly, no other complications were observed.

Although the patient reached an unfortunate turning point, we propose that zoledronate is an effective and safe treatment for HHM with cardiorenal complications.

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