Parallel development and course of pheochromocytoma and giant squamous cell carcinoma of the leg: a new paraneoplastic syndrome?

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KEY WORDS

squamous cell carcinoma, pheochromocytoma, paraneoplastic syndrome

SUMMARY

Paraneoplastic syndromes (PS) are diseases or symptom complexes associated with malignancy, usually of internal origin, but not directly related to mass effects, invasion, or metastatic spread. Rarely, cutaneous squamous cell carcinoma (SCC) may be associated with PS. We present a patient with a giant SCC located on the right leg and a pheochromocytoma. Considering the concurrent onset and parallel course of both pheochromocytoma and SCC in this patient, and the complete resolution of the endocrine abnormalities after resection of the skin tumor, it was possible to conceive of the pheochromocytoma as a paraneoplastic phenomenon. To our knowledge, this association has not been previously described.

Introduction

Squamous cell carcinoma (SCC) of the oral cavity, esophagus, pharynx, larynx, bronchus, lung, and cervix are well-known malignancies associated with paraneoplastic phenomena (1–4). However, paraneoplastic syndromes (PSs) related to cutaneous SCC are rarely reported. PSs are diseases or symptom complexes associated with malignancy, usually internal, but not directly related to mass effects, invasion, or metastatic spread (5). Although the pathogenesis remains unclear, these symptoms may be secondary to substances secreted by the tumor, such as hormones or their precursors, steroid metabolites, enzymes, and various cytokines, or may be the result of antibodies directed against tumors that cross-react with other tissues (5).

Case Report

A 36-year-old Caucasian man presented with a fast-growing, ulcerated, and exophytic tumor located in the pretibial region of the right leg. The lesion measured approximately 18 × 12 cm and had been developing for 1 month (Fig. 1). The patient mentioned a previous dermatosis in that location diagnosed as hypertrophic lichen planus around the age of eighteen, but had no other significant history. Upon initial examination, the patient was in critical condition, with a wasting syndrome, hypertensive crisis, and bilateral inguinal lymph node enlargement. He denied a history of persistent arterial hypertension but complained of frequent headaches, tremors, and a pounding heartbeat during the prior 3 weeks and high arterial tension

Table 1. Evolution of urinary cathecolamines.

Urine analysis	Before surgery	3 weeks after surgery	2 months after surgery	Reference range
VMA	**7.6**	4.9	2.5	1.4-6.5 mg/24h
Epinephrine	16	10	11	< 27 μg/24h
Norepinephrine	**125**	43	37	< 97 μg/24h
Dopamine	486	141	126	< 500 μg/24h
Metanephrine	**405**	216	103	74-297 μg/24h
Normetanephrine	**596**	316	154	88-444 μg/24h

VMA – vanillylmandelic acid.

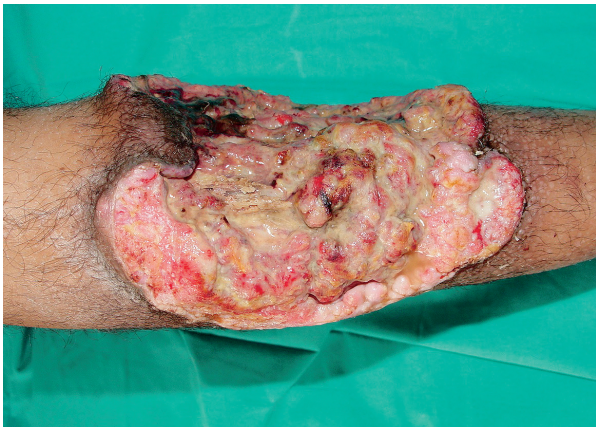

Figure 1. Clinical appearance of the tumor lesion, located on the anterior aspect of the right leg.

detected 2 weeks before our examination. Ancillary investigations revealed severe hypochromic microcytic anemia, requiring several blood transfusions, and both erythrocyte sedimentation rate and C-reactive protein were slightly increased. Liver and kidney function tests, plasma electrolytes, protein electrophoresis, autoimmune screening, serum cortisol, and ACTH were negative or within the normal range. Elevated fractional catecholamines and metanephrines were detected in the 24-hour urine collection (Table 1). Thoraco-abdominopelvic computed tomography revealed bilateral inguinal adenomegalies, but renal ultrasonography and adrenal magnetic resonance imaging were unremarkable. However, iodine-131–labeled metaiodobenzylguanadine (^{131}I-MIBG) scintigraphy found bilateral enlargement of the suprarenal glands. A bacteriological culture from the ulcer surface was positive for *Pseudomonas aeruginosa* and a polymerase chain reaction for *Mycobacterium tuberculosis* DNA in a biopsy specimen was negative. Several tissue samples from various locations in the tumor mass were collected, revealing the presence of a SCC with moderate differentiation and muscle involvement (Fig. 2). The patient was submitted to a right above-knee (supracondylar) amputation and bilateral inguinal lymph node dissection. Histopathological examination confirmed a SCC with moderate differentiation, extensive areas of necrosis, and involvement of muscle and bone without lymphovascular invasion. The resection was microscopically complete and there were no lymph-node metastases. The patient's final disease stage was T4N0M0R0G2 (stage III). Before and during surgery blood pressure levels were normalized with phenoxybenzamine. The patient had an uneventful postoperative course, with normalization of blood pressure levels and urinary cathecolamines and metanephrines, and was discharged without any specific medications (Table 1). After 6 years of follow-up the patient remains well, with neither relapse of the tumor nor symptoms of pheochromocytoma.

Discussion

Although up to 10 to 15% of cancer patients can experience PSs (6), reports of cutaneous SCC-induced PSs are uncommon. An exception is paraneoplastic hypercalcemia-hyperleukocytosis, which—although very rare—has been described in the setting of cutaneous SCC (7). It probably involves the secretion of hormones or cytokines by the neoplastic cells, including PTHrP and G-CSF (7). Moreover, it seems that descriptions of paraneoplastic pheochromocytoma are scarce in the medical literature. Pheochromocytoma is a rare catecholamine-secreting tumor derived from chromaffin cells (8). Because of excessive catecholamine secretion, these neoplasms are able to precipitate life-threatening hypertension or cardiac arrhythmias. Catecholamines typically secreted, either intermittently or continuously, include norepinephrine and epinephrine, and rarely dopamine. The most valuable tests for the diagnosis of pheochromocytoma in adults are the urinary free metanephrines, which are superior to urinary vanillylmandelic acid (VMA), urinary catecholamines, and plasma catecholamines

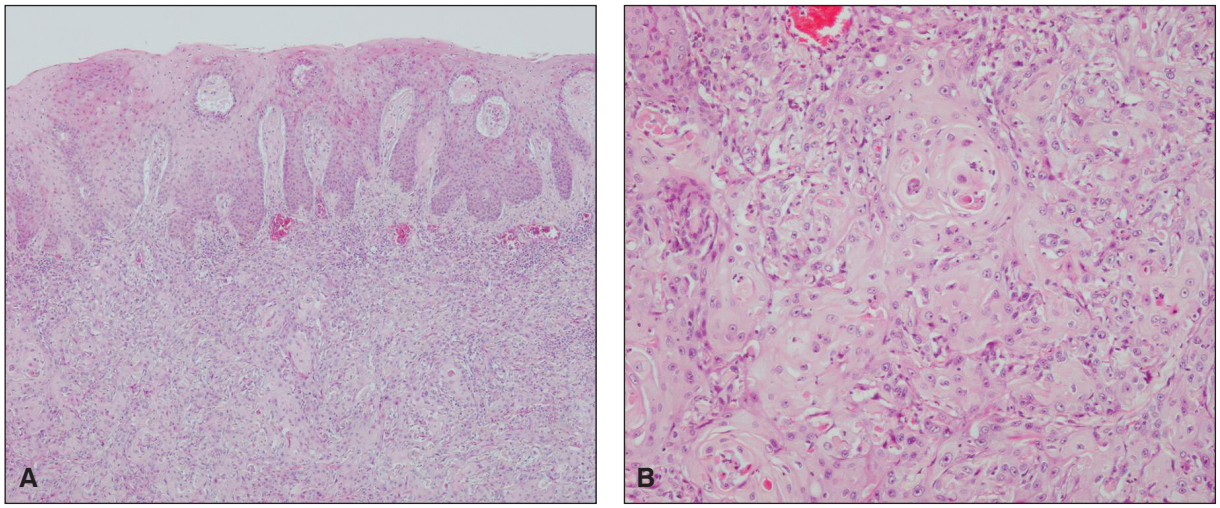

Figure 2. Histopathology of a biopsy specimen (hematoxylin and eosin [H&E]) showed a moderately differentiated squamous cell carcinoma. Original magnification: (a) ×10; (b) ×200.

(8, 9). In fact, our patient presented increased levels of metanephrine and normetanephrine, as well as VMA and norepinephrine. In addition, uncontrolled arterial tension values and a bilateral enlargement of suprarenal glands were noticed. These clinical, laboratory, and imaging profiles were compatible with the diagnosis of pheochromocytoma. Considering the concurrent onset and parallel course of both pheochromocytoma and SCC and the complete resolution of the endocrine abnormalities after resection of the tumor, it is possible to conceive of the former condition as a paraneoplastic phenomenon, in good agreement with Helen Curth's postulate (10). To our knowledge, this specific association has not been previously described. This clinical picture of pheochromocytoma in the setting of a SCC was possibly caused by the local production of unidentified adrenal stimulating factors.

Another aspect to be focused on is the development of SCC in the setting of long-standing hypertrophic lichen planus (HLP). HLP on the legs tends to persist and has a propensity for malignant transformation even in young patients, which must be kept in mind (11). Therefore, nonhealing ulcers overlying such lesions should be viewed with great suspicion and biopsied in order to rule out SCC.

In this case, the giant aspect of the skin tumor, its rapid evolution, and the endocrine abnormalities detected make it a very atypical presentation. We believe that uncommon clinical manifestations in a patient with cancer should lead to prompt consideration of a PS, and pheochromocytoma must be added to this list of syndromes.

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