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Cutaneous Manifestations in a Patient with a Long-Term History of Untreated ACTH-Dependent Cushing's Syndrome

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SUMMARY Cushing's syndrome is accompanied by many different skin symptoms. A case of a 43-year-old female patient with unrecognized adrenocorticotropic hormone (ACTH)-dependent Cushing syndrome is reported. Besides numerous skin lesions, the patient presented with a rapidly progressive leg ulcer due to venous thrombosis. The initial skin symptoms appeared on her lower leg one month prior to admission. The patient was treated with oral prednisone, however, rapid progression of the skin lesion was observed. On admission the patient presented with a large, very painful ulceration, partially covered with a crust, on the right lower leg with several satellite smaller ulcerations. The other leg showed no changes. Moreover, the patient had pronounced hirsutism and skin darkening on the face, and Muehrcke's lines were observed on all her nails. Microscopic findings of skin biopsy were uncharacteristic, with some signs of angiopathy and vasculitis. Based on the elevated serum levels of ACTH and cortisol, and the result of dexamethasone suppression test, ACTH-dependent Cushing syndrome was diagnosed. Sonography of leg veins revealed a recanalized thrombus of the right popliteal vein with reflux. The patient was transferred to surgical department where both suprarenal glands were removed. Upon suprarenal gland removal, significant improvement of the patient's general condition and rapid healing of the leg ulcer were observed. Briefly, this patient is presented to point out that a leg ulcer caused by venous insufficency may mimic fulminant purpura or some other type of vasculitis in patients with Cushing syndrome.

KEY WORDS: Cushing disease, skin manifestation, nails, ulcus cruris

INTRODUCTION

Cushing syndrome is defined as a constellation of clinical signs and symptoms resulting from chronic adrenal glucocorticoid excess (1). If the high glucocorticosteroid serum level is the result of pituitary hypersecretion of adrenocorticotropic hormone (ACTH), the condition is called ACTH-dependent Cushing syndrome. When the high level of glucocorticoids is provoked by adenoma, carcinoma or hyperplasia of suprarenal glands, an ACTH-nondependent Cushing syndrome may be diagnosed. Hypercortisolemia may also be the result of ectopic production of ACTH by different

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malignancies such as small-cell lung carcinoma, carcinoid and others (ectopic ACTH-dependent Cushing syndrome). The classic physical features of Cushing syndrome include centripetal obesity with rounded moon face, fat accumulation over a cervical spine prominence, and supraclavicular fat pads (2). Cushing syndrome is accompanied by many different skin symptoms including abdominal striae, hyperpigmentation, acne, ankle edema, easy bruisability, hirsutism, and thin, papery skin (1-3). Moreover, wound healing tends to be very poor and patients with Cushing syndrome may demonstrate cutaneous anergy, therefore being predisposed to opportunistic fungal infections including that caused by *Candida* sp. (2). As Cushing syndrome may also induce many other symptoms such as hypertension, oligomenorrhea or amenorrhea, myopathy, psychological changes, glucose intolerance and many others, this condition remains a challenge for many branches of medicine. Here we present a patient with unrecognized Cushing disease, who presented, besides numerous skin lesions, a rapidly progressive leg ulcer due to venous thrombosis, thus to alert practitioners that this condition may be misdiagnosed with fulminant purpura or other types of vasculitis.

CASE REPORT

Disease history and clinical symptoms

A 43-year-old female patient was referred to our department because of a large, rapidly progressive ulceration of the right lower leg. First skin symptoms appeared on the lower leg one month prior to admission as several bullous lesions which spontaneously converted into small ulcerations. The patient was treated with orally administered prednisone as the suspicion of primary vasculitis was raised by her family doctor. However, rapid progression of the skin lesions was observed in spite of therapy. After two weeks edema and reddening of the lower leg appeared. On admission, the patient presented with a large, very painful ulceration, partially covered with a crust, of the right lower leg, with several satellite smaller ulcerations (Fig. 1). The left leg was unchanged. Moreover, the patient had pronounced hirsutism and skin darkening on the face ("plethoric face") (Fig. 2), while Muehrcke's lines (transverse leukonychia) were seen on all her nails (the bands were parallel to the lunula and were separated apart from each other and from lunula by strips of pink nail) (Fig. 3). The skin was generally very thin and smooth. No other skin lesions, including abdominal striae, were found.

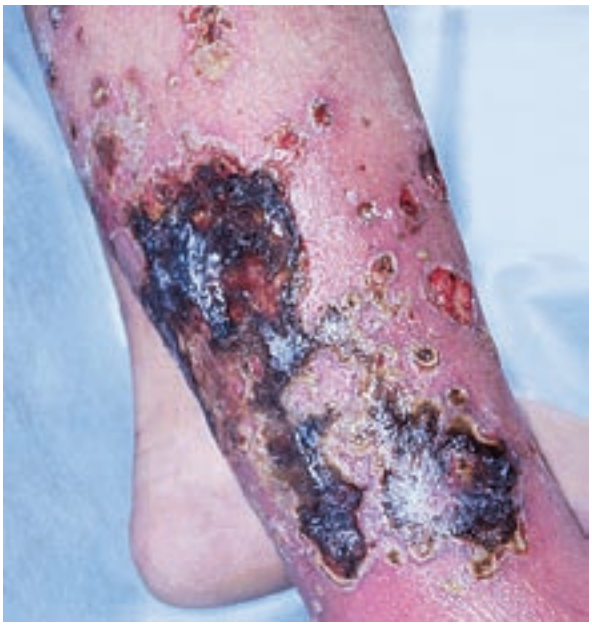

Figure 1. Large ulceration, partially covered with a crust, of the right lower leg with several small satellite ulcerations.

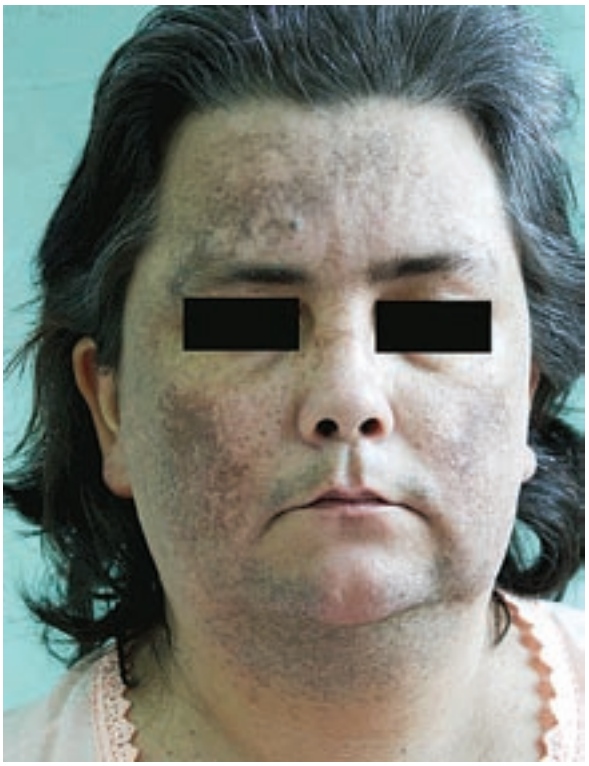

Figure 2. Pronounced hirsutism and skin darkening of the face ("plethoric face").

The patient suffered from hypertension for more than 12 years. She had also had acute pancreatitis with a complicated course 4 years before; since that time she had been reoperated for pancreatic

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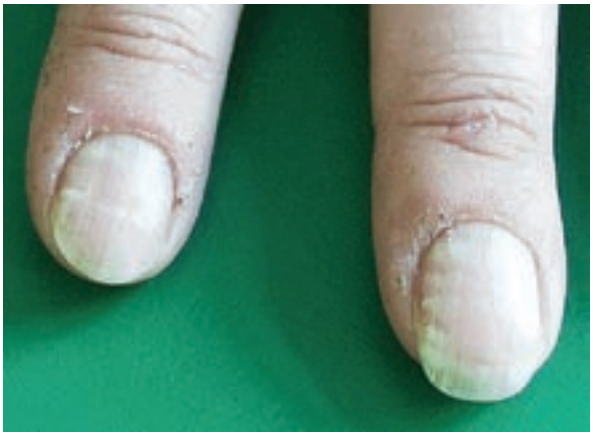

Figure 3. Muehrcke's lines in the nails: transverse bands parallel to the lunula, separated from one another and from the lunula by strips of pink nail.

cysts and abdominal abscesses on several occasions. Her family history revealed the patient's sister to suffer from hyperthyroidism, whereas her mother died from malignant neoplasm of the reproductive organs.

Skin histology

As the cause for leg ulcer was not fully obvious, skin biopsy from the edge of the ulceration was obtained. Histologically, the epidermis was thinned, the layer of the dermis was very narrow with marked fibrosis, and subcutaneous tissue was massively edematous. Subepidermally, slight polymorphic infiltrations around the small dermal vessels with thickened walls and widened lumina were seen. No leukocytoclasis was found. The microscopic picture was very uncharacteristic with some signs of angiopathy and vasculitis (Fig. 4).

Additional studies

Laboratory testing revealed elevated leukocyte count in peripheral blood smear (14200/μL) with a high percentage of neutrophils. Platelet count was also raised (579000/μL). The patient had anemia (erythrocytes 3300000/μL and hemoglobin 10.2 g/dL) and tachycardia (120-130/min). Blood pressure was slightly elevated, and so were serum levels of glucose (7.7 mmol/L) and creatinine (201 μmol/L). Erythrocyte sedimentation rate (ESR) at 1 hour was 105 mm and the level of fibrinogen was quite high (770 mg%). Other parameters of coagulation as well as nuclear antibodies, antineutrophil antibodies, the level of anti-streptolysin and complement were normal or negative.

The level of ACTH (61.7 pg/mL, normal <46 pg/mL) as well as the level of cortisol in serum (444.3 ng/mL at 6 a.m., normal 94-260 ng/mL, and 296.2 ng/mL at 8 p.m., normal 18-127 ng/mL) and in 24-h urine collection (134 μg/24 h, normal: 21-85 μg) were elevated. Additionally, serum levels of androgens were increased (testosterone: 1.6 ng/mL, normal <0.8 ng/mL; dehydroepiandrosterone: 570 μg/dL, normal 35-430 μg/dL). The levels of other hormones (prolactin, estradiol, luteotropin, follicle-stimulating hormone, thyrotropin, thyroxine, triiodothyronine, and parathormone) were within the normal range. In the long dexamethasone suppression test, a significant decrease of ACTH output (serum level of ACTH decreased from 61 pg/mL to 6.3 pg/mL) and concomitant reduction of cortisol in serum (from 443 ng/mL to 12.6 ng/mL) and in 24-h urine collection (from 134 μg/24 h to 12.6 μg/24 h) were observed. A significant decrease of all these parameters was observed both after 2 mg (on day 2 of the test) and after 8 mg (on day 4 of the test) dexamethasone.

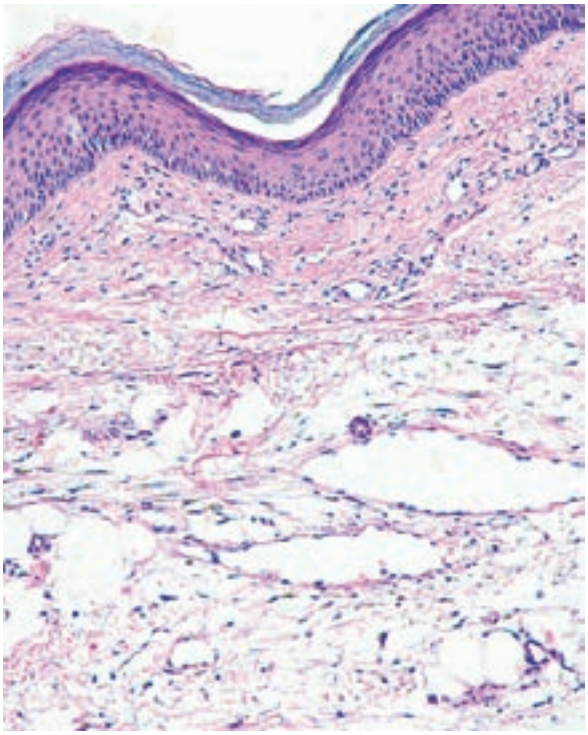

Figure 4. Histology: the epidermis is thinned, the layer of the dermis is also very narrow with marked fibrosis, and the subcutaneous tissue is massively edematous. Slight subepidermal polymorphic infiltrations around the small dermal vessels with thickened walls and widened lumina. No leukocytoclasis is present. (H&E, original magnification x100).

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Imaging

Although the high level of ACTH and suppression test with dexamethasone indicated pituitary gland as an organ responsible for hypercortisolemia, magnetic resonance (MR) did not reveal any macroscopic changes within pituitary gland. Computed tomography of the abdominal cavity demonstrated two liquid reservoirs (8.4x3.0 cm and 6.0x2.3 cm); the suprarenal glands were normal. Chest x-ray was also normal and Doppler sonography of leg veins revealed a recanalized thrombus of the right popliteal vein with reflux. Other blood vessels were unchanged. Densitometry indicated osteopenia.

Treatment and course

Based on the high levels of ACTH and cortisol, the result of dexamethasone suppression test and accompanying clinical symptoms, an ACTH-dependent Cushing syndrome was diagnosed. A short-term inhibition treatment with aminoglutetimide and ketoconazole had no substantial effect on the serum levels of glucocorticoids and the general condition of the patient was rapidly worsening. Therefore, the patient was transferred to surgical department for total resection of suprarenal glands, as only this kind of treatment guaranteed fast reduction of the high serum cortisol level. During the surgical procedure two abdominal abscesses were additionally removed. Microbiologic examination of a pus specimen revealed the presence of *Pseudomonas aeruginosa.* Histology of the removed suprarenal gland revealed diffuse adrenocortical hyperplasia.

The treatment of leg ulcer included a wide variety of topical agents, however, no remarkable improvement was observed as long as the high level of glucocorticosteroids was present. Upon the suprarenal gland removal, the patient was prescribed supplementary corticoids. The injections of calcium nadroparin with a combination of topical silver sulfathiazole resulted in rapid and complete healing of the skin ulcer. Nowadays, the patient has remained in good general condition.

DISCUSSION

Cushing syndrome is often accompanied by a wide spectrum of characteristic skin abnormalities (1-4). Our patient demonstrated characteristic hyperpigmentation of the face skin ("plethoric face") and hirsutism. Her skin was thin and smooth. Interestingly, despite pronounced skin changes, the disease was misdiagnosed for a very long period of time. In the course of the disease, the patient developed unilateral leg ulcers, which clinically resembled vasculitis. However, we do believe that the ulceration was due to disturbances in microcirculation. The abnormal microcirculation in the affected leg could be the result of angiopathic alteration of blood vessels caused by prolonged hypercortisolemia and/or the result of vein insufficiency as a recanalized thrombus of the right popliteal vein with retrograde blood flow was deteced by sonography. We were not able to exclude completely the hypothesis that the primary reason of the ulceration was bacterial infection, as the patient was admitted to our department one month after the initial lesions had appeared and mixed flora was found on microscopic examination. Moreover, the patient was nearly completely anergic as she demonstrated hardly any clinical symptoms of two large abdominal abscesses, which is typical for patients on immunosuppression. It is widely accepted that patients with Cushing syndrome are predisposed to both bacterial and fungal infections (2,5). We describe this patient to underline that patients with Cushing syndrome may present many skin lesions including atypical leg ulcers. Although the skin lesions in our patient resembled vasculitis, therapy with oral corticosteroids resulted only in rapid progression of ulceration.

Interestingly, the patient also had Muercke lines (transverse leukonychia) within her nails. The most common nail changes found in Cushing syndrome include longitudinal pigmented bands (6,7). These patients are also predisposed to primary distal and lateral onycholysis as well as to chronic paronychia due to *Candida* sp. (6). To the best of our knowledge, there is no previous report of transverse leukonychia in patients suffering from Cushing syndrome. These nail changes have mainly been described in patients with hypoalbuminemia. However, white finger nails preceded by multiple transverse white bands have also been reported with normal albumin levels (6). Other known reasons for Muercke lines are therapy with cytotoxic drugs and repeated trauma (6,8,9). Apparent leukonychia was also observed in a patient with vascular impairment (6). In our patient the serum albumin level was within the normal range, and she had not been previously taking any cytotoxic drugs. We suspect that the observed nail lesions were caused by disturbances in the microcirculation, similarly to the big ulceration on the right leg.

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