Discussion | Cystinosis is caused by the accumulation of free cystine within lysosomes.1 Cystine is derived from protein degradation within the lysosome and is normally transported through the lysosomal membrane to the cytosol where it is transformed into cysteine and reused.5 In cystinosis, a mutation in the CTNS gene (on chromosome 17p13),6 which encodes cystinosin, leads to a defect in the transport system. The low solubility of cystine leads to the precipitation of intracellular needle-shaped crystals as lysosomal cystine levels rise.3 The accumulation of cystine in various tissues in the body has been known to cause renal failure as well as extrarenal effects leading to ocular, hepatic, thyroid, pancreatic, muscular, dental, gonadal, and neurologic tissue damage.1,3

However, we know of only 3 prior reports of cutaneous accumulation of cystine crystals in patients with cystinosis. The first 2 published reports described subcutaneous infiltration of a palpable amorphous material with skin atrophy and telangiectasia mimicking premature aging2 and scattered small erythematous hyperkeratotic macules and papules on sun-exposed areas.3 The third published report involved normal-appearing skin on the forearms of patients with infantile cystinosis examined with in vivo reflectance confocal microscopy.4 To our knowledge, the present case report is the first to describe multiple skin-colored, dome-shaped, firm facial papules in a patient with long-term cystinosis.

A definitive diagnosis of cystinosis can be made based on an elevated cystine content in peripheral blood leukocytes.1 Early detection of cystinosis is crucial because early treatment with oral cysteamine improves growth and survival, prevents hypothyroidism, reduces ocular impairment, and can preserve renal function.1 Given the improved prognosis for patients with cystinosis who receive renal transplantation and/or cysteamine therapy, the prevalence of extrarenal effects, including cutaneous manifestations, may become more apparent over time. Finally, examination of biopsy specimens under electron microscopy may be required to accurately diagnose cutaneous cystinosis.

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Subacute Cutaneous Lupus Erythematosus Induced by Mitotane

Drug-induced subacute cutaneous lupus erythematosus (DISCLE) presents similar clinical and serological characteristics to idiopathic SCLE. The following report describes a case of DISCLE induced by mitotane.

Case Report | A woman in her 60s was diagnosed with a non-functioning stage II right adrenocortical carcinoma (ACC) and began treatment with mitotane (300 mg, 3 times daily) with supplementary hydrocortisone (200 mg/d). One month later, she had developed an itchy eruption without systemic involvement and she was referred for dermatologic consult.

She presented with a widespread papulosquamous eruption, predominantly on the upper chest and upper back (Figure 1) as well on the extensor surfaces of both arms. No malar erythema was present. She had no history of photosensitivity. DISCLE was suspected, and a blood test and a skin biopsy of 1 lesion on her back were performed. Laboratory findings revealed only a mild elevation of liver enzymes. Antinuclear antibody, anti-Ro/SSA, and anti-La/SSB findings were all negative. The skin biopsy specimen revealed a superficial and perivascular infiltrate accompanied by a vacuolization of
the dermoepidermal membrane along with some necrotic keratinocytes (Figure 2A). An iron colloidal stain revealed a large mucin deposit in both papillary and reticular dermis (Figure 2B). These histological results were compatible with lupus erythematosus.

Mitotane treatment was suspended, and the lesions improved gradually until complete resolution within 3 weeks. Mitotane treatment was not resumed because no signs of ACC recurrence were observed in a computed tomographic study at 1-year follow-up.

Discussion | DISCLE was first described by Reed et al in 1985. It is a now rare drug-related lupus that presents similar clinical and serological characteristics to idiopathic SCLE. Lesions are usually papulosquamous or annular polycyclic. No specific diagnostic criteria have been proposed, although certain guidelines have been laid out, such as the absence of clinical indicators for lupus erythematosus prior to administering the drug and complete clinical resolution after ending drug treatment.

Several different groups of drugs have been associated with DISCLE, including calcium channel blockers, β-blockers, diuretics, antifungals, and more recently, chemotherapeutics and immunomodulators. Among chemotherapeutics, pyrimidine analogue drugs (fluorouracil, capecitabine, and gemcitabine), mitosis inhibitors (docetaxel, paclitaxel), anthracyclines (doxorubicin with cyclophosphamide), and antiestrogens (tamoxifen) have been reported to induce DISCLE. The mean time for induction in these cases ranged from 4 to 6 months, presenting with no clinical or serological differences from DISCLE related to other drugs. All the reported cases resolved after discontinuation of treatment with the drug. Photosensitivity, a translocation of the Ro/SS-A antigen to the cell surface of keratinocytes, or the release of nucleosomes due to apoptosis—all induced by chemotherapeutic drugs—are the main mechanisms proposed as pathogenic triggers for an autoimmune response.

Mitotane is an analogue of the insecticide dichlorodiphenyltrichloroethane with adrenolytic properties, approved as adjuvant treatment for ACC. The most common adverse effects include fatigue, diarrhea, nausea, and mild elevation of liver enzymes. We conducted a search for cases of DISCLE related to mitotane therapy in the MEDLINE and PubMed databases and found no reports. Mitotane cytostatic and cytotoxic effects lead to an increase in adrenal cell apoptosis, which might lead to a release of nucleosomes. As has been theorized with regard to other chemotherapeutic agents, this phenomenon could trigger an autoimmune reaction.
Our patient developed a skin eruption that was clinically and histologically compatible with SCLE after 1 month of mitotane therapy, which resolved after treatment with the drug was stopped. Although test results for serological antibodies were negative, she met some of the guideline conditions for drug-induced LE,4 sufficient to diagnose DISCLE according to our criteria.

In conclusion, we report the first case to our knowledge of DISCLE induced by mitotane. It is important for the clinician to enquire about drug intake history when evaluating patients presenting with SCLE.

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Metastatic Cutaneous Apocrine Adenocarcinoma Treated With a Combination of Pertuzumab-Based Targeted Therapy and Taxane Chemotherapy: A Case Report

There is no effective treatment for metastatic cutaneous apocrine carcinoma (CAC). In some cases of CAC, human epidermal growth factor receptor 2 (HER2) is overexpressed.1,2 We report the case of a patient with metastatic CAC for whom a combination of the anti-HER2 humanized monoclonal antibodies with taxane chemotherapy was effective.

Report of a Case | A man in his 50s presented with an asymptomatic erythematous tumor and lymph nodes fused with the right chest wall, axillary artery, and vein of the right axilla. (Figure 1A). A biopsied specimen from the axilla revealed that atypical tumor cells had proliferated in the dermis to the subcutis (Figure 2A). Immunohistochemically, these tumor cells were positive for gross cystic disease fluid protein 15 and HER2 (immunohistochemical score of 3+) (Figure 2B and C) and negative for mammaglobin and estrogen and progesterone receptors. From these findings, we diagnosed the tumor as CAC. Computed tomography (CT) revealed fused lymph nodes in the right axilla, which infiltrated the right chest wall, axillary artery, and vein. The CT findings enabled us to determine that there was no surgical indication. Therefore, considering that the tumor cells strongly expressed HER2, we administered the combination of pertuzumab and trastuzumab, which are HER2 inhibitors, with taxane chemotherapy according to the treatment of HER2-positive metastatic breast cancer (MBC).3-5 These drugs were intravenously administered every 3 weeks. Pertuzumab and trastuzumab were administered at fixed dosages of 420 mg and 6 mg/kg, respectively, and docetaxel was administered at a dosage of 75 mg/m². After 7 cycles of this combination therapy, erythematous lesions and fused lymph nodes dramatically decreased (Figure 1B). At this point, we determined that it was possible for the patient to undergo surgical treatment. We performed a wide local excision of the primary lesion and regional lymph node dissection, and the defect was reconstructed using the latissimus dorsi musculocutaneous flap (Figure 1C). Pathological results showed that there were viable tumor cells in dissected lymph nodes; however, the accessory mammary gland was not identified. Additional radiotherapy was administered on the right axilla with a total dose of 60 Gy, and subsequent trastuzumab monotherapy was administered. Following 11 cycles of this monotherapy, CT showed complete response (CR). At the last follow-up, 11 months after surgical treatment, the patient was disease free.

Discussion | The National Comprehensive Cancer Network guidelines recommend the combination of pertuzumab and trastuzumab with docetaxel as a preferred option for first-line treatment of patients with HER2-positive MBC.3 In general, CAC has a histological similarity to the apocrine subtype of breast cancer. Therefore, if patients with metastatic CAC have overexpression of HER2, HER2 inhibitors, such as pertuzumab and trastuzumab, are expected to be effective for them.

Pertuzumab and trastuzumab are more active in combination than when used alone because these 2 agents bind to different HER2 epitopes and provide a comprehensive signaling blockade.6 According to a randomized clinical trial of patients with HER2-positive MBC,4,5 the combination of pertuzumab and trastuzumab with docetaxel compared with placebo and trastuzumab with docetaxel significantly improved both progression-free and overall survival. Therefore, the addition of pertuzumab plays an important role in the improvement of outcomes for patients with HER2-positive MBC. However, with regard to HER2-positive metastatic CAC, to our knowledge, there are no reports of therapy with pertuzumab. In the present case, the tumor cells dramatically regressed with the combination of pertuzumab and trastuzumab with