the skin, and basal cell carcinoma were collected for patients with concomitant diagnosis of morphea or systemic sclerosis. As a control, we compared these values with those of the general JHH patient population and then calculated the odds ratios (ORs) and *P* values for each comparison using a 95% confidence interval (CI) (Table I). We found that, compared with the general population of patients at JHH, patients with morphea were 6.6 times more likely to have melanoma (OR 6.6, 95% CI 4.1-10.9; $P < .0001$), 12.8 times more likely to have squamous cell carcinoma of the skin (OR 12.8, 95% CI 8.8-18.6; $P < .0001$), and 13.1 times more likely to have basal cell carcinoma (OR 13.1, 95% CI 9.7-17.5; $P < .0001$). The prevalence of these skin cancers was also significantly elevated in patients with systemic sclerosis compared with the general population, although not to the same degree. This increased risk for skin cancer in patients with morphea and systemic sclerosis was still present after stratifying by race (Table I). In both our morphea and systemic sclerosis cohorts, most patients with concomitant skin cancer were white females (Table II).

This is the first report describing an increased risk for both melanoma and nonmelanoma skin cancer in patients with morphea. There are several explanations for this association. One is that the treatment of morphea—either with immunosuppressive agents or ultraviolet light therapy—increases the risk for epithelial malignant transformation. Chronic inflammation and elevated levels of the cytokine transforming growth factor β in patients with morphea might contribute to malignant transformation of epithelial tissue as well.[5] Another explanation is that the anticancer immune response to epithelial malignancy leads to attack of normal host tissue, resulting in autoimmunity. Patients with a genetic predisposition for autoimmune disease might also be predisposed to the development of cancer, and it is possible that the inciting exposure for both outcomes is the same.

Limitations of this study include an inability to determine a temporal relationship between the diagnosis of skin cancer and morphea. Further, patients with morphea or systemic sclerosis are more likely to be seen by either a rheumatologist or dermatologist, who are skilled at diagnosing skin cancer. The characteristics of morphea or treatments associated with a greater risk for epithelial malignancy should be evaluated in future studies to determine which patients might benefit from an increased frequency of skin cancer screening.

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A retrospective study: Application site pain with the use of crisaborole, a topical phosphodiesterase 4 inhibitor

To the Editor: Topical corticosteroids are among the cornerstone treatments of atopic dermatitis (AD); however, prolonged use is associated with skin atrophy, hypopigmentation, and telangiectasia.[1] Nonsteroidal alternatives include topical calcineurin inhibitors such as pimecrolimus and tacrolimus and the phosphodiesterase 4 inhibitor crisaborole, which have application site pain as a side effect. The

Table I. Characteristics of the cohort of patients with AD, comparing those with and without application site pain

Characteristic	All participants (N = 41)	Patients with application site pain (n = 13)	Patients without application site pain (n = 28)
Sex, n (%)			
Male	23 (56.1)	5 (21.7)	18 (78.3)
Female	18 (43.9)	8 (44.4)	10 (55.6)
Ethnicity, n (%)			
White	15 (36.6)	6 (40.0)	9 (60.0)
Asian	13 (31.7)	3 (23.1)	10 (76.9)
Black	6 (14.6)	2 (33.3)	4 (66.7)
Hispanic	5 (12.2)	1 (20.0)	4 (80.0)
Other	2 (4.9)	1 (50.0)	1 (50.0)
Mean age, y (SD)	35.9 (21.5)	36.7 (18.7)	35.6 (23)
BSA, mean, median	10.6, 6.0	17.3, 8.0	5.6, 3.5
Mean IGA score, median score	3.1, 3.0	3.1, 3.0	3.2, 3.0
Prior use of calcineurin inhibitors, n (%)	21 (51.2)	9 (42.9)	12 (57.1)
Application site pain with calcineurin inhibitor, n (%)	7 (33.3)	4 (57.1)	3 (42.9)
Areas of application, n (%)			
Face only	10 (24.4)	5 (50.0)	5 (50.0)
Face and nonfacial areas	6 (14.6)	3 (50.0)	3 (50.0)
Nonfacial areas only	25 (60.9)	5 (20.0)	20 (80.0)

BSA, Body surface area; *IGA*, Investigator's Global Assessment; *SD*, standard deviation.

mechanism by which crisaborole induces pain is unknown.

We performed an institutional review board–approved retrospective chart review of patients to whom crisaborole was prescribed at Tufts Medical Center to assess the incidence of application site pain defined as burning and/or stinging and analyze whether certain factors predispose patients to pain. Patients were advised to apply a thin layer of crisaborole over the affected area(s) twice daily and were regularly assessed at follow-up by provider questioning for safety.

A total of 41 patients (mean age, 35.9 years [standard deviation, 21.5]) with AD were eligible for the study (Table I). Of the 41 patients, 13 (31.7%) reported application site pain, which typically occurred within a few minutes after application. Length of crisaborole use varied depending on whether patients could tolerate the pain, if present.

Of the 10 patients who applied crisaborole exclusively to the face, 5 (50%) developed pain, whereas of the 25 patients who applied crisaborole to nonfacial sites, 5 (20%) had pain ($P = .048$). A total of 6 patients applied crisaborole to both the face and nonfacial sites, of whom 3 (50%) developed pain (2 had pain only on the face, whereas the third had pain at all sites).

In all, 21 patients in our cohort reported prior use of a topical calcineurin inhibitor. Five of these patients had pain with crisaborole but not with a calcineurin inhibitor, 3 had pain with the calcineurin inhibitor but not with crisaborole, 4 had pain with both, and 9 had no pain with either.

Crisaborole shows promise as a nonsteroidal alternative in the topical management and treatment of AD. However, in clinical practice, application site pain can limit its use, with more patients reporting pain in our study than in the phase III clinical trials (31.7% vs 4.4%). Furthermore, facial application was associated with significantly higher rates of application site pain ($P = .048$).

Differences between our patient cohort and those in the phase III studies include a lower affected body surface area (10.6% vs 18.3%), an older average age (35.9 vs 12.2 years), and lack of a control vehicle.[2] Limitations of the study include its small number of patients, retrospective design, and recall bias that was potentially heightened in those responses elicited by provider questioning. It is hoped that future analysis of larger data sets will provide more data regarding which patients are at highest risk of application site pain.

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Idiopathic Stevens-Johnson syndrome and toxic epidermal necrolysis: Prevalence and patients' characteristics

To the Editor: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered severe cutaneous adverse reactions to drugs. However, in some cases, no causative drug is identified. Cases of "nontoxic" SJS/TEN have been associated with *Mycoplasma pneumoniae* infection or connective tissue diseases or considered idiopathic.[1] Very few data about idiopathic cases of SJS/TEN are available.

Our retrospective study included 193 patients who were hospitalized in our center (ie, the French Referral Center for Epidermal Necrolysis) for SJS/TEN during the period from 2005 to 2016. Four patients were excluded from the analyses (Fig 1). For 2 patients (1.1%) of the 189 studied, *M pneumoniae* infection was identified as the most probable cause of SJS/TEN (Fig 1). The diagnosis of SJS/TEN-like connective tissue was made for 3 other patients (1.6%) (Fig 1). The disease of 2 of them was diagnosed as lupus erythematosus. For the other, a history of Sjogren syndrome, progressive cutaneous involvement over a 13-day period, concomitant arthralgia, positive antinuclear antibody test result (titer, 1/320), and positive anti–double-stranded DNA test result (titer, 20 IU/mL) made the diagnosis of SJS/TEN-like connective tissue disease possible. Lastly, 12 patients without underlying connective tissue disease or *Mycoplasma pneumonia* infection (6.3%) were considered to have idiopathic SJS/TEN. For these patients, no initiation of systemic drug was found within the month preceding the start of skin and/or mucous symptoms despite a thorough drug investigation (that included the patient, relatives, general practitioner, and/or pharmacy). One of these patients was 2 months pregnant, and another had concomitant streptococcal abscessed tonsillitis. Compared with patients with drug-induced SJS/TEN, those with idiopathic SJS/TEN were younger and tended to have less severe skin involvement (Table I). No biologic parameters measured routinely on admission were clearly discriminative.

Few data are available regarding SJS/TEN cases that are not related to drug exposure. Review articles often report that no causative drug is identified in 20% of 30% of SJS/TEN cases,[2,3] even though lower proportions (ie, ≤15%) have been found in cohort studies.[3,4] However, these proportions include both patients with no drug exposure and patients exposed to drugs for whom the causality assessment for each drug is considered very unlikely or unlikely when an algorithm for assessment of drug causality is used.[5]

In a previous study of 379 patients included in the EuroSCAR study between 1997 and 2001, 7 patients (1.8%) had not received any systemic drug in the 4 weeks before the onset of the skin/mucous symptoms.[4] More recently, in the United States, the Society of Dermatology Hospitalists SJS/TEN Study Group found that 8.7% of SJS/TEN cases (n = 405) occurred in patients not exposed to a culprit drug.[3]

In conclusion, even though systematic screening for *M pneumoniae* infection or lupus erythematosus could be considered in all patients with SJS/TEN for whom no culprit drug is identified, these etiologies are unlikely to account for the majority of SJS/TEN cases not induced by drugs, as suggested by our study. Inadvertent intake of drugs, for instance by consuming meat or milk containing occult veterinary drugs such as nonsteroidal anti-inflammatory drugs, has been hypothesized as a possible cause of idiopathic SJS/TEN.[5] However, this hypothesis has not been confirmed so far.[5]