Eruptive squamous atypia (also known as eruptive keratoacanthoma): Definition of the disease entity and successful management via intralesional 5-fluorouracil

Syril Keena T. Que, MD, MPH,[a] Leigh A. Compton, MD, PhD,[b,c] and Chrysalyne D. Schmults, MD, MSCE[d]
Indianapolis, Indiana; St. Louis, Missouri, and Boston, Massachusetts

Background: Eruptive squamous atypia (ESA), which is an idiopathic, sometimes koebnerizing, proliferation of atypical but well-differentiated keratinocytes (also termed *eruptive keratoacanthoma*), is often misdiagnosed as cancer and managed by excisional surgery, provoking further koebnerization. A clear definition of this phenomenon and treatment outcome data are lacking.

Objective: To define ESA and evaluate efficacy of intralesional (IL) 5-fluorouracil (5-FU) treatment.

Methods: A retrospective cohort study examined patients with ESA that arose spontaneously or within a recent surgical scar and was treated with IL 5-FU at a tertiary academic center between January 2008 and December 2016. Complete clearance, partial clearance, and number of surgical excisions performed were tabulated.

Results: Of 30 patients with 136 ESA lesions, 20 (67%) had resolution of ESA with IL 5-FU monotherapy. In all, 10 patients (33%) required additional therapy (topical 5-FU, steroids, cryotherapy, or acitretin). No IL 5-FU–treated ESA lesions required surgical excision. The number of excisional procedures decreased significantly (P = .006), with 27 patients (90%) needing fewer excisions 12 months after versus 12 months before initiation of IL 5-FU therapy. Dyspigmentation was the only adverse event.

Limitations: Limitations include retrospective analysis and use of data from a single institution.

Conclusion: With close clinical monitoring, IL 5-FU can be used to successfully treat ESA. (J Am Acad Dermatol 2019;81:111-22.)

Key words: atypical squamous proliferation; eruptive keratoacanthoma; eruptive squamous atypia; hypertrophic lichen planus-like reactions; infundibulocystic hyperplasia; intralesional 5-flourouracil; post-surgical koebnerization; pseudoepitheliomatous hyperplasia; squamous cell carcinoma; squamous dysplasia; squamous proliferation.

Eruptive squamous atypia (ESA) is a clinical entity that has been recognized by several terms over the years, the most common being *eruptive keratoacanthoma* (Table I[1-24]). We have chosen to use the term *ESA* because many lesions in this disease do not meet the clinical and histologic criteria for keratoacanthoma[25] and may represent keratoacanthoma mimics such as pseudoepitheliomatous hyperplasia or infundibulocystic hyperplasia. Additionally, the term

From the Department of Dermatology, Indiana University School of Medicine, Indianapolis[a]; Department of Pathology and Immunology[b] and Division of Dermatology, Washington University School of Medicine, St. Louis[c]; and Department of Dermatology, Brigham and Women's Hospital, Boston.[d]

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Correspondence to: Syril Keena T. Que, MD, MPH, Indiana University School of Medicine, 545 Barnhill Dr, EH 139, Indianapolis, IN 46202. E-mail: keenaq@gmail.com; Chrysalyne D. Schmults, MD, MSCE, Brigham and Women's Hospital, 1153 Centre St, Boston, MA 02130. E-mail: cschmults@bwh.harvard.edu.

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keratoacanthoma has come to be nearly synonomous with squamous cell carcinoma (SCC).[26] Misdiagnosis of ESA as multiple aggressive SCCs or recurrent SCC is common in our experience, and the term *eruptive keratoacanthoma* may contribute to this confusion. We thus propose the clinical term *ESA* to more readily separate this entity from aggressive recurrent SCC and to include the histologic spectrum of ESA lesions beyond keratoacanthoma.

To illustrate the current under-recognition of ESA and confusion with aggressive SCC, the case of a 62-year-old otherwise healthy man is briefly summarized. In the past year, this patient underwent 3 surgical excisions on the bilateral aspect of the legs for biopsy-proven SCC (Fig 1). When he subsequently developed new papules at and around the surgical sites, he was presumed to have multiple SCCs with in-transit metastases and referred to our center for consideration of cemiplimab (anti—programmed cell death protein 1) therapy as part of an ongoing phase II trial for unresectable locally advanced SCC. This patient fit the clinical criteria for ESA (as described later in this article) and had no high-risk features noted on the pathology report. Treatment with intralesional (IL) 5-fluorouracil (5-FU) was therefore initiated and led to regression of all treated lesions. Acitretin, 20 mg PO daily administered orally, was added to decrease formation of new lesions. Surgery has not been required.

Several similar patients have presented to our clinic after having failed multiple attempts via surgery and radiation to control what was thought to be aggressive, poorly controlled SCC. They have likewise responded to treatment for ESA, as detailed in this article.

We define ESA as an idiopathic, sometimes koebnerizing, proliferative process that is clinically identifiable. In the analysis in this article, we have classified cases as being of 1 of 2 morphologic types: (1) focal koebnerized ESA (FK-ESA), in which at least 1 papule or plaque develops within 3 months of localized trauma, including after a clear-margin surgical excision (Fig 2), and (2) diffuse ESA (D-ESA), which presents as multiple, hyperkeratotic papules that develop concurrently, often over the extremities (Fig 3). Both patterns may occur concurrently (as in Fig 1). When a biopsy is performed, the ESA lesions are confined to the dermis and lack high-grade histologic features. Table II summarizes our working definition of ESA.

At our institution, we use IL 5-FU as first-line treatment for ESA, with biopsies and surgery reserved for large (approximately ≥1.5 cm) or thick lesions that are unlikely to resolve with IL chemotherapy.

Although other nonsurgical therapies have been used (eg, cryotherapy, curettage, topical and IL corticosteroids, acitretin, and IL methotrexate), we utilize IL 5-FU because it directly targets the atypical and rapidly proliferating keratinocytes encountered in this phenomenon and does not cause scarring that can mask recurrence or incomplete regression.

This study was undertaken to assess the safety and efficacy of IL 5-FU in the management of ESA.

CAPSULE SUMMARY

- Eruptive squamous atypia is often misdiagnosed as cancer and treated with excisional surgery.
- Eruptive squamous atypia can resolve in two-thirds of patients receiving intralesional 5-fluorouracil monotherapy, and in the remainder, it can resolve with addition of an adjunct treatment (topical steroid or 5-fluorouracil, cryotherapy, or acitretin). No lesions treated with intralesional 5-fluorouracil required surgery.

METHODS

A retrospective cohort study was performed at the Brigham and Women's Hospital and Dana Farber Cancer Institute. Study entry date was defined as first-time exposure to IL 5-FU for treatment of cutaneous neoplasms meeting the definition of ESA. Excisional procedures on the extremities were recorded. Subjects were followed until the last recorded clinic encounter. The study protocol was approved by the institutional review board of Partners Healthcare.

Study population

Eligible participants included adults 18 years or older with ESA treated for the first time with IL 5-FU between January 2008 and December 2016, with at least 1 month of follow-up before and after IL 5-FU treatment. A subgroup analysis was performed for patients with D-ESA versus with FK-ESA.

Exposure and its assessment

The exposure of interest was the first documented treatment with IL 5-FU. Our standard practice involves first administering 1% lidocaine with 1:100,000 epinephrine to mitigate any discomfort associated with IL 5-FU. A 27-gauge needle is then used to intradermally inject IL 5-FU at 50 mg/mL, for

Abbreviations used:

5-FU:	5-fluorouracil
D-ESA:	diffuse eruptive squamous atypia
ESA:	eruptive squamous atypia
FK-ESA:	focal koebnerizing eruptive squamous atypia
IL:	intralesional
SCC:	squamous cell carcinoma

a total of 0.1 to 1 mL, until the lesion blanches in color. If lesions are still present during a 2- to 4-week follow-up period, the patient receives a repeat injection.

Outcomes and their assessment

Assessment of treatment response was determined by review of photographic documentation and clinical records. Response was classified by using the following terminology: *complete clearance*, *partial clearance*, and *no clearance*.

The primary outcome was complete clearance. Secondary outcomes included partial clearance and number of excisional procedures performed on the extremities treated with IL 5-FU. Any pathology slides corresponding to ESA lesions were reviewed by a board-certified dermatopathologist (L.C.).

Covariates and their assessment

Baseline patient and lesion characteristics were collected; they included age, sex, immunosuppression status and type, history of skin cancer, concurrent use of acitretin and other adjunctive therapies, lesion location(s), lesion diameter, morphologic category (D-ESA vs FK-RSA), and number of lesions treated on the date of initiation of IL 5-FU treatment.

Statistical analysis

Descriptive statistics are presented with means, medians, and percentages as appropriate. To assess baseline characteristics, a chi-square test was performed for categoric variables and a Wilcoxon 2-sample test was performed for continuous variables. A Wilcoxon signed rank test was used to analyze the median number of excisional procedures per patient before and after IL 5-FU treatment. All analyses were conducted with SAS software (version 9.4, SAS Institute Inc, Cary, NC).

RESULTS

Demographic characteristics of patients with ESA

Table III summarizes baseline patient and lesion characteristics. In all, 30 patients (mean age, 73.5 years [standard deviation, 13.5 years]; 70% female; and all white) with a total of 136 ESA lesions were included. All 30 patients had a history of keratinocyte carcinoma and 10 of them (33%) had a history of immunosuppression. Of these 30 patients, 24 (80%) had treated lesions located only on the lower extremities, 3 (10%) had treated lesions located only on the upper extremities, and 3 (10%) had treated lesions located on both upper and lower extremities.

A subset of 11 patients (37%) had 24 lesions of FK-ESA treated, with a median time between the surgical procedure and presentation for FK-ESA of 11 weeks (range, 2-17); 19 (63%) patients had 112 lesions of D-ESA treated. Patients with D-ESA often displayed background pruritus, inflammatory disease, immunosuppression, or diffuse actinic damage. The only statistically significant difference between FK-ESA and D-ESA was the number of lesions treated: most patients with FK-ESA had a single lesion (range, 1-5 lesions), whereas patients with D-ESA had 1 to 15 lesions ($P = .0075$).

The median follow-up for all patients was 2 years (range, 0.1-7.2). There were 22 patients (73%) who had follow-up of 1 year or more.

Patients received a median dose of 0.5 mL of IL 5-FU per lesion (range, 0.1-1.0). The median cumulative dose for all lesions treated at the date of the first injection session was 2 mL (range, 0.5-6). The median number of treatments received by each patient was 2 (range, 1-8). The median interval between office visits for IL 5-FU injections was 3 weeks (range, 2-8.5).

Histopathologic diagnoses of ESA cases

Because treatment with IL 5-FU is generally undertaken on the basis of a lesion's appearance and clinical context, a small fraction of the ESA lesions in this study (27 of 136 lesions [20%]) had associated biopsies, of which 6 (22%) were punch biopsies, 6 (22%) were disk excisions to the reticular dermis, and 15 (55%) were dermal shave biopsies. Seven biopsies (26%) were interpreted histopathologically as well-differentiated SCC, 6 (22%) as atypical endophytic squamous proliferation, 6 (22%) as squamous dysplasia/actinic keratosis, 3 (11%) as epidermal hyperplasia with reactive atypia or pseudoepitheliomatous hyperplasia, 3 (11%) as verrucous squamous proliferation, 1 (4%) as spongiotic dermatitis, and 1 (4%) as nonspecific hyperkeratosis/parakeratosis.

FK-ESA outcomes

The majority of patients with FK-ESA (10 of 11 [91%]) achieved complete clearance of their lesion(s)

Table I. Previous reports describing eruptive squamous atypia

Author, journal (year of publication)	No. of patients	Name of entity	Setting	Treatment modalities
Vickers and Ghadially, *Br J Dermatol* (1961)[1]	1	Keratoacanthoma	Psoriasis flare	None, self-resolved
Rossman et al, *Arch Dermatol* (1964)[2]	1	Multiple keratoacanthomas	Idiopathic	Oral aminopterin, oral methotrexate
Winkelmann and Brown, *Arch Dermatol* (1968)[3]	3	Generalized eruptive keratoacanthoma	Idiopathic	Topical vitamin A, oral methotrexate, antihistamines
Street et al, *J Am Acad Dermatol* (1990)[4]	1	Multiple keratoacanthomas	Idiopathic	Topical and intralesional 5-fluorouracil, oral retinoids
Shaw et al, *J Am Acad Dermatol* (1990)[5]	1	Multiple keratoacanthomas	After radiation therapy for a mucosal SCC	Oral isotretinoin
Okuyama et al, *Dermatology* (1997)[6]	1	Keratoacanthoma	After cryotherapy for prurigo nodularis	Excisional biopsy
Gewirtzman et al, *Dermatol Surg* (1999)[7]	1	Eruptive keratoacanthoma	After carbon dioxide laser resurfacing	Electrodesiccation and curettage
Sanders et al, *Dermatol Surg* (2002)[8]	1	Keratoacanthoma	Multiple eruptive keratoacanthomas	Intralesional corticosteroid
Pattee and Silvis, *J Am Acad Dermatol* (2003)[9]	2	Keratoacanthoma	-Intradermal thorn injury -Site of dog scratch	Intralesional methotrexate, then surgical excision
Cox, *Dermatol Surg* (2003)[10]	1	Keratoacanthoma	After chemical peel	Diclofenac sodium 3% topical gel
Goldberg et al, *J Am Acad Dermatol* (2004)[11]	6	Keratoacanthoma	Postsurgical	Excision, electrodesiccation and curettage, oral isotretinoin
Kossard et al, *Arch Dermatol* (2004)[12]	3	Hypertrophic lichen planus-like reactions with infundibulocystic hyperplasia	-Burn injury -After surgery, around graft sites	Oral acitretin
Kaptanoglu and Kutluay. *J Eur Acad Dermatol Venereol* (2006)[13]	1	Keratoacanthoma	After cryotherapy	Surgical excision
Kleinerman et al, *J Drugs Dermatol* (2007)[14]	1	Keratoacanthoma	Developed in tattoo	Mohs micrographic surgery
Chorny et al, *Arch Dermatol* (2007)[15]	1	Eruptive keratoacanthoma	Developed in a new tattoo	Surgical excision
Pini et al, *J Am Acad Dermatol* (2008)[16]	1	Eruptive keratoacanthoma	Developed after topical imiquimod was used for in situ SCC of the skin	Surgical excision
Kluger et al, *J Cutan Pathol* (2008)[17]	1	Keratoacanthoma	Developed in a tattoo	Surgical excision
Goldenberg et al, *J Cutan Pathol* (2008)[18]	1	Eruptive squamous cell carcinomas	Developed in a new tattoo	Surgical excision
Mamelak et al, *Dermatol Surg* (2009)[19]	2	Eruptive keratoacanthomas	After fractional photothermolysis	Excisional biopsy
Bangash et al, *J Am Acad Dermatol* (2009)[20]	5	Eruptive squamous cell carcinoma	After surgery	Mohs micrographic surgery with or without oral acitretin

Hadley et al, *Dermatol Surg* (2009)[21]	3	Multiple recurrent reactive keratoacanthomas	After surgery	Excision, intralesional 5-fluorouracil, intralesional methotrexate
Toll et al, *J Am Acad Dermatol* (2010)[22]	2	Hypertrophic lichen planus-like reactions with infundibulocystic hyperplasia	After surgery	High-potency topical corticosteroids, oral acitretin
Clark et al, *J Am Acad Dermatol* (2015)[23]	1	Keratoacanthomatous atypical squamous proliferation	After surgery, after wide local excision of SCC, followed by split-thickness skin graft	Oral acitretin, cryosurgery, topical 5-fluorouracil under occlusion
Veerula et al, *Cutis* (2016)[24]	1	Keratoacanthoma	After surgery	Intralesional methotrexate

SCC, Squamous cell carcinoma.

(Fig 4, *A*). One patient's lesion did not improve after 2 sessions of IL 5-FU, which prompted a biopsy. Histopathologic examination revealed a benign squamous proliferation (Fig 5) that resolved after biopsy with no need for additional treatment.

D-ESA outcomes

Compared with the FK-ESA group, the D-ESA group had a lower percentage of complete clearance after IL 5-FU treatment (91 % vs 53%, respectively [P = .03]). In all but 1 case of refractory D-ESA, the addition of adjunctive treatments (topical 5-FU under occlusion [n = 3], cryotherapy [n = 2], clobetasol [n = 1], or acitretin [n = 2]) resulted in complete clearance (Fig 4, *B* and *C,* and Table IV). One patient with D-ESA who did not experience complete resolution after a single session of IL 5-FU treatment underwent a shave biopsy of the unresponsive lesion. The biopsy specimen showed epidermal hyperplasia with reactive atypia and stasis changes (Fig 6) with no features of SCC. It resolved with the biopsy and no further intervention was required.

Number of excisional surgerical procedures avoided

Though no lesions treated with IL 5-FU required surgery, 19 patients required surgery for SCC arising within the IL 5-FU–treated extremity during the study period (37 SCCs were excised before initiation of IL 5-FU treatment, and 9 SCCs were excised afterward).

Per-patient analysis. In the 12 months preceding initiation of IL 5-FU treatment, each patient had an average of 1.3 excisions (range, 0-7) for SCC in their IL 5-FU–treated extremity. In the 12 months after initiation of IL 5-FU, the number of excisions decreased for each patient to an average of 0.3 (range, 0-2). The mean reduction in the number of excisions for SCC arising in the IL 5-FU–treated extremity per patient in the 12 months before versus after IL 5-FU treatment was 1.0 (P = .006). Only 3 patients (10%) had more excisions after initiation of IL 5-FU treatment than before IL 5-FU had been administered (Fig 7).

Cohort analysis. For the cohort as a whole, there was a notable decrease in the number of excisions for SCC arising in the IL 5-FU–treated extremity in the 12 months after initiation of IL 5-FU treatment as compared with baseline (Fig 8). This low number was sustained over 5 years for the 6 patients who had follow-up data to that point. The median number of excisions per patient in years 2 to 5 after initiation of IL 5-FU therapy was 0 (range, 0-3).

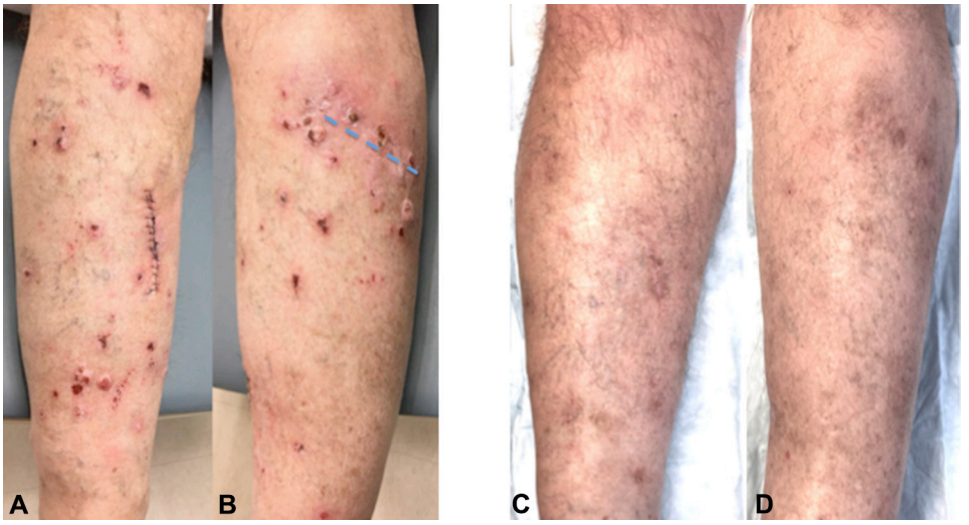

Fig 1. A case demonstrating overlap between focal koebnerizing ESA (FK-ESA) and diffuse ESA (D-ESA). **A,** Right leg. D-ESA over the entire leg and sutures demonstrating a recent excision. **B,** Left leg. D-ESA over the entire leg, with FK-ESA directly over a surgical scar (*above blue dotted line*). **C,** Right leg. Improvement in D-ESA after 3 months of therapy with intralesional 5-fluorouracil and acitretin. **D,** Left leg. Improvement in D-ESA and FK-ESA after 3 months of therapy with intralesional 5-fluorouracil and acitretin.

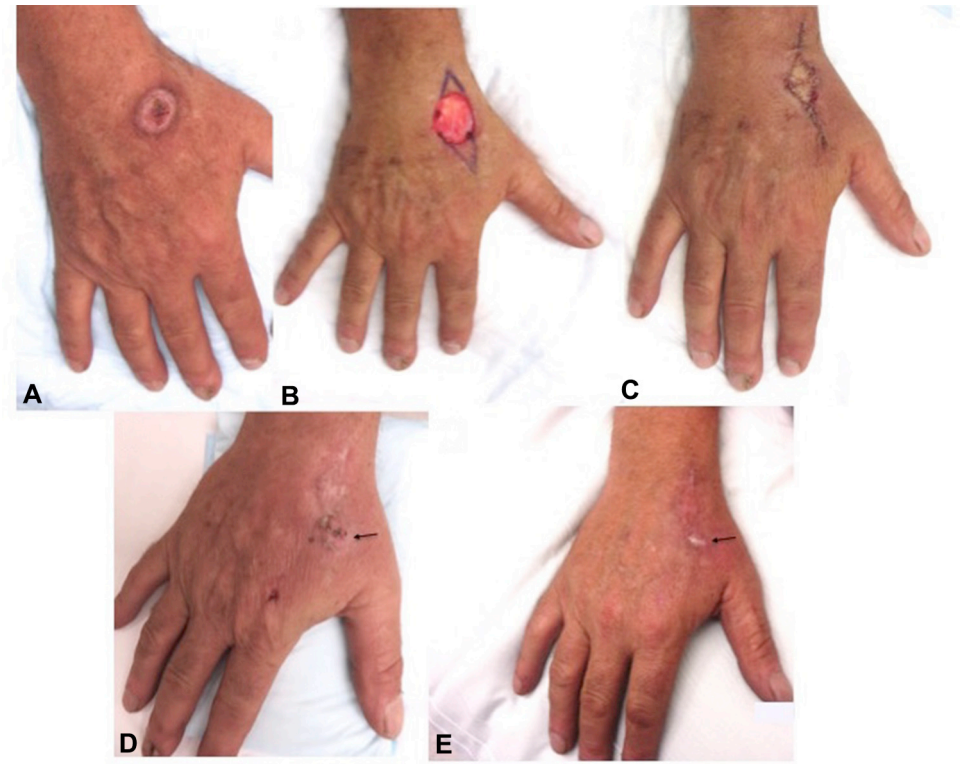

Fig 2. Focal koebnerizing eruptive squamous atypia (FK-ESA) on the dorsal aspect of the hand. **A,** A 1-cm well-circumscribed crateriform pink nodule with keratotic core, consistent with keratoacanthoma-type SCC. **B,** A surgical defect after Mohs micrographic surgery achieved clear margins **C,** A surgical defect repaired with a Burows graft. **D,** A 0.7-cm pink hyperkeratotic plaque (*arrow*), consistent with FK-ESA, that developed distal to the skin graft 6 weeks after Mohs micrographic surgery at the site of the repair. **E,** Improvement in FK-ESA 3 weeks after the intralesional 5-fluorouracil injection.

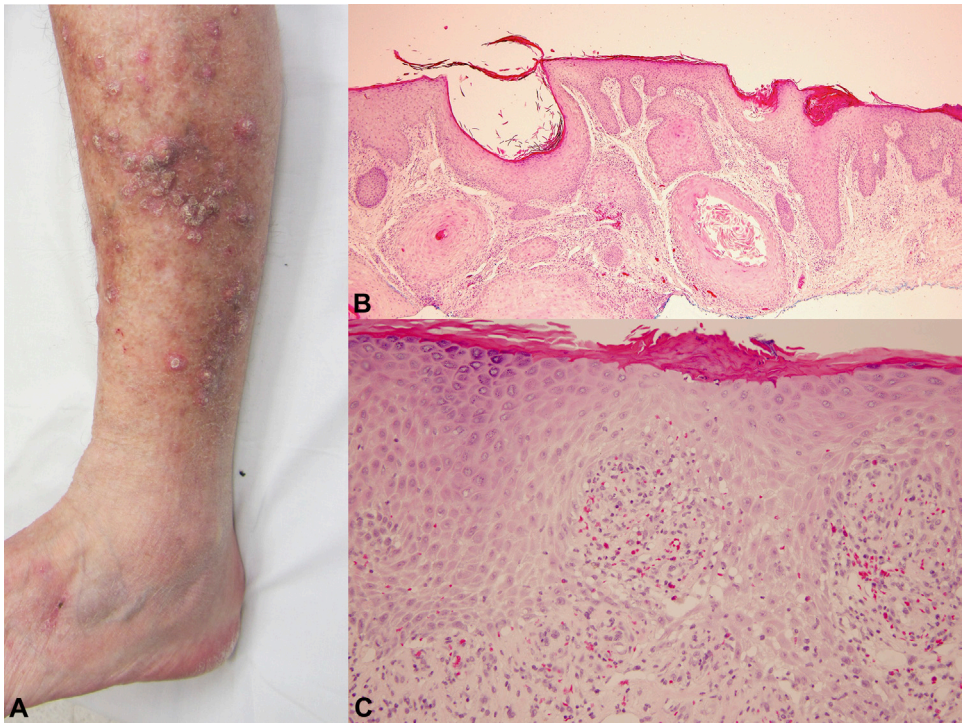

Fig 3. Diffuse eruptive squamous atypia. **A,** Numerous eruptive papules and plaques suggestive of prurigo nodularis versus eruptive keratoacanthoma. A biopsy of a representative lesion was performed to rule out malignancy. **B,** Histopathologic examination revealed the superficial portion of invasive well-differentiated squamous cell carcinoma, though the clinical picture and presence of numerous eruptive lesions is more consistent with a reactive process. **C,** Histopathologic examination showed surrounding subacute spongiotic dermatitis with numerous eosinophils, which is consistent with background hypersensitivity dermatitis. (**B** and **C,** Hematoxylin-eosin stain; original magnifications: **B,** × 4; **C,** × 20.)

Table II. Eruptive squamous atypia: Clinical and histologic criteria

Criteria and characteristics
Clinical criteria
Required characteristics
Multiple hyperkeratotic papules and plaques that erupt synchronously over a region on the body
OR
Development of ≥1 hyperkeratotic papule or plaque over an area of localized trauma or within 3 months of a clear-margin surgical excision
Supporting characteristics
Location on the extremities
Uniformity in the diameter and appearance of the hyperkeratotic papules
Evidence of koebnerization
Histologic characteristics*
Required characteristics
A squamous cell proliferation that is composed of dysplastic or atypical cells and has benign, premalignant, or low-grade (eg, keratoacanthomatous) malignant features
Supporting characteristics
Changes suggestive of a reactive process (eg, epidermal or pseudoepitheliomatous hyperplasia, mild atypia)
Features precluding diagnosis of eruptive squamous atypia
Moderate or poor differentiation
Perineural invasion
Lymphovascular invasion
Infiltrative growth pattern
Invasion beyond the dermis

*Our management approach with intralesional 5-fluorouracil does not necessitate a preinterventional biopsy for confirmation of diagnosis. However, a biopsy is recommended for lesions that are not resolving or continue to enlarge despite treatment.

Table III. Baseline demographics and lesion characteristics

Characteristics	All patients in cohort (N = 30)	Patients with FK-ESA (N = 11)	Patients with D-ESA (n = 19)
Patient characteristics			
Mean age at diagnosis, y (SD)	74 (14)	69 (13)	76 (13)
Sex			
Male, n (%)	9 (30)	5 (45)	4 (21)
Female, n (%)	21 (70)	6 (55)	15 (79)
Immunosuppressed, n (%)	10 (33)	5 (45)	5 (26)
History of kidney transplant, n (%)	5 (16)	3 (27)	2 (10)
History of liver transplant, n (%)	1(3)	1 (9)	0 (0)
Lymphoproliferative disease, n (%)	3 (10)	1 (9)	2 (10)
Psoriatic arthritis, n (%)	1 (3)	0 (0)	1 (5)
History of keratinocyte carcinoma, n (%)	30 (100)	11 (100)	19 (100)
History of melanoma, n (%)	4 (13)	1 (9)	3 (16)
ESA lesion characteristics			
Median no. of lesions treated per patient (range)	4 (1-15)	1 (1-5)	5 (1-15)
Medium maximum lesion diameter, cm (range)	0.7 (0.4-2.0)	0.7 (0.4-2.0)	0.7 (0.4-2.0)
Location of lesion(s), (%)			
Upper extremities only	3 (10)	1 (9)	2 (11)
Lower extremities only	24 (80)	10 (91)	14 (74)
Both upper and lower extremities	3 (10)	0 (0)	3 (16)

ESA, Eruptive squamous atypia; *D-ESA*, diffuse-eruptive squamous atypia; *FK-ESA*, focal koebnerized-eruptive squamous atypia; *SD*, standard deviation.

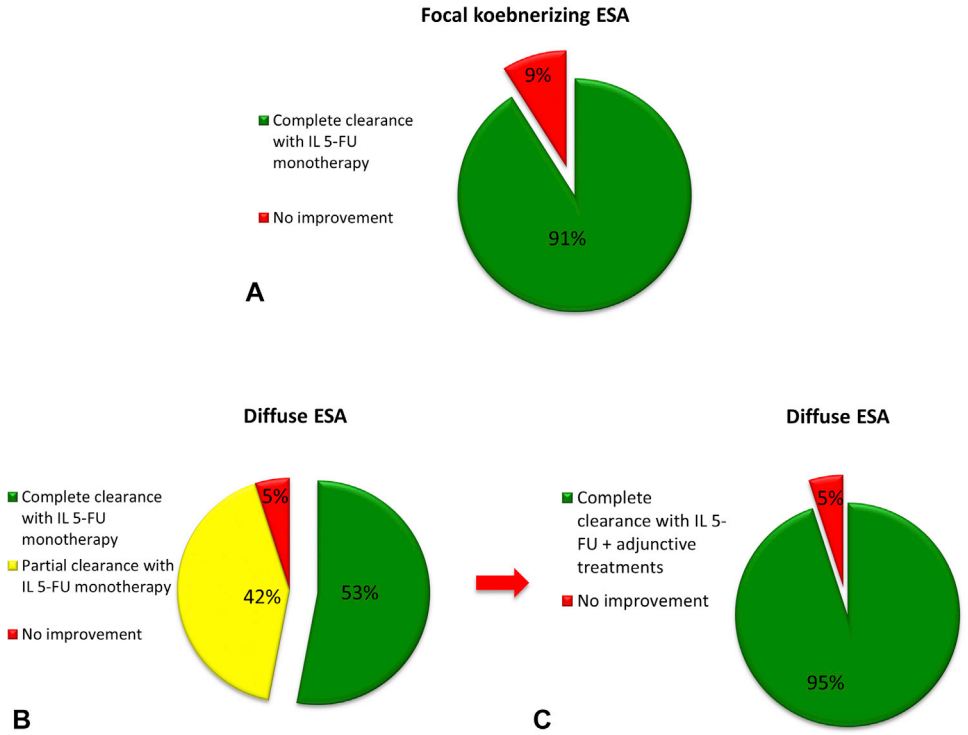

Fig 4. A, Response of patients with focal koebnerizing eruptive squamous atypia (ESA) to intralesional (IL) 5-fluorouracil (5-FU) monotherapy. Of the patients in this subcohort, 10 (91%) achieved complete clearance with IL 5-FU monotherapy; 1 patient (9%) had a lesion that did not resolve with 2 treatment sessions of IL 5-FU. Shave biopsy showed a benign squamous proliferation, and the lesion resolved with the biopsy. **B,** Response of patients with diffuse ESA to IL 5-FU monotherapy. Of the patients in this subcohort, 10 (53%) achieved complete clearance with IL 5-FU monotherapy; 8 patients (42%) achieved partial clearance, and 1 patient (5%) had a lesion that did not resolve. A biopsy specimen of the lesion that did not resolve was obtained; it showed epidermal hyperplasia with reactive atypia and stasis changes. The lesion resolved with the biopsy. **C,** Effective clearance rate for patients with diffuse ESA treated with either IL 5-FU monotherapy *or* multimodal therapy (IL 5-FU and other therapies [topical 5-FU under occlusion, acitretin, cryotherapy, or clobetasol]).

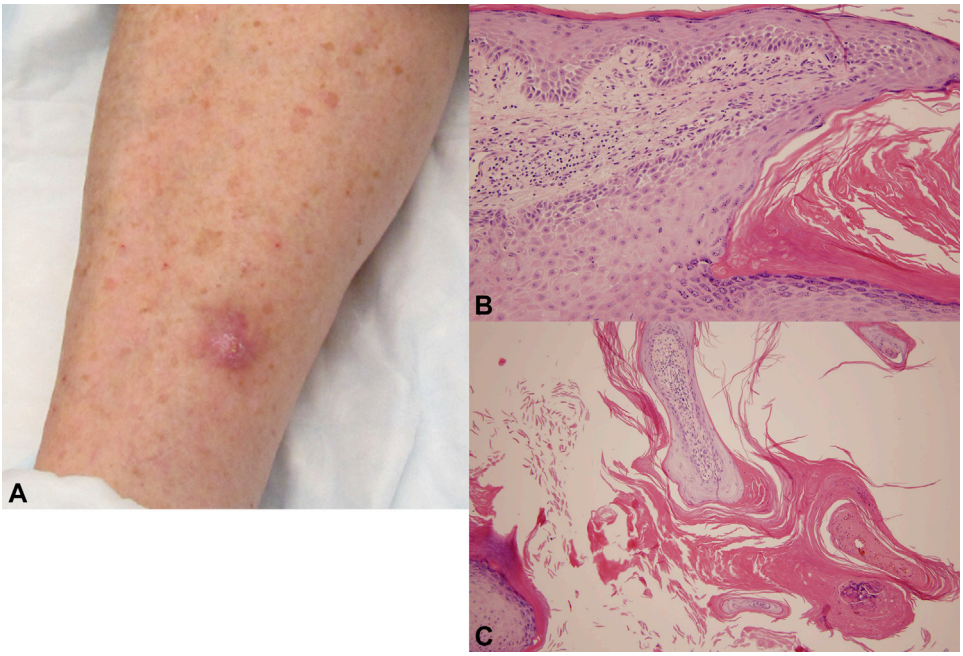

Fig 5. A case of focal koebnerizing eruptive squamous atypia unresponsive to intralesional 5-fluorouracil treatment. **A,** A 5-mm pink hyperkeratotic papule on the right anteromedial aspect of the leg appearing 3 months after Mohs micrographic surgery on the right anteromedial aspect of the leg followed by second-intention healing. **B,** Histopathologic examination that was performed when the lesion did not clear after intralesional 5-fluorouracil treatments showed features of a verrucoid squamous proliferation and focal chunky keratohyaline granules in the valleys between the verrucous projections and glassy chromatin. **C,** Histopathologic examination showed parakeratosis and entrapped blood clots. (**B** and **C,** Hematoxylin-eosin stain; original magnifications: **B,** × 20; **C,** × 10.)

Safety of IL 5-FU

No serious adverse events were documented. Side effects were mild; they included cutaneous dyspigmentation and shallow erosions or ulcerations after treatment that healed within 2 to 4 weeks.

DISCUSSION

Previous reports have described an eruptive process of hyperproliferation associated with prior surgeries, trauma, or underlying inflammation or immune dysfunction—what we term *ESA*. ESA is both an under-recognized and poorly defined phenomenon. To our knowledge, this is the first study proposing diagnostic criteria for ESA (aka eruptive keratoacanthoma) and measuring efficacy of IL 5-FU by clinical resolution and surgical requirement.

In this 30-person cohort, none of the 136 ESA lesions treated with IL 5-FU required surgery. The majority of patients (three-fourths) required no surgery after initiation of IL 5-FU therapy. The need for SCC excisions with IL 5-FU treatment was low, with 23, 5, and 2 patients requiring 0, 1, and 2 excisions, respectively, in the 12 months after initiation of IL 5-FU treatment.

A total of 7 patients (23%) required excision of a new SCC arising on the IL 5-FU–treated extremity after IL 5-FU treatment was initiated, illustrating that patients with ESA may develop bona fide SCC. Clinical judgment should therefore be used when distinguishing between ESA and high-grade SCC. The risk of missing an aggressive SCC is a valid concern when deciding on a nonsurgical treatment modality. However, the 9 SCCs excised in this study after initiation of IL 5-FU treatment were well differentiated, with no extension into fat, perineural involvement, or lymphovascular invasion. They were excised (rather than treated with IL 5-FU) because they were larger than 1.5 cm, which may potentially inhibit the even distribution of 5-FU throughout the lesion.

In our practice, a diagnosis of ESA is made without a biopsy because ESA is primarily a clinical diagnosis based on the presence of multiple concurrent keratotic lesions on the extremities or a single such lesion occuring within 3 months of a clear-margin excision (a time frame in which koebnerizing ESA is more likely than recurrent cancer, particularly if the original cancer had no high-risk features). Patients

Table IV. Adjunctive treatments used in select patients in addition to IL 5-FU

Treatment	Concentration/dose	Administration	Notes
Topical 5-FU under occlusion	5-FU	Apply thin layer of 5-fluorouracil and occlude with plastic wrap overnight for 4 wk OR Apply Unna boot for 1 wk over thin layer of 5-FU	
Cryotherapy	N/A	Apply 3 freeze-thaw cycles to lesions	
Topical clobetasol	0.05% ointment	Apply topically twice daily for 1-2 wk or as needed for pruritus	For diffuse, shallow erosions or in the context of diffuse pruritus
Oral acitretin	10 mg every other day to 20 mg daily	Slow up-taper suggested to minimize side effects, eg, • 10 mg po every other day for 1 month, then • 10 mg po daily for 1 mo, then • Alternate between 10 mg and 20 mg po every other day for 1 mo, then • 20 mg po daily as the standing dose Obtain baseline CBC, lipid level, liver function levels, and creatinine level. Monitor monthly until stable dose is reached, at which point laboratory tests can be repeated every 4 mo (or more frequently, as indicated)	For severe or refractory disease

CBC, Complete blood count; *5-FU*, 5-fluorouracil; *IL*, intralesional; *N/A*, not available; *po*, orally.

are re-evaluated 2 to 4 weeks after injection. In the unlikely event that the treated lesion fails IL 5-FU treatment, it can still be excised within an appropriate time frame.

Although IL 5-FU requires multiple office visits, it has distinct advantages over surgical excision. It is quick and easy to administer; decreases the morbidity and inconvenience for the patient associated with unnecessary, repeated excisional procedures; and carries a lower risk of bleeding and infection, a shorter healing time, and lower costs. A 1-cm^3 syringe costs $8. Administration of IL 5-FU is billed under code 96405 (IL chemotherapy for up to 7 lesions), which is reimbursed at $30.86 as per the 2017 published Medicare facility rates ($82.90 for nonfacility administration). Most importantly, a nonsurgical approach is central to proper management of ESA because surgery often exacerbates this reactive, koebnerizing process. Although there is no set standard dose, the maximum total dose used per patient for all lesions treated in 1 session was 6 mL. Patients receiving this dose did not experience any harmful side effects or exhibit signs of systemic absorption of the medication.

Study limitations include the retrospective single-institution design and lack of complete histopathologic confirmation. However, as already discussed, ESA is primarily a clinical diagnosis. Histologic appearances and diagnoses of ESA lesions vary, making a single histologic classification of ESA impossible. However, a unifying finding is the presence of an atypical but well-differentiated keratinocytic proliferation. This helps to separate ESA from other entities with similar clinical presentations, such as lichen simplex chronicus, prurigo nodularis, or transepidermal elimination disorders. The 30-patient sample size, though larger than that in prior studies, was insufficient for multivariate analysis of factors affecting response to treatment. However, given that 0 of 136 treated lesions recurred and 90% of the cohort experienced a reduction in surgical requirement, a rather large study would

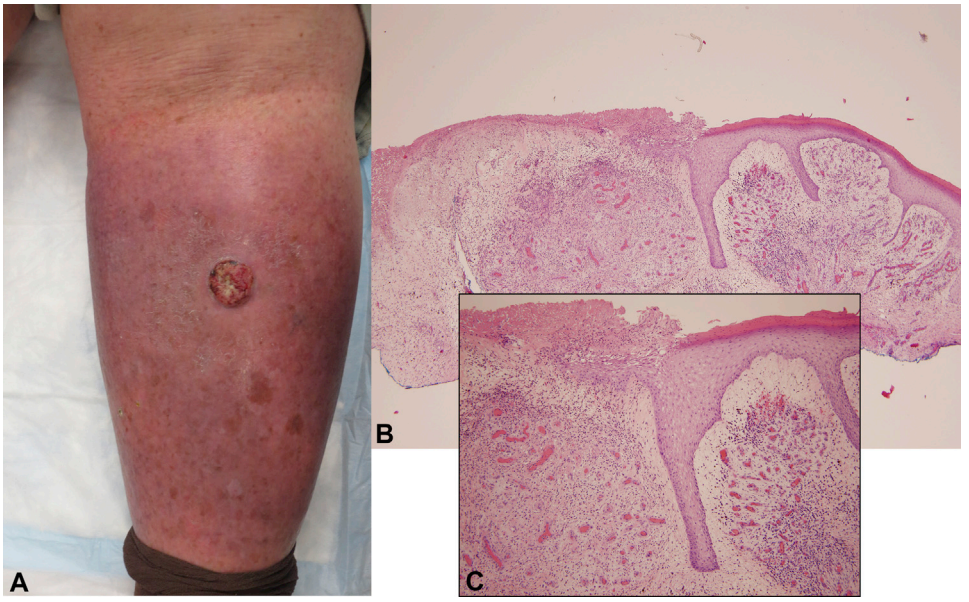

Fig 6. A case of diffuse eruptive squamous atypia (ESA), with 1 lesion that did not respond to intralesional (IL) 5-fluorouracil (5-FU) treatment. **A,** A 1-cm hyperkeratotic plaque remaining after treatment of surrounding lesions with IL 5-FU. **B,** Histopathologic examination of the left anterior aspect of the shin after the lesion failed to clear with IL 5-FU treatment revealed epidermal hyperplasia with reactive atypia, ulcerated, with dermal chronic inflammation, granulation tissue formation, and marked stasis changes. **C,** Inset. (**B** and **C,** Hematoxylin-eosin stain; original magnifications: **B,** × 4; **C,** × 10.)

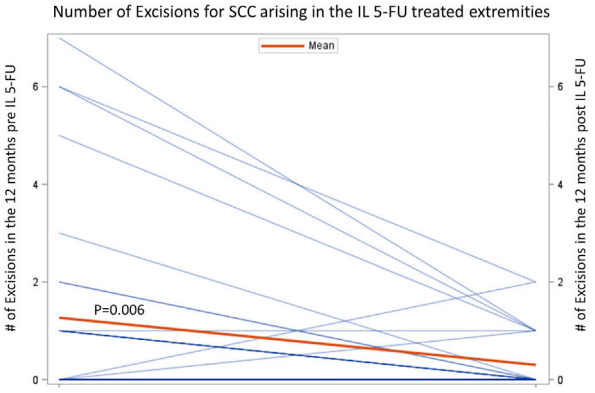

Fig 7. Each line connects the number of excisions undergone by a given patient for squamous cell carcinoma (SCC) in the intralesional (IL) 5-fluorouracil (5-FU)-treated extremity in the 12 months before versus after initiation of IL 5-FU treatment. A downward trend for all but 3 patients and a mean reduction of 1 excision per patient are shown (P = .006).

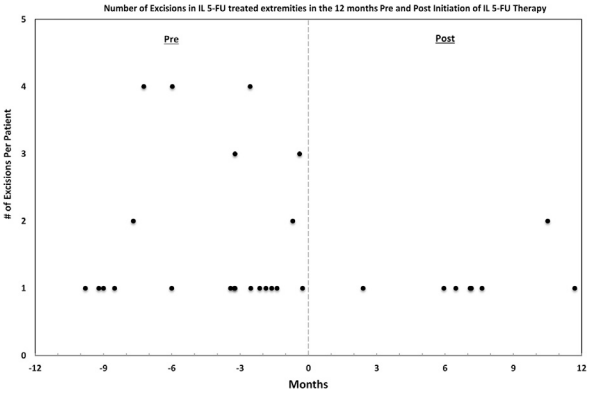

Fig 8. Scatterplot of the number of excisions that patients underwent for squamous cell carcinomas arising in their intralesional (IL) 5-fluorouracil (5-FU)-treated extremity over time. Each dot represents a patient who underwent 1 or more excisions at a given time point in relation to initiation of his or her IL 5-FU therapy. Time 0 is the first IL 5-FU therapy session. The plot shows that fewer excisions were required after initiation of IL 5-FU therapy.

likely be needed to determine factors predicting such rare treatment failures. Lastly, follow-up was limited for some patients (eg, 2 patients had only slightly more than a month of follow-up data), which limits our ability to assess long-term outcomes for the complete cohort.

CONCLUSION

A clinical diagnosis of ESA should be considered when a hyperkeratotic papule develops over an area of localized trauma (or within 3 months of a clear-margin excision) or when multiple keratotic papules erupt concurrently, especially over the extremities.

IL 5-FU can be used to treat ESA, with disease resolution in 67% of ESA patients. Addition of topical 5-FU under occlusion, topical steroids (for diffuse shallow lesions), or acitretin (in more severe or refractory presentations) can help achieve clearance. Close clinical and photographic monitoring is needed every 2 to 4 weeks for as long as lesions persist. For lesions that do not resolve or are enlarging despite treatment, a biopsy is advised to rule out high-grade SCC. After clearance of the ESA lesions has been achieved, follow-up for skin cancer screening should follow conventional guidelines, as determined by personal and family history of skin cancer and level of actinic damage.

Although we have proposed a definition for ESA and outlined a treatment strategy, the biologic significance and molecular mechanisms of this phenomenon remain largely unknown. Research advances may eventually lead to an improved classification scheme, but for the time being, we propose *ESA* as a descriptive clinical term for squamous proliferations likely to respond to IL 5-FU treatment.

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