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CASE REPORT | ESOPHAGUS

Development of Esophageal Epidermoid Metaplasia in a Pediatric Patient After Stevens-Johnson Syndrome

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ABSTRACT

Esophageal epidermoid metaplasia (EEM) is a rare condition that has not been described in Stevens-Johnson syndrome (SJS) and has only been described once in pediatrics. Neither the relationship, treatment, nor surveillance between SJS, esophageal strictures, and EEM has been established. We report the first case of EEM in an 8-year-old girl with esophageal stricture after SJS. Pediatric patients presenting with dysphagia after SJS should be evaluated for esophageal stricture and subsequent EEM development. Owing to EEM's, association with esophageal squamous cell cancer, close follow-up, biopsy surveillance for dysplasia, endoscopic treatment, and TP53 genetic sequencing should be considered.

KEYWORDS: epidermoid esophageal metaplasia; Stevens-Johnson syndrome; pediatric; esophageal stricture

INTRODUCTION

Esophageal epidermoid metaplasia (EEM), also known as esophageal leukoplakia (EL), is a rare condition primarily found in older adults with dysphagia.[1] Risk factors include tobacco and alcohol use.[1] EEM is a potentially premalignant condition associated with esophageal cancer; thus, close follow-up and treatment for dysplasia are recommended after diagnosis.[2,3]

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, potentially fatal skin reactions resulting in skin loss, possible mucous membrane involvement, and systemic symptoms.[4] Since 1949, only 14 pediatric cases with gastrointestinal manifestations after SJS/TEN have been described. The most common presentation was progressive dysphagia due to an esophageal stricture.[5]

Of note, EEM has not been described in patients with SJS/TEN. Thus, treatment and surveillance for EEM after SJS/TEN have not been established. In addition, the relationship between esophageal stricture and subsequent EEM development is unknown.

We report the first case of EEM in an 8-year-old girl with esophageal stricture after SJS.

CASE REPORT

A previously healthy 3-year-old girl presented to the emergency department lethargic with a diffuse skin rash. She was diagnosed with SJS/TEN of unclear etiology (although suspected to be aspirin induced), with 56% body surface area involvement. A skin biopsy confirmed TEN, and she was treated with intravenous immunoglobulin and supportive care by dermatology, ophthalmology, and gynecology due to skin, ocular, and vaginal involvement.

Six months after her diagnosis of SJS/TEN, she developed dysphagia. Upper gastrointestinal series, esophagram, and ultimately esophagoduodenoscopy (EGD) confirmed a long segment mid-esophageal stricture. Endoscopically, the stricture was balloon

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dilated from 6 mm to 12 mm. She also received Kenalog injections monthly for the first 3 months. She was then temporarily lost to follow-up.

Three years after her initial SJS/TEN diagnosis, she was seen for recurrent globus sensation. EGD confirmed persistent esophageal stricture. Over the next 2 years (years 4 and 5 post-SJS/TEN diagnosis), she underwent 6 endoscopic balloon dilations, dilating from 10 mm to 12 mm. Respective biopsies during this time were unremarkable without evidence of EEM/EL (Figures 1 and 2). By the sixth year after her SJS/TEN diagnosis, a white patch was visualized endoscopically with biopsy reports showing EEM (Figures 3 and 4). Subsequent EGD biopsies revealed similar results without any evidence of dysplasia. She continues on routine endoscopic surveillance to this date and has not yet needed additional therapy.

DISCUSSION

This case illustrates the first report of EEM in a pediatric patient with esophageal stricture, after SJS/TEN. Esophageal stricture is the most common gastrointestinal complication after SJS/TEN and can be seen as early as 1 month post-SJS/TEN.[6,7] Differential diagnoses for esophageal strictures in pediatric patients include gastroesophageal reflux disease (GERD), congenital anomalies, caustic ingestion, esophageal atresia, and eosinophilic esophagitis.[8] Since 1949, only 5 pediatric cases of isolated esophageal stricture after SJS/TEN have been identified.[5] Similar to our patient, all 5 presented with dysphagia weeks to years after SJS/TEN diagnosis.[5] However, why our patient subsequently developed EEM is unknown.

In our patient, EEM was diagnosed 5 years after her diagnosis of an SJS/TEN-induced esophageal stricture. Although the exact timing of EEM is unclear, this delay in development is in line with our speculation that EEM typically takes years to develop as it previously has only been reported in older adults (mean, 61.5 years). Studies suggest, however, that once metaplasia occurs, it can develop rapidly. In one report, EEM developed after esophageal intramural pseudodiverticulosis and candidiasis 6 months after a previous unremarkable endoscopic examination.[9] Authors suspect that the patient's long-standing candidiasis could have played a principal role in the pathogenesis. The patient was also an ex-smoker and had a history of moderate alcohol intake.[9]

EEM typically presents in the mid to distal esophagus as white plaque-like areas endoscopically and as hyperkeratosis with a prominent granular layer histologically. Endoscopically, the differentials include candidiasis, GERD, eosinophilic esophagitis, and nutritional deficiency.[10] Histologically, hyperkeratosis can occur in nutritional deficiency, pill esophagitis, caustic ingestions, and sloughing esophagitis.[10] In the largest case series (n = 40) reported by Kamnboj et al, nearly half the cases had

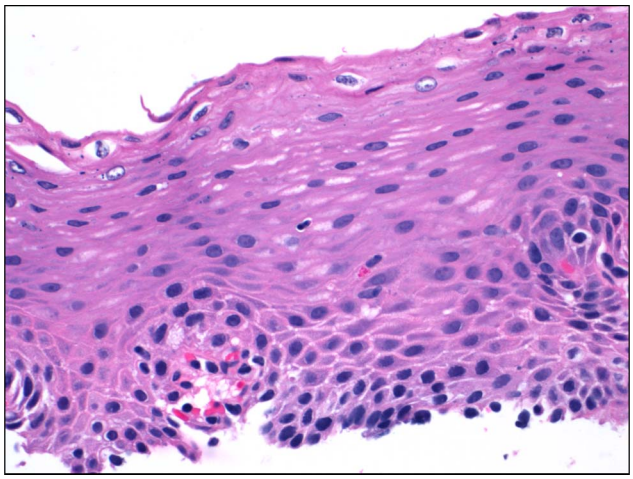

Figure 2. The corresponding biopsy (40×) to the endoscopic photograph in Figure 1 showing normal esophageal squamous mucosa without evidence of esophageal epidermoid metaplasia/esophageal leukoplakia.

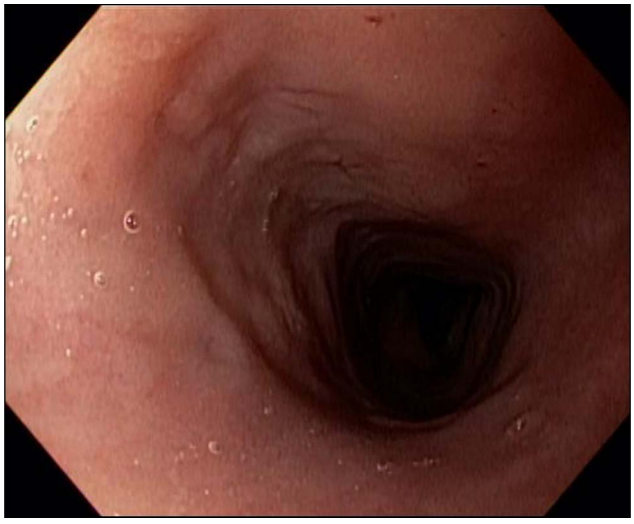

Figure 1. Endoscopically normal-appearing mucosa of the middle esophagus.

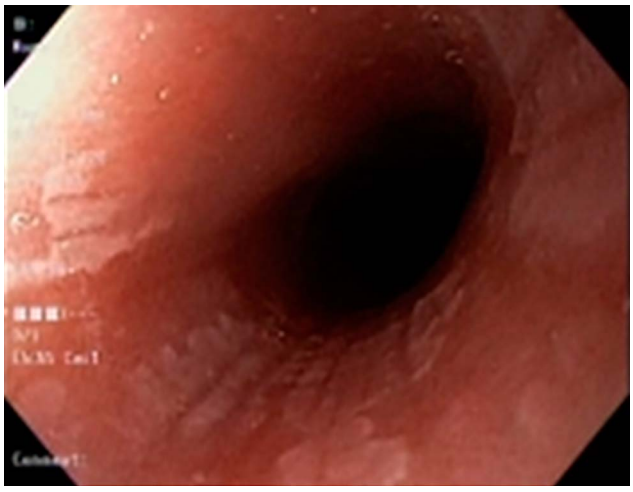

Figure 3. Endoscopic appearance of the middle esophagus with interval development of white plaque-like areas.

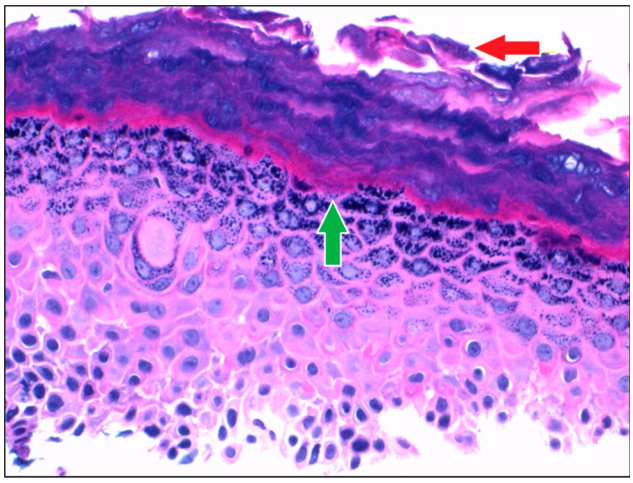

Figure 4. Biopsy (40×) of esophageal mucosa showing new development of epidermoid metaplasia with a prominent granular layer (green arrow) and abundant superficial keratin (red arrow).

undergone EGD and interpretation within the preceding 6 months without EEM diagnosis.[2] This suggests either rapid development of metaplasia or under recognition and/or lack of awareness by both endoscopists and pathologists.

The etiology and pathophysiology of EEM is unknown. Fukui et al hypothesized that EEM develops as a response to chronic esophageal injury caused by gastric acid reflux disease (GERD).[11] However, few patients had GERD in other EEM studies.[1,12] Similarly, our patient did not have significant GERD symptoms. In a recently reported case image, EEM in a pediatric patient with vitamin A deficiency was reversed with vitamin A supplementation, suggesting possible association vs causality.[10] Historically, vitamin A deficiency has been associated with transformation of the epithelium in skin, endocervix, and ectocervix into the keratinizing squamous stratified phenotype.[13] Our patient, however, was on a well-balanced diet and had no known nutritional concerns.

Other considerations include chronic esophageal trauma from repetitive dilations; however, if this was a significant risk factor, we would expect a higher rate of EEM in other conditions associated with esophageal strictures dilations, including eosinophilic esophagitis, surgical strictures, caustic injuries, and Crohn's esophagitis.

In one case series, Singhi et al[1] collected 25 cases from 18 adult patients with EEM. History was significant for tobacco or chronic second-hand smoking in 61% of patients and significant alcohol intake in 39% patients. They concluded that both tobacco smoke and excessive alcohol are risk factors for EEM. They also found a slight female predominance (56%). Our case of pediatric EEM without prior second-hand smoke exposure or alcohol use warrants further investigation.

The urgent need to understand EEM is driven by its association with esophageal squamous cell cancer (ESCC). Kamnboj et al highlighted squamous neoplasia occurring before, with, or after EEM.[2] According to Singhi et al, genetic mutations may be driving ESCC development secondary to EEM.[14] In their study, targeted next-generation sequencing revealed 12 of 18 (67%) EEM specimens' harbored alterations in genes often associated with ESCC, the most common being TP53 (n = 10).[14] TP53 mutation EEM specimens correlated with concurrent or progression to high-grade squamous dysplasia/ESCC. The authors concluded that EEM is a precursor to in situ and invasive esophageal squamous neoplasia and that detecting TP53 mutations in EEM may serve as an early detection biomarker for high-grade squamous dysplasia/ESCC.

In pediatric patients with SJS, esophageal involvement should be considered when presenting with dysphagia.[5,15] With the association of EEM and ESCC, close follow-up and endoscopic treatment should be considered. As there are no current management and surveillance guidelines for pediatric patients with EEM, we recommend the following adult guidelines shared in previous studies. Management is recommended for all lesions with dysplasia. In particular, endoscopic mucosal resection should be performed for small dysplastic, lesions while endoscopic ablation should be performed for larger lesions with dysplasia.[2,3] For surveillance, repeat EGD with 4-quadrant biopsies every 1-2 cm should be performed in 6 months for lesions that are not easily resectable and do not harbor dysplasia.[2,3,16] If no dysplasia or disease progression is detected, repeat EGDs should be performed yearly.[2,3,16]

DISCLOSURES

Author contributions: ME Sanchez-Anguiano: substantial contributions to the conception or design of the work, acquisition, analysis, and interpretation of data for the work; drafting the work. KB Schaberg: substantial contributions to the conception or design of the work; reviewing it critically for important intellectual content and final approval of the version to be published. TT Truong: substantial contributions to the conception or design of the work, reviewing it critically for important intellectual content, final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved and is the article guarantor.

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