IMPORTANT WARNINGS AND PRECAUTIONS USING PHOTOFRIN® INCLUDE:

Gastroesophageal Fistula and Perforation: Do not initiate PHOTOFRIN with photodynamic therapy (PDT) in patients with esophageal tumors eroding into the trachea or bronchial tree or bronchial wall.

Pulmonary and Gastroesophageal Hemorrhage: Assess patients for tumors eroding into a pulmonary blood vessel and esophageal varices. Do not administer light directly to an area with esophageal varices.

High-Grade Dysplasia (HGD) in Barrett's Esophagus (BE): After treatment of HGD in BE, conduct endoscopic biopsy surveillance every 3 months, until 4 consecutive negative evaluations for HGD have been recorded.

Photosensitivity and Ocular Photosensitivity: Observe precautions to avoid exposure of skin and eyes to direct sunlight or bright indoor light for at least 30 days. Instruct patients when outdoors to wear dark sunglasses which have an average light transmittance of <4% for at least 30 days and until ocular sensitivity resolves.

Use Before or After Radiotherapy: Allow 2-4 weeks between PDT and subsequent radiotherapy.

Chest Pain: Substernal chest pain can occur.

Airway Obstruction and Respiratory Distress: Administer with caution to patients with tumors in locations where treatment-induced inflammation can obstruct the main airway. Monitor patients closely between the laser light therapy and the mandatory debridement bronchoscopy for any evidence of respiratory distress.

Esophageal Strictures: Esophageal strictures can occur.

Hepatic and Renal Impairment: Patients with hepatic or renal impairment may need longer precautionary measures for photosensitivity.

Thromboembolism: Thromboembolic events can occur.

Embryo-Fetal Toxicity: May cause embryo-fetal toxicity. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

MOST COMMON ADVERSE REACTIONS reported during clinical trials (>10% of patients) are:

Esophageal Cancer: Anemia, pleural effusion, pyrexia, constipation, nausea, chest pain, pain, abdominal pain, dyspnea, photosensitivity reaction, pneumonia, vomiting, insomnia, back pain, pharyngitis.
Obstructing Endobronchial Cancer: Dyspnea, photosensitivity reaction, hemoptysis, pyrexia, cough, pneumonia.
Superficial Endobronchial Tumors: Exudate, photosensitivity reaction, bronchial obstruction, edema, bronchostenosis.
High-Grade Dysplasia in Barrett's Esophagus: Photosensitivity reaction, esophageal stenosis, vomiting, chest pain, nausea, pyrexia, constipation, dysphagia, abdominal pain, pleural effusion, dehydration.

Other photosensitizing agents may increase the risk of photosensitivity reaction. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with PHOTOFRIN and for 5 months after the last dose.

Please see full Prescribing Information for PHOTOFRIN® (porfimer sodium) for Injection at: www.photofrin.com

FOR MORE INFORMATION about PHOTOFRIN®, or if there are any questions regarding the information provided, visit **www. photofrin.com** or please contact the Medical Information Department at **1-866-248-2039**. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch**, or call **1-800-FDA-1088**.

ADP-054 07/2020

References:
1. Cottreau, J., et al., Prevalence of oesophageal epidermoid metaplasia in 1048 consecutive patients and 58 patients with squamous neoplasms. Histopathology, 2016. 68(7): p. 988-95.
2. Singhi, A.D., et al., Targeted next-generation sequencing supports epidermoid metaplasia of the esophagus as a precursor to esophageal squamous neoplasia. Mod Pathol, 2017. 30(11): p. 1613-1621.

PDT with PHOTOFRIN® [porfimer sodium] for injection

PINNACLE BIOLOGICS

Epidermoid metaplasia (Squamous dysplasia) after paraesophageal hernia repair

Steven R. DeMeester, M.D., FACS
The Oregon Clinic - Gastrointestinal & Minimally Invasive Surgery.

Patient History

The patient is a 78-year-old woman with a history of paraesophageal hernia repair in 2008 who developed an esophageal stricture and a recurrent hernia in 2011. The stricture responded to dilations, and she had good symptom control on acid suppression medications. In 2019 she presented with recurrent dysphagia. The dysphagia was primarily for solids and had been progressive over the past six months. She denies heartburn or regurgitation symptoms but takes a Proton pump inhibitor (PPI) daily. She drank socially in the past but stopped in 2013, and never smoked cigarettes or used tobacco.

Examination

Evaluation with high-resolution manometry showed normal lower esophageal sphincter (LES) pressure and length, intragastric pressure (IRP) 11, small hiatal hernia, 100% peristalsis in the esophageal body with a normal distal contractile integral (DCI). Esophageal pH testing of acid suppression medications showed normal esophageal acid exposure. An esophagogastroduodenoscopy (EGD) showed very abnormal appearing esophageal mucosa from 18-28 cm with furrows, rings, and white plaque, suggestive of advanced eosinophilic esophagitis. From 28 cm to the Gastro-esophageal junction (GEJ) at 30 cm, the squamous mucosa appeared normal (Figure 1). No stricture was present, but the fundoplication was partially disrupted and herniated. Esophageal biopsies showed no evidence of eosinophilic esophagitis but instead showed hyperkeratosis, hypergranulosis, and parakeratosis, consistent with epidermoid metaplasia. There was no dysplasia, but heavy mucosal involvement by bacterial organisms was reported (Figure 2).

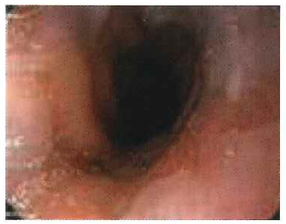

Figure 1 – Squamo-columnar junction in distal esophagus, note the normal appearance to the squamous mucosa at this location.

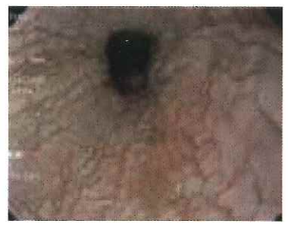

Figure 2 – Initial appearance of proximal esophagus with epidermoid metaplasia. Biopsies did not show any dysplasia but there was heavy bacterial growth in the abnormal mucosa

Vitals: Height: 60 in. Weight: 168.5 lbs w/shoes. Body mass index (BMI): 33.03. Heart Rate: 82/min; First Blood Pressure (BP) is 118/70 (left arm).
Constitutional: Well developed and well-nourished. No acute distress.
Abdominal exam: benign, no mass or hernia.

See important prescribing and safety information for PHOTOFRIN® (porfimer sodium) for Injection on pages 3 and 4.

Diagnostic Evaluation (or Clinical impression)

The cause of the dysphagia was presumed to be the epidermoid metaplasia. She was treated with oral antibiotics and antifungals to see if this improved her symptoms and the appearance of the esophageal mucosa, with a plan for repeat endoscopy in 3 months. A repeat EGD in December 2019, the findings were unchanged, but now biopsies showed mild to moderate dysplasia arising in the background of epidermoid metaplasia (Figure 3). No invasive carcinoma was present. Given the progression of the disease with squamous dysplasia now present, the decision was made to ablate the abnormal mucosa. Given the extent of the disease and the very proximal starting point at the level of the upper esophageal sphincter, the decision was made to use photodynamic therapy (PDT).

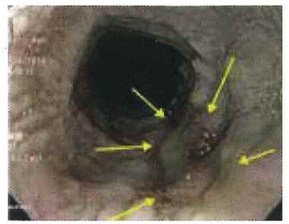

Figure 3 – Ulcers, nodules and irregular appearance (arrows) in the area of epidermoid metaplasia on follow-up endoscopy. Biopsies now show dysplasia.

Course of Treatment

The patient was administered the standard 2 mg/kg of PHOTOFRIN® (porfimer sodium) for Injection intravenously in January 2020, and 48 hours later underwent endoscopy. At endoscopy, there was evidence of further disease progression with mucosal ulceration present proximally and nodular, white mucosa extending to 28 cm. The squamous mucosa from 28 cm to the squamocolumnar junction (SCJ) at 30 cm appeared normal. A 5-cm rigid catheter was positioned from 18-23 cm and treated to 125 joules. She returned seven days later for the treatment of the more distal disease. EGD showed that the mucosa was sloughing in the treatment area from 17-23 cm. The 5 cm rigid catheter was positioned at 23-28 cm and treated to 76 joules.

Clinical Outcomes

She was scheduled for follow-up EGD in 8 weeks to evaluate the impact of therapy, but this therapy was delayed until she called with recurrent dysphagia symptoms in April 2020. EGD showed normal appearing squamous mucosa with a stricture at 20 cm and another at 28 cm (Figure 4).

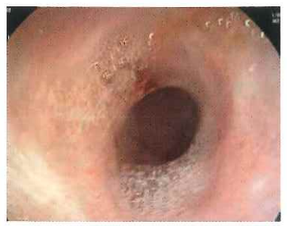

Figure 4 – View of the proximal and mid-esophagus after PDT showing normal appearing squamous mucosa with a stricture distally. Biopsies confirmed normal squamous mucosa.

Both were successfully dilated with a through-the-scope balloon. Biopsies from the proximal, mid and distal esophagus showed normal squamous mucosa with no diagnostic abnormality.

Discussion

Epidermoid metaplasia is a relatively rare esophageal condition characterized by leukoplakia or a white appearance to the squamous esophageal mucosa. It is diagnosed by biopsy showing a characteristic dense granular layer and overlying hyperorthokeratosis. Parakeratosis, a much more common finding, lacks the dense granular layer of epidermoid metaplasia[1]. Epidermoid metaplasia most commonly occurs in elderly females and is believed to occur in the context of mucosal irritation.

It has been associated with a history of alcohol and tobacco use although neither were present to a significant degree in this patient. It typically occurs in the mid to distal esophagus but in this patient was involving the proximal esophagus as well. It has been linked to esophageal squamous cell cancer[2]. Given the extensive esophageal involvement and progression to dysplasia the decision was made to ablate the tissue, and PDT was selected as the ideal approach. To avoid overlapping treatment areas the proximal esophagus was treated first followed a week later by the distal esophagus. The more diseased proximal esophagus was treated with a dose of 125 J, while the less diseased mid to distal esophagus was treated with 76 J. This resulted in complete clearance of the epidermoid metaplasia and dysplasia. Biopsies confirmed normal squamous mucosa in the entire length of treated esophagus. This confirms the efficacy of lower PDT doses to treat disease limited to the mucosa, in contrast to the 300 J commonly used to treat deeply invasive tumors. The strictures post-PDT were located proximally in the area of the worst disease and distally at the junction with the normal squamous mucosa. Both were easily dilated and subsequently her dysphagia symptoms have resolved. PDT should be considered first line therapy for dysplastic epidermoid metaplasia and other superficial squamous lesions that often involve extensive portions of the esophageal mucosa.

The information contained in this case study has been supplied by the medical professional whose name appears here. The advice, opinion, statements, materials and other information expressed and contained in this case study are from the authors and reflect their personal experience with the specific patient. Results may vary. Pinnacle Biologics, Inc. makes no claim that similar treatment will result in a similar outcome.

PHOTOFRIN® (porfimer sodium) for Injection Indications

Palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with Nd:YAG laser therapy.
Treatment of microinvasive endobronchial non–small cell lung cancer (NSCLC) in patients for whom surgery and radiotherapy are not indicated.
Reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial NSCLC.
Ablation of high-grade dysplasia (HGD) in Barrett's esophagus (BE) patients who do not undergo esophagectomy.

Important Safety Information About PHOTOFRIN® (porfimer sodium) for Injection

PHOTOFRIN® should not be used in patients with porphyria, existing tracheoesophageal or bronchoesophageal fistula, tumors eroding into a major blood vessel, emergency treatment of patients with severe acute respiratory distress caused by an obstructing endobronchial lesion because 40 to 50 hours are required between injection of PHOTOFRIN® and laser light treatment, and esophageal or gastric varices or esophageal ulcers >1 cm in diameter.