

Sebaceous Gland Ectopia of the Esophagus: A Challenging Clinical Diagnosis

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Abstract. *Background/Aim: Sebaceous gland ectopia (SGE) defines the presence of normal sebaceous tissue in an unusual location. This condition is rare and was first described in ectodermal-derived organs, such as the oral cavities and palms, and later in endodermal-derived tissues including the esophagus. SGE of the esophagus is believed to represent a form of acquired metaplasia. SGE is asymptomatic and usually discovered during routine endoscopic examinations for other gastrointestinal complaints and symptoms. It is a benign entity and to date no cases of malignant transformation have been reported. Once diagnosed, SGE requires no further work up or follow up, and does not require treatment. Case Report: We present two cases of SGE arising in the esophagi of two female patients who presented with complaints of gastro-esophageal reflux and underwent endoscopy. These lesions presented as patchy yellow-white nodules in the mid and upper esophagus and were endoscopically interpreted as suggestive of candidiasis or glycogen acanthosis. Biopsies showed foci of non-keratinizing squamous mucosa overlying the sebaceous glands. These glands exhibited a characteristic lobulated structure with germinative cells at the periphery and vacuolated, well-differentiated cells in the center of the lobules. After histologic examination, the endoscopic impressions of candidiasis and acanthosis were ruled out*

and the final diagnosis of SGE was made. There was no evidence of dysplasia or malignancy in our cases. Conclusion: Histopathology examination is important to differentiate SGE from malignant and infectious conditions that are more common, and which can be clinically and endoscopically similar to SGE.

Sebaceous gland ectopia (SGE) is a term denoting the occurrence of normal sebaceous tissue in an unusual location (1). In 1896, John Addison Fordyce first described the presence of ectopic sebaceous glands on the lips and oral cavities as intra oral sebaceous granules and the condition was known as Fordyce's disease (2, 3).

SGE is rare, and most commonly arises from ectodermal-derived tissues such as oral cavities, genitalia, eyes, orbits, palms, and soles. The occurrence of sebaceous ectopia in tissues with endodermal origin, *e.g.*, the esophagus, is extremely rare and only a few cases have been reported in the English language medical literature. Esophageal sebaceous ectopia was first described by De La Pava and Pickren in 1962 and since then less than 50 cases have been identified and presented in the medical literature (4). Prior to the invention of endoscopic techniques, SGE was only a postmortem diagnosis (5, 6). The pathogenesis of esophageal sebaceous ectopia is not currently well known. It is postulated that the entity is an acquired metaplastic process, but it could also represent a congenital abnormality. From a clinical standpoint, it is an asymptomatic condition with most cases being incidentally found during routine upper endoscopy for other reasons (4, 7).

Macroscopically, SGE is defined as multiple patchy yellowish-gray nodules discovered during routine endoscopy. The number of nodules can be as high as 100 and they can be located in any part of the esophagus (7, 9).

The presence of lobules of cells with sebaceous differentiation in the lamina propria and occasional proliferating basal cells within the epithelium are characteristic findings for SGE. The above histology is further supported by immunostains for keratins and epithelial membrane antigens,

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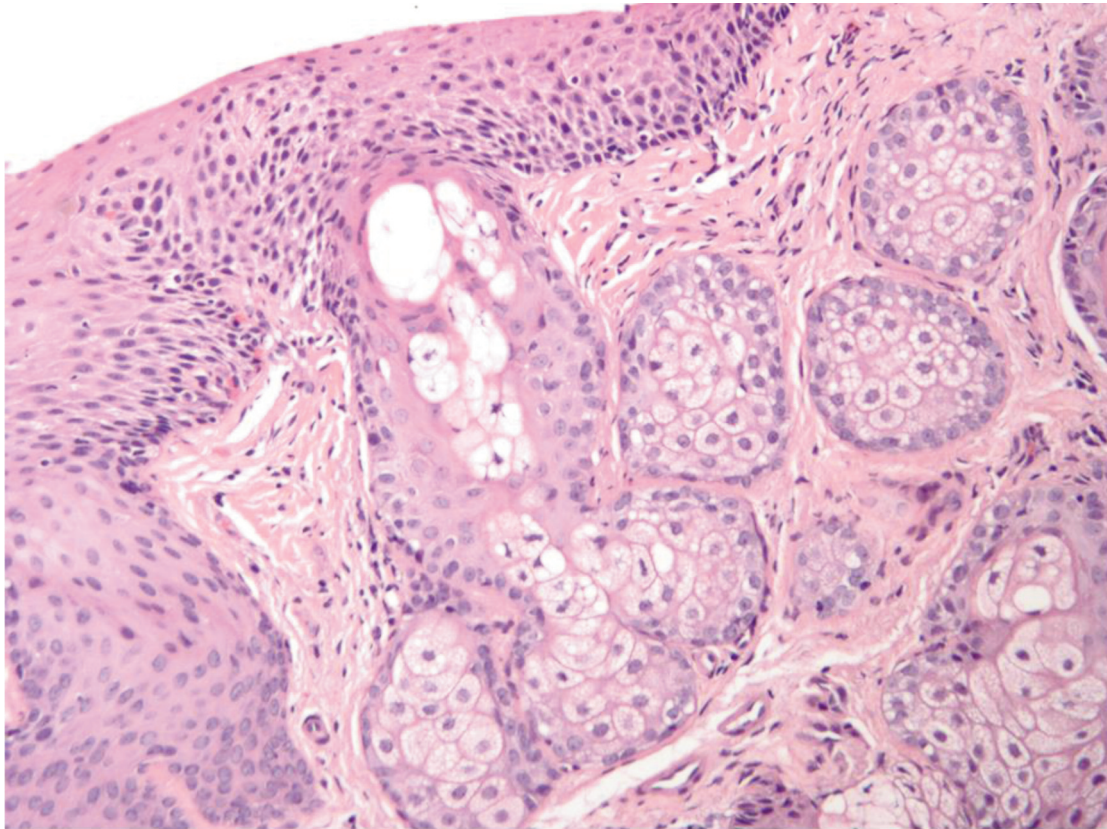


Figure 1. Esophageal squamous epithelium with underlying glands showing sebaceous differentiation. No hair follicles are identified (H&E, $\times 100$).

which label both heterotopic sebaceous glands and bulbous nests (5, 10). As in a normal sebaceous gland, SGE includes an excretory duct. However, hair follicles within these ectopic glands have not been described (2, 9, 11).

Here, we present two cases of esophageal SGE, which were found during endoscopic studies for other GI complaints and were endoscopically interpreted as possible fungal infection and glycogenic acanthosis.

Case Report

Case #1. A 63-year-old female patient underwent upper endoscopy for her gastro-esophageal reflux disease (GERD) symptoms and dysphagia. The endoscopic study revealed multiple small, pale, submucosal plaques in her esophagus. Multiple biopsies were taken with forceps and sent for further pathology examinations. Four fragments of tan tissue from the mid/distal esophagus measuring up to $8 \times 2 \times 1$ mm were received in formalin. The histopathologic examination result was consistent with squamous mucosa with atypical islands demonstrating apparent sebaceous differentiation (Figure 1) and reactive changes, negative for any dysplasia

or malignancy. An Alcian Blue Periodic acid Schiff (ABPAS) study was negative for fungi and intestinal metaplasia.

Case #2. A 61-year-old female underwent an endoscopy to follow up on her GERD, Barrett's esophagus, and gastroparesis symptoms. The endoscopic diagnosis was candidiasis, and the sample was sent to pathology for further assessment. One fragment of tan tissue measuring up to $1 \times 1 \times 1$ mm was received in formalin. Histopathology examination was consistent with reflux esophagitis. The squamous mucosa also revealed a focus of ectopic sebaceous glands (Figure 2). The ABPAS special stain was negative for fungi and intestinal metaplasia. There was no eosinophilic esophagitis, dysplasia, or malignancy.

Discussion

It is hypothesized that metaplasia of a pluripotent stem cell, rather than derivation from islands of misplaced epidermis, is responsible for the development of ectopic tissue in a purely endodermal tissue (12). Endoscopic and autopsy studies have not supported the embryological misplacement theory (2).

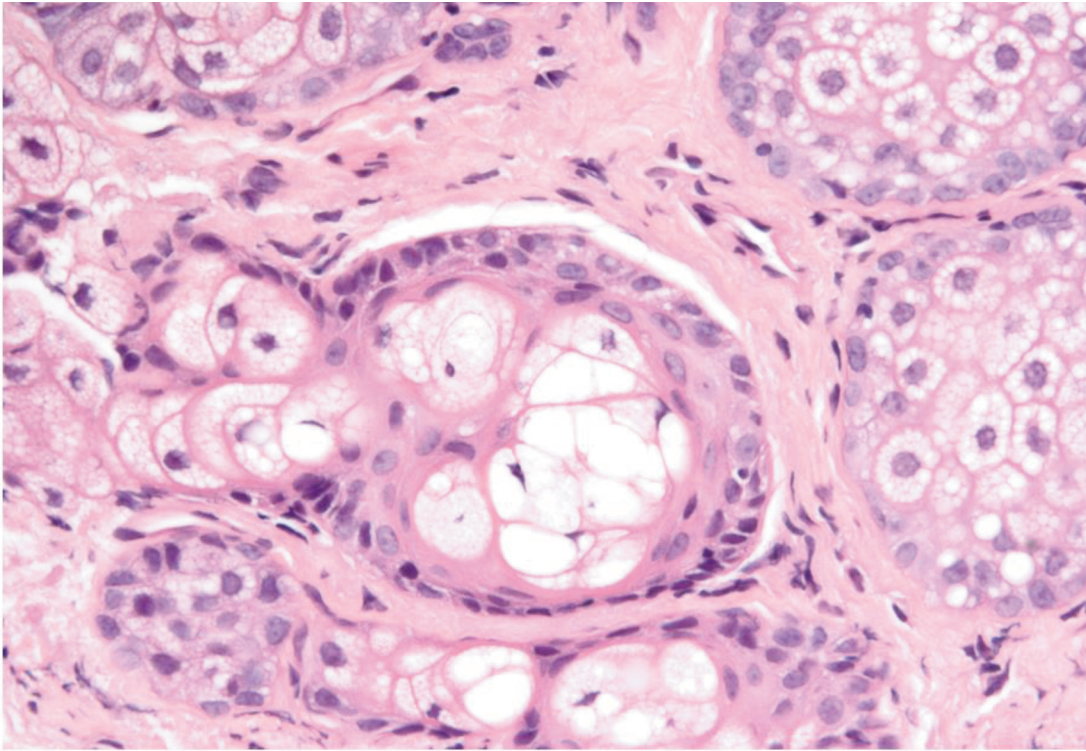


Figure 2. Sebaceous glands exhibiting the germinative cells at the periphery and multivacuolated sebaceous cells in the center (H&E, $\times 400$).

It has also been shown that ectopic Hedgehog signaling initiates the formation of sebaceous glands in the areas of footpads normally lacking any hair follicles or associated structures from the epidermis. The Hedgehog pathway thus plays a key role in sebocyte cell development and might be a potential target for studying other similar disorders related to abnormal sebaceous gland function (13).

SGE has been described in both male and female patients. SGE lesions are found mostly in the upper thoracic esophagus followed by the middle and lower thoracic esophagus (14). Histopathologically, SGE consists of lobules of polygonal cells with small nuclei and abundant clear cytoplasm showing typical sebaceous differentiation and covered by a 2-4 mm non-keratinized stratified squamous epithelium with no to minimal lymphocytic infiltration (2).

SGE should be differentiated from infectious conditions (*e.g.*, candidiasis) and other non-infectious conditions such as glycogen acanthosis (8), sub mucosal and mucosal lesions including granular cell tumor, leiomyoma, papilloma (2), carcinoid, and xanthoma (15).

The accumulation of foamy histiocytes results in xanthoma, or a rare non-neoplastic lesion (15). When differentiating xanthoma from SGE, it might help to know that in xanthoma, the patient will have cutaneous manifestations associated with

hyperlipidemia (15). The most common site of granular cell tumors (GCTs) is the esophagus where they are usually found as an incidental finding during endoscopy. In contrast to SGE, a GCT presents as a single small nodule or plaque but with the same grayish-yellow appearance as seen in SGE (16). Glycogenic acanthosis of the esophagus is a common benign entity, consisting of multifocal plaques of hyperplastic squamous epithelium and abundant intracellular glycogen deposits (17). The cells containing intracytoplasmic glycogen are histologically empty and do not show the granularity seen in the sebaceous cells. Also, a periodic acid-Schiff stain used in combination with diastase will confirm the presence of glycogen in glycogenic acanthosis. Drinking, smoking or hyperlipidemia have not been implicated in the pathogenesis of SGE (14). There was no evidence of dysplasia or malignancy detected in our cases. Surveillance follow up endoscopic studies at 8 months, 2 years, and 5 years have shown no changes in the number, size or behavior of the sebaceous glands of SGE and there has been no malignant transformation reported within these lesions (2, 11). Due to the benign nature of this lesion, follow up endoscopic studies or resection is not recommended (18).

If concomitant gastroesophageal reflux disease is present, it will be treated with anti-reflux regimens (2, 8).

Conclusion

Considering the wide differential diagnosis that comes with this condition during endoscopic macroscopic studies, it is important to conduct careful histopathology examinations and to properly differentiate this rare and benign condition from other commonly seen diagnoses. Exclusion of infections and malignant conditions will prevent further unnecessary work ups and treatments and will reassure patients.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Caterina Baffa collected clinical data and helped drafting the manuscript; Amanda Naaman reviewed the drafted manuscript, Domenico Coppola identified the cases, provided the figures, initiated, and finalized the manuscript.

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References

- 1 Marcial MA and Villafaña M: Esophageal ectopic sebaceous glands: endoscopic and histologic findings. *Gastrointest Endosc* 40(5): 630-632, 1994. PMID: 7988832. DOI: 10.1016/s0016-5107(94)70268-3
- 2 Bhat RV, Ramaswamy RR and Yelagondahally LK: Ectopic sebaceous glands in the esophagus: a case report and review of literature. *Saudi J Gastroenterol* 14(2): 83-84, 2008. PMID: 19568506. DOI: 10.4103/1319-3767.39624
- 3 De Felice C, Parrini S, Chitano G, Gentile M, Dipaola L and Latini G: Fordyce granules and hereditary non-polyposis colorectal cancer syndrome. *Gut* 54(9): 1279-1282, 2005. PMID: 15879014. DOI: 10.1136/gut.2005.064881
- 4 De la Pava S and Pickren JW: Ectopic sebaceous glands in the esophagus. *Arch Pathol* 73: 397-399, 1962. PMID: 13884272.
- 5 Grube-Pagola P, Vicuña-González RM, Rivera-Salgado I, Alderete-Vázquez G, Remes-Troche JM and Valencia-Romero AM: Ectopic sebaceous glands in the esophagus. Report of three cases. *Gastroenterol Hepatol* 34(2): 75-78, 2011. PMID: 21339017. DOI: 10.1016/j.gastrohep.2010.10.016
- 6 Bae JY, Chon CY and Kim H: Sebaceous glands in the esophagus. *J Korean Med Sci* 11(3): 271-274, 1996. PMID: 8843011. DOI: 10.3346/jkms.1996.11.3.271
- 7 Bertoni G, Sassatelli R, Nigrisoli E, Conigliaro R and Bedogni G: Ectopic sebaceous glands in the esophagus: report of three new cases and review of the literature. *Am J Gastroenterol* 89(10): 1884-1887, 1994. PMID: 7942688.
- 8 Marín-Serrano E, Jaquotot-Herranz M, Casanova-Martínez L, Tur-González R and Segura-Cabral JM: Ectopic sebaceous glands in the esophagus. *Rev Esp Enferm Dig* 102(2): 141-142, 2010. PMID: 20361850. DOI: 10.4321/s1130-01082010000200009
- 9 Hoshika K, Inoue S, Mizuno M, Iida M and Shimizu M: Endoscopic detection of ectopic multiple minute sebaceous glands in the esophagus. Report of a case and review of the literature. *Dig Dis Sci* 40(2): 287-290, 1995. PMID: 7851191. DOI: 10.1007/BF02065411
- 10 Nakanishi Y, Ochiai A, Shimoda T, Yamaguchi H, Tachimori Y, Kato H, Watanabe H and Hirohashi S: Heterotopic sebaceous glands in the esophagus: histopathological and immunohistochemical study of a resected esophagus. *Pathol Int* 49(4): 364-368, 1999. PMID: 10365859. DOI: 10.1046/j.1440-1827.1999.00874.x
- 11 Wang WP, Wang WS and Tsai YC: Multiple tiny ectopic sebaceous glands discovered throughout entire esophageal tract. *Dig Dis Sci* 54(12): 2754-2757, 2009. PMID: 19117122. DOI: 10.1007/s10620-008-0676-1
- 12 Zak FG and Lawson W: Sebaceous glands in the esophagus. First case observed grossly. *Arch Dermatol* 112(8): 1153-1154, 1976. PMID: 952538.
- 13 Allen M, Grachtchouk M, Sheng H, Grachtchouk V, Wang A, Wei L, Liu J, Ramirez A, Metzger D, Chambon P, Jorcano J and Dlugosz AA: Hedgehog signaling regulates sebaceous gland development. *Am J Pathol* 163(6): 2173-2178, 2003. PMID: 14633591. DOI: 10.1016/S0002-9440(10)63574-2
- 14 Fukuchi M, Tsukagoshi R, Sakurai S, Kiriya S, Horiuchi K, Yuasa K, Suzuki M, Yamauchi H, Tabe Y, Fukasawa T, Naitoh H and Kuwano H: Ectopic sebaceous glands in the esophagus: endoscopic findings over three years. *Case Rep Gastroenterol* 6(1): 217-222, 2012. PMID: 22701398. DOI: 10.1159/000338651
- 15 Bang CS, Kim YS, Baik GH and Han SH: Xanthoma of the esophagus. *Clin Endosc* 47(4): 358-361, 2014. PMID: 25133126. DOI: 10.5946/ce.2014.47.4.358
- 16 Nie L, Xu G, Wu H, Huang Q, Sun Q and Fan X: Granular cell tumor of the esophagus: a clinicopathological study of 31 cases. *Int J Clin Exp Pathol* 7(7): 4000-4007, 2014. PMID: 25120777
- 17 Ghahremani GG and Rushovich AM: Glycogenic acanthosis of the esophagus: radiographic and pathologic features. *Gastrointest Radiol* 9(2): 93-98, 1984. PMID: 6745598. DOI: 10.1007/BF01887812
- 18 Thalheimer U, Wright JL, Maxwell P, Firth J and Millar A: Sebaceous glands in the esophagus. *Endoscopy* 40(Suppl 2): E57, 2008. PMID: 18633905. DOI: 10.1055/s-2007-967059

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