Pitfall of heterotopic sebaceous gland metaplasia of the esophagus 
without pathological review

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Abstract

**Background:** Heterotopic sebaceous gland metaplasia (HSGM) of the esophagus may not have significant clinical symptoms but is a valuable differential diagnosis of other esophageal lesions.

**Aim:** The purpose of this study is to clarify the incidence of this disease and the endoscopic looking for the clinical make sense.

**Method:** From January 1, 1998 to May 31, 2012, 33 endoscopists conducted 215,046 endoscopic studies comprising 35,302 tissue biopsies that included 864 esophagoscopies, 650 nasoendoscopies, and 213,532 gastroscopies in our endoscopic unit. Cases of pathologically proven HSGM were enrolled in the clinical analysis and endoscopic description.

**Result:** Six cases of pathologically documented HSGM from 10 endoscopic studies were identified over these 14.5 years. The incidence was 0.00465%, and the occurrence rate was 0.41 per year in this study. A total of 66.7% (4/6) patients with HSGM came from health screening center, while 33.3% (2/6) came from outpatient clinics. Of 110,022 (51.2%) total endoscopies performed, the 16,012 (14.5%) endoscopic biopsies were performed by 7 senior endoscopists, an average of 2,287 biopsies each. Four biopsies per senior endoscopist and 4 (57.1%) endoscopists diagnosed HSGM in 8 studies.
(including a senior 1 of 3 times, senior 2 of 2 times, senior 3 of 3 times, and senior 4 in 1 time). In contrast, of the 105,024 (48.8%) endoscopies performed by 26 junior endoscopists, 19,290 (18.4%) endoscopic biopsies were performed; an average of 741.9 biopsies per junior endoscopists, and 2 (7.7%) endoscopists identified HSGM in only 2 episodes (2 different junior endoscopists had the same finding 1 time each). Significantly fewer endoscopic biopsies were performed by the senior endoscopists than by the junior endoscopists (P = 0.0001), and more cases of HSGM were identified by senior endoscopists than by junior endoscopists (P = 0.01). The misdiagnosis rate by diagnosis was 30% (3/10) in xanthoma, 20% (2/10) in candidiasis, 20% (2/10) in papilloma, and 10% (1/10) with a negative description. There was a rate of 0% recognized in the first look endoscopic study and 0% recognized in the second study without reviewed tissue pathology. After pathological review, a 100% (2/2) positive diagnosis existed in the second and third studies in 3.03% (1/33) of our endoscopies.

**Conclusion:** HSGM of the esophagus is a rare condition that is easily missed and not recognized in endoscopy studies omitting pathological review. Differential diagnosis of a benign nature should be kept in mind in daily practice but may be never seen clinically.
Key words: Esophagus, sebaceous gland, metaplasia, heterotopic, endoscope, endoscopist
**Introduction**

Heterotopic sebaceous gland metaplasia (HSGM), with light yellow tiny macules of the esophageal mucosa, tends to be incidentally observed during autopsy or esophageal resection (1-2). From the point of differential diagnosis of esophageal lesions, HSGM becomes of scientific interest during endoscopic studies. Unusual lesions of the esophagus that endoscopists should take the first look at unusual lesions (3).

Although reports have attempted to determine whether HSGM was the result of a metaplastic process or a congenital anomaly, histological examination of endoscopic biopsies is the traditional procedure for the pathological diagnosis in daily practice (2). Biopsied tissue can be taken for histological and marker studies of human and non-human primates with HSGM (4-5). Due to the benign nature of HSGM-containing endoscopic readings (6), the diagnosis is commonly missed when tissue biopsies are not reviewed. Therefore, we proposed this study to clarify the incidence of HSGM and identify the reasons for the endoscopic looking with clinical makes sense.
Method: According to our data bank from January 1, 1998 to May 31, 2012, 33 endoscopists performed 215,046 gastroscopic studies with 35,302 tissue biopsies in the endoscopic unit of Kaohsiung Chang Memorial Hospital. The endoscopic studies comprised 864 esophagoscopies, 650 nasoendoscopies, and 213,532 gastroscopies. Cases of pathologically proven HSGM were enrolled in the clinical analysis and endoscopic description. Cases of endoscopic ultrasound of the upper gastrointestinal tract, endoscopic retrograde cholangiopancreatography, and double-balloon enteroscopy from the oral route were excluded from this study.

By definition, an endoscopist with >20 years’ experience was defined as a senior endoscopist, while an endoscopist with <20 years’ experience was defined as a junior endoscopist. Accordingly, there were 7 senior and 26 junior endoscopists in our department. The total number of the endoscopic studies and endoscopic biopsies comprised 110,022 (51.2%) and 16,012 (14.5%) by senior endoscopists and 105,046 (48.8%) and 19,290 (18.4%) by junior endoscopists, respectively. Histological examination of the endoscopic biopsies was put a favorable interpretation by an expert pathologist. The present study has written informed consent from the patients for publication all
of the medical records and information. The work was approved by the Ethics Committee of Chang Gung Memorial Hospital with a reference number 101-2819B.

Statistical analyses were performed using SPSS software (version 12.0; SPSS, Chicago, IL, USA). Comparison of the endoscopic biopsy parameters and HSGM frequency between the senior and junior endoscopists was performed using Chi-square test and Fisher’s exact test. \( P \) values <0.05 were considered statistically significant.

**Results**

Among 215,046 endoscopic studies in the 14.5-year time span of Jan 1, 1998 to May 31, 2012, there were 6 cases of pathologically documented HSGM in 10 endoscopic studies. The incidence was 0.00465\% and the occurrence rate was 0.41 per year in this study. The male:female ratio was 3:1. The mean age was 57.6 years with a range of 46–71 years. A total of 66.7\% (4/6) of the cases with HSGM came from a health screening center, while the other 33.3\% (2/6) came from outpatient clinics. All of the cases (100\%; 6/6) had a heterotopic sebaceous gland located at the middle-lower esophagus (Figure 1).
The missed diagnosis rate classified by diagnosis was 30% (3/10) in xanthoma, 20% (2/10) in candidiasis, 20% (2/10) in papilloma, and 10% (1/10) with a negative description (Table 1). No cases (0/6) of HSGM were recognized by senior endoscopists 1, 2, 3, and 4 or junior endoscopists 1 and 2 in the first endoscopic study, and no cases (0/3) of HSGM were recognized by senior endoscopists 2 or 4 or junior endoscopist 1 in the second study without tissue pathology review (Table 1). After pathological review, there was a 100% (2/2) positive diagnosis experienced in the case 2 with second and third looking in 3.03% (1/33) of our endoscopists.

Among 6 pathologically confirmed cases of HSGM, 5 were diagnosed in the first endoscopic study with tissue biopsy, while the other case was diagnosed in the second endoscopic study with tissue biopsy (Table 1). Among the 7 senior endoscopists who performed 110,022 (51.2%) endoscopies, 16,012 (14.5%) endoscopic biopsies were performed, an average of 2,287 biopsies each. Four biopsies per senior endoscopist and 4 (57.1%) endoscopists diagnosed HSGM in 8 episodes (included a senior 1 of 3 times, senior 2 of 2 times, senior 3 of 3 times, and senior 4 in 1 time). In contrast, of the 105,024
(48.8%) endoscopies performed by 26 junior endoscopists, 19,290 (18.4%) endoscopic biopsies were performed, an average of 741.9 biopsies per junior endoscopists, and 2 (7.7%) endoscopists identified HSGM in only 2 episodes (included junior 1 once and junior 2 once). Significantly fewer endoscopic biopsies were performed by the senior endoscopists than by the junior endoscopists ($P = 0.0001$), and significantly more cases of HSGM were identified by senior endoscopists than by junior endoscopists ($P = 0.01$) (Table 2).

Endoscopic biopsy showed multiple light yellow plaques 2–5 mm in diameter with clustering distribution that embedded the surface of the esophagus (Figure 1). In 100% (6/6) of cases, sebaceous glands were located at the lower to middle esophagus. Pathological analysis revealed stratified squamous epithelium with lobules of sebaceous glands abutting the lower epithelium. No associated polymorphic nuclear or cellular infiltration was noted.

**Discussion**

The present study demonstrated that HSGM is a very rare esophageal condition with an incidence around 0.00465% and an occurrence rate of 0.41
per year. There was no doubt of the pathological diagnosis of HSGM (7-8), but endoscopic biopsy should make an important impact on the incidence of HSGM. In the real world, endoscopic biopsy is performed by endoscopists for 2 possible reasons: a suspected malignant lesion, or a lesion that is difficult to identify under endoscopic study. Such lesions look benign, especially in narrow band imaging (9-10), so a busy endoscopist might not take a biopsy. As such, the incidence of HSGM is likely underestimated.

In the present series, senior endoscopist 1 encountered HSGM 3 times (cases 1, 2, and 3) in 1998, 1999, and 2002. After the endoscopic biopsy and pathological review in the first case, a 100% (2/2) endoscopic diagnosis rate of senior endoscopist 1 was noted in cases 2 and 3. In contrast, senior endoscopist 2 missed an endoscopic diagnosis in a xanthoma due to a lack of pathological review despite the first case being proven. Senior endoscopist 2 also missed an endoscopic diagnosis in a papilloma that was biopsied but not pathologically reviewed.

In the meantime, senior endoscopist 4 also missed an endoscopic diagnosis in a papilloma in case 4 due to lack of pathological review. In HSGM cases 5 and
6, the endoscopic diagnosis of candida esophagitis was made by junior endoscopist 2 and senior endoscopist 3. Junior endoscopist 2 had performed an endoscopic biopsy in case 5, but senior endoscopist 3 did not in case 6.

Due to the lack of a pathological review, junior endoscopist 1 made a negative endoscopic diagnosis in case 5 during a scheduled health screen. In contrast, senior endoscopist 2 also missed the endoscopic diagnosis in HSGM case 6 due to the lack of a response to candida infection treatment in the follow-up clinic. Because endoscopic biopsy and pathological review were both performed, 6 cases of HSGM were documented in our series.

Our series showed that 66.7% of the cases of HSGM came from health screen centers, in which cases the pathology reports were not returned to the ordering endoscopist. In addition, the interpreting doctor at the health screen center was not the original endoscopist, and the patient did not return to the outpatient clinic due to there being no evidence of malignancy. To overcome the diagnostic underestimation demonstrated here, endoscopists need to actively follow up each pathological report after endoscopic biopsy, or the computer management system should send the final pathological report to the
original endoscopist on a weekly basis. Therefore, the accurate diagnosis of HSGM requires both endoscopic biopsy and pathological review (11).

Studies have reported that candida infection (Figure 2) was most common endoscopic diagnosis to appear like HSGM (7, 8). In the present study, the common endoscopic findings were 30% in xanthomas, 20% in candida infections, and 20% in papillomas (Figure 3). The same situation was the first impression as candida infection of the esophagus but no medication response to it in our case 6 (12). HSGM case 6 was documented by subsequent pathological review. For most endoscopists, the first thought would be glycogenic acanthosis (Figure 4), perhaps with minor atypical features. All of the above situations belong to the benign nature of the etiology of HSGM. It should not be getting alert to take endoscopic biopsy. Therefore, missing endoscopic diagnosis occurs easily in situations in which both endoscopic biopsy and pathological review are not both performed.

In our series, the interesting finding was the difference in endoscopic biopsy attempt rates between the senior and junior endoscopists. More cases were examined by the senior endoscopists than by the junior endoscopists (51.2%
vs. 48.8%), but the endoscopic biopsy rate was the opposite (14.5% vs. 18.4%). The large difference in the number of biopsies taken by senior (21.2%) vs. junior endoscopists (78.8%) might give a false impression in statistical analysis. Senior endoscopists had a 3× higher number of endoscopic biopsies compared to junior endoscopists (2287.4 vs. 741.9 endoscopic biopsies per endoscopist). Senior endoscopists had more change to look for HSGM than did junior endoscopists.

In conclusion, asymptomatic esophageal HSGM is a rare condition that occurs in old age (>50 years) and is male dominant. Differential diagnosis of a benign non-inflammatory nature should be kept in mind in daily practice with endoscopic biopsies and pathological review but may be never seen clinically.

Authors’ contributions

KW C and SS C co-wrote the manuscript. Both authors read and approved the final manuscript.

Competing interests

The authors have no competing interests to declare.
## References


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Table legends

Table 1. The clinical profile, pre-biopsy diagnosis, biopsy diagnosis, and pathological review of the 6 cases with heterotopic sebaceous gland metaplasia (HSGM)

Table 2. The difference in senior and junior endoscopist diagnosis rates of heterotopic sebaceous gland metaplasia (HSGM) from Jan 1, 1998 to May 31, 2012.
Figure 1. Sebaceous glands in the esophagus.
Figure 2. Candida infection of the esophagus.
Figure 3. Papilloma of the esophagus.
Figure 4. Glycogenic acanthosis of esophagus.
Additional files provided with this submission:

Additional file 1: Table 1.doc, 37K
http://www.biomedcentral.com/imedia/1981169781910893/supp1.doc
Additional file 2: Table 2.doc, 32K
http://www.biomedcentral.com/imedia/243380598567671/supp2.doc