Esophageal Granular Cell Tumor and Eosinophils: A Multicenter Experience

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Research

Keywords: granular cell tumor, eosinophilic esophagitis, goblet cell metaplasia

DOI: https://doi.org/10.21203/rs.3.rs-318646/v1

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Abstract

Background: Esophageal granular cell tumor (eGCT) is rare, and the recent literature suggests a link between eosinophilic esophagitis (EoE) and eGCT. The aim of our study was to determine if EoE or other disorders associated with eosinophilia are consistently associated with eGCT.

Methods: We retrospectively searched pathology databases of three academic institutions from 1999 to 2018 for eGCTs. The archived slides and medical records were reviewed.

Results: From 294,855 esophagogastroduodenoscopy procedures, 45 patients (17 males and 28 females) with eGCTs were identified. The patients were 30-73 years in age (median 50) had eGCT (0.2 – 2.0 cm, average 0.71). Thirteen had a history of gastroesophageal reflux disease, 5 had Barrett esophagus/goblet cell metaplasia and 1 had EoE. Thirty-four eGCTs had intralesional eosinophils (14 with peak >10 eosinophils/400x hpf); of these, 21 also had eosinophils in lamina propria (9 with peak >10 eosinophils/hpf). eGCT with atypical features (including nuclear enlargement and prominent nucleoli) were more likely to have increased eosinophils in non-epithelial compartments than those without atypia. Pleomorphism and spindled cells were seen in 3 eGCT cases (mean peak intralesional eosinophils: 43 per hpf); 2 of these had goblet cell metaplasia. We found no association between EoE and eGCT, p= 0.5966, (95% C.I. 0.0276, 6.5389, Fisher’s exact test). Instead, most patients had gastroesophageal reflux disease or Barrett esophagus.

Conclusion: Eosinophilia, common in eGCT and adjacent stroma, likely drives atypical/reactive histologic features, but a pathogenic relationship between eosinophil rich inflammatory conditions and eGCT has not yet been established.

1. Background

Granular cell tumor (GCT) was first described in the tongue by Abrikossoff in 1926, other names for this entity are granular cell myoblastoma and Abrikossoff’s tumor [1–2]. Although the lesion is most commonly seen in the skin, soft tissue and tongue, 8–11% of cases occur in the gastrointestinal tract [1–5]. In 1931, Abrikossoff first described GCT in the esophagus, which we now know is the most common site of involvement within the gastrointestinal tract, primarily the distal segment of the esophagus [3–4].

In the esophagus, eosinophilic esophagitis (EoE) is a clinicopathologic disease that has been more consistently recognized with increasing apparent prevalence since the initial publication of consensus recommendations in 2007 [6]. It is a chronic, immune/antigen-mediated disease with eosinophil-predominant inflammation that leads to esophageal dysfunction [7]. Given that GCTs have been previously linked to sites of injury and inflammation, some have postulated that these lesions might be reactive in nature [8]. There have been a few reported cases of concomitant esophageal granular cell tumor (eGCT) and EoE cases in both adults and pediatric patients [9–11]. More recently, two separate single center case series proposed an association between the two entities [12–13]. In order to further
study this possible link, we conducted a multi-center study constituting three separate academic center institutions from different regions of the country.

2. Methods

Pathology databases from University of Washington Medical Center (UWMC), Duke University Medical Center (DUMC) and University of Michigan Medical Center (UMMC) were retrospectively searched for cases of eGCT, from January 1999 to January 2018. The patient medical records were reviewed for demographic information, presenting clinical symptoms, endoscopic findings and follow-up. There were a total of 108,244 EGD procedures performed at UWMC from January 1999 to January 2018, and 1,704 patients had diagnosis of EoE by ICD9 and ICD10 codes since 2008 to 2018. The endoscopy procedure data was available from DUMC, from January 2006 to January 2018, where a total of 77,295 esophagogastroduodenoscopy (EGD) procedures were performed, and 1,481 patients had diagnosis of EoE by ICD9 and ICD10 codes. From UMMC, there were a total of 64,316 EGD procedures and 2692 cases of EoE by ICD9 and ICD10 codes from June 2012 to May 2020.

Cases of eGCT were retrieved from the archives and blindly reviewed to confirm pathologic diagnosis and to assess atypical histologic features such as necrosis, spindling, nuclear pleomorphism, increased mitotic activity \( \geq 2 \text{ mitosis/ 400x} \), increased nuclear size (at 100x), and large nucleoli (at 100x) [12,14]. The lesions, the stroma surrounding and supporting them and the esophageal epithelium overlying them were evaluated for eosinophilia and the peak eosinophil count in each compartment was documented at 400x magnification (hpf). The statistical significance of observed versus expected (assuming no association) rates of simultaneous eGCT and EoE was analyzed using Fischer's exact test, calculated using STATA version 14 (STATA Corp LP, TX). Based on the hypothesis test with a two-side p-value, \( p < 0.05 \) was considered statistically significant.

3. Results

We pooled data from 294,855 EGD procedures at three academic medical centers and identified 45 patients with eGCT (Table).

3.1 Clinical Findings

All 45 patients were adults; 17 were males and 28 were females, with a male to female ratio of 1:1.65. The age ranged from 30–73 years, with a median of 50. The most common presenting symptoms were dysphagia, gastroesophageal reflux disease and abdominal pain. Other diseases that were reported clinically or by histology were gastroesophageal reflux disease (13 patients), Barrett esophagus/goblet cell metaplasia (5 patients) and EoE (1 patient). There were three patients with prior history of eGCT by biopsy or fine needle aspirate diagnosis who later underwent endoscopic resection. The majority of patients had their lesion removed by endoscopic mucosal resection. The patients had follow-up ranging from 0 to 216 months, with an average of 45, and no evidence of metastatic eGCT.
3.2 Endoscopic Findings

The size of the eGCTs ranged from 0.2–2.0 cm, with an average of 0.71. The most common site was the distal segment of the esophagus and most patients presented with a single nodule. There were two patients with multiple nodules, one of which had multifocal disease involving all the segments of the esophagus.

3.3 Histologic Findings

Histologic specimens for evaluation were derived from either endoscopic biopsies (42%) or endoscopic mucosal resections with/without additional sampling of the esophagus (58%). Two patients had eGCT as an incidental finding during microscopic evaluation. One of them had eGCT in the proximal segment with a history of EoE with rings; the other underwent esophagogastrectomy for squamous cell carcinoma status post neoadjuvant therapy, and was found to have eGCT in the distal segment.

In the single case of EoE, the accompanying eGCT had minimal cytologic atypia and intralesional eosinophils (Fig. A). Thirty-four eGCTs had intralesional eosinophils (14 cases with peak > 10 eosinophils/400x hpf); of these, 21 also had eosinophils in lamina propria (9 cases with peak > 10 eosinophils/hpf).

Among 21 cases of eGCT with atypical features, fourteen had ≤ 2 atypical features (increased nuclear size and presence of prominent nucleoli). In these cases, the mean peak intralesional eosinophil count was up to 10 eosinophils per hpf. The remaining seven cases with atypia had additional atypical features (spindling and nuclear pleomorphism), and the peak intralesional eosinophils for these cases was up to 112 eosinophils per hpf (Fig. B).

Of the 5 cases with Barrett esophagus/goblet cell metaplasia (Fig. C), two had four atypical features in the accompanying eGCT with areas of spindling, pleomorphism, increased nuclear size and prominent nucleoli (Fig. D). There were no cases of eGCT with necrosis or increased mitosis. In addition there was no association between patient’s age and eGCT with atypical features.

When the EGD procedures performed at three institutions with diagnosis of EoE and eGCT were considered collectively, we found no association between EoE and eGCT, \([p = 0.5966, (95\% \text{ C.I. } 0.0276, 6.5389, \text{ Fisher's exact test})]\). Even though the single case of eGCT in our study that was associated with EoE came from the UWMC cohort, the latter when considered alone also failed to show an association between EoE and eGCT \([p = 0.3058, (95\% \text{ C.I. } 0.0688, 17.6042, \text{ Fisher's exact test})]\).

4. Discussion

EoE is an antigen-driven allergic condition with both genetic and environmental contributions [15–16]. Although EoE occurs in most racial and ethnic groups, there is a predominance in non-Hispanic whites [7]. EoE is more common in patients from rural regions and cold climate zones; it is inversely associated with Helicobacter pylori infection both in adult and pediatric studies [16]. In our study we attempted to control...
for inherent differences in patient population and geographical region by collating data from multiple tertiary care centers located in different regions of the country.

Recent studies have reported the concurrence of eGCT and significant esophageal intraepithelial eosinophilia, most frequently in the pediatric population [9, 11–12]. In our multicenter retrospective study of eGCT from 294,855 EGD procedures, 40% of cases had gastroesophageal reflux disease or Barrett esophagus, but only one case in our series of 45 adults had concomitant EoE and eGCT (2%). The apparent rate of concomitant EoE and eGCT in our adult cohort is considerably less than that observed in prior studies, both of which included pediatric patients. Riffle et al. reported an overall rate of 33% from >30,000 esophageal cases. They identified 18 patients with eGCT, 6 of whom had both EoE and eGCT. Four of these patients were adults and two were adolescents [12]. Nojkov et al. reported an overall rate of 31% from 167,434 EGD procedures, including 5 of 16 cases of eGCT that were associated with EoE. Four of these were identified in adults, while 1 was diagnosed in an adolescent [13].

Interesting, although the absence of pediatric patients in our multi-institutional cohort likely affected our observed rate of concomitant EoE and eGCT, this does not completely account for the differences between our study and those of prior retrospective studies. A larger multicenter prospective study may be warranted to further investigate the reported association and to determine the underlying pathophysiology of EoE and eGCT.

In addition to the single case of EoE in our eGCT group, there were two other cases with significant intraepithelial eosinophilic infiltrates. One was a resection specimen from squamous cell carcinoma status post neoadjuvant therapy with complete response. The other was in biopsies from the distal esophagus, suggesting a closer relationship to severe reflux esophagitis. Reflux disease or heart burn was the presenting symptom in 28% of our patients. The eGCTs found in these patients were in the distal segment of the esophagus (66%), ranging in size from 0.3 to 2.0 cm, in greatest dimension. These findings raise the possibility that the eGCT, by potentially impairing function of the gastroesophageal junction, may have contributed to the onset or severity of reflux esophagitis in these patients. In addition, a case report of an esophageal leiomyoma that apparently caused reflux esophagitis in a patient emphasizes this point [17]. It is tempting, with these observations in mind, to suggest the inclusion of mass lesions including eGCT in the different diagnosis of new onset reflux esophagitis.

There are reports of concomitant presentation of eGCT and other neoplasms, both benign and malignant, including leiomyoma, squamous cell carcinoma and intramucosal adenocarcinoma in the setting of Barrett esophagus [18–20]. The latter illuminates one of the more interesting and novel findings of our study: the presence of eGCT in patients with an established diagnosis of Barrett esophagus or histologic evidence of goblet cell metaplasia having eGCT. It is also of interest that these cases of eGCT with background goblet cell metaplasia showed more atypical features, along with significantly increased intratumoral eosinophils.

Neither Nojkov et al., nor Riffle et al. identified eGCT patients with Barrett esophagus/goblet cell metaplasia. Nonetheless, the latter report included observations similar to those in our study, including a high number of eGCTs (67%) with increased intratumoral eosinophilia and a disproportionately high
number of eosinophils in eGCT with atypical features [12]. In our study, 76% of eGCT cases had increased intralesional eosinophils and 47% of the cases had eosinophils in the lamina propria of the overlying esophageal mucosa. Given the reproducibility of these findings, we postulate that eosinophilia within the eGCT and adjacent stroma may be driving the observed atypical/reactive histologic features.

Although eGCT is commonly considered a benign entity; there are rare cases that presented with lung and liver metastases [21–23]. There is a single report of eGCT secreting a serum tumor marker (carbohydrate antigen 19 – 9) [24]. Notably, we had no cases of metastatic eGCT in our patient cohort.

Although our study of eGCT is the largest to date, drawing on patient populations from three tertiary care medical centers located in different geographic regions of the country, our retrospective study nonetheless has limitations. Most significantly, our patient cohort consists of only adults and no pediatric patients. We had two eGCT that were diagnosed incidentally by histology. The standard esophageal biopsies encountered in daily practice are limited, containing only the esophageal epithelium that is immediately superficial to the lesion. With the lack of submucosa in these biopsy specimens, our sample set likely underestimates the prevalence of eGCT in these populations. Also of note, 9 patients in our cohort were diagnosed within the 2001–2007 year period, before the consensus guidelines for EoE was established [6–7]. If EoE was widely recognized as a disease entity earlier, more diagnostic and follow up material would have been available for histologic evaluation and we may have diagnosed additional cases of eGCT.

5. Conclusion

To summarize, most patients with eGCT in our cohort had gastroesophageal reflux disease (29%) or an established diagnosis of Barrett esophagus (11%). These patients have frequent follow up with higher rate of endoscopy; hence, the finding of eGCT may be coincidental. Importantly, we found no association between EoE and eGCT. The eosinophilia within the lamina propria likely drives atypical/reactive histologic features within the eGCT, but a pathogenetic relationship between eosinophil mediated inflammatory conditions, such as EoE, and eGCT has not yet been established.

Abbreviations

- Granular cell tumor (GCTs)
- Eosinophilic esophagitis (EoE)
- Esophageal granular cell tumor (eGCT)
- University of Washington Medical Center (UWMC)
- Duke University Medical Center (DUMC)
- University of Michigan Medical Center (UMMC)
- Esophagagogastroduodenoscopy (EGD)
Declarations

- Ethics approval and consent to participate: Institutional IRB approved study
- Consent for publication: Not applicable
- Availability of data and materials: All data generated or analyzed during this study are included in this published article.
- Competing interests: The authors declare that they have no competing interests.
- Funding: Not applicable
- Contribution Statement: DR: Primary corresponding author drafted the manuscript; CC: Collated data from University of Washington Medical Center; DC: Principal investigator from Duke University Medical Center; MS: Collated pathology and patient data from Duke University Medical Center; MW Principal investigator from University of Michigan Medical Center; EM: Collated data from University of Michigan Medical Center; YT: Statistics; LC: Collated endoscopy procedure data from Duke University Medical Center; PES : Principal investigator from University of Washington Medical Center.
- Acknowledgement: Not applicable

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Tables

| TABLE | Clinical and histologic findings of 45 patients with esophageal granular cell tumor |
| Patient no. | Age (yr) | Sex | Clinical symptom(s) | eGCT atypical feature(s) | Peak Eos/HPF in GCT | Peak Eos/HPF in lamina propria | Peak Eos/HPF in overlying epithelium |
|------------|---------|-----|---------------------|--------------------------|----------------------|-------------------------------|---------------------------------|
| 1          | 50      | F   | GERD                | None                     | 2                    | 9                             | 2                               |
| 2          | 53      | F   | GERD                | Mild increased nuclear size | 4                    | 10                            | 5                               |
| 3          | 58      | F   | GERD                | None                     | 0                    | 0                             | 0                               |
| 4          | 53      | M   | GERD                | None                     | 49                   | 43                            | 2                               |
| 5          | 41      | F   | Reflux              | Increased nuclear size, nucleoli, pleomorphic | 20                   | 1                             | 1                               |
| 6          | 50      | M   | Reflux              | Increased nuclear size, nucleoli | 26                   | 15                            | 0                               |
| 7          | 40      | M   | Heartburn, anemia, vomiting | None                     | 0                    | 2                             | 0                               |
| 8          | 49      | F   | Heartburn, Dysphagia | Increased nuclear size, nucleoli | 0                    | NA                            | 0                               |
| 9          | 52      | M   | GERD                | Increased nuclear size, nucleoli | 33                   | 39                            | 0                               |
| 10         | 48      | F   | Reflux and dyspepsia | Increased nuclear size, nucleoli, pleomorphic | 0                    | 4                             | 0                               |
| 11         | 58      | F   | GERD and pain       | None                     | 0                    | 1                             | 1                               |
| 12         | 45      | M   | Heartburn and dysphagia | None                     | 0                    | NA                            | 0                               |
| 13         | 33      | M   | GERD, diarrhea, weight loss | Increased nuclear size | 1                    | NA                            | 0                               |
| 14         | 61      | M   | Barrett and duodenal adenoma | Increased nuclear size* | 0                    | 0                             | 0                               |
| 15         | 45      | M   | Barrett              | None                     | 2                    | 6                             | 1                               |
| 16         | 50      | M   | Barrett              | Increased nuclear size | 13                   | 8                             | 60                              |
| 17         | 66      | M   | Long segment        | Increased nuclear size, nucleoli, | 6                    | 5                             | NA                              |
| #  | Age | Sex | Symptoms                          | Findings                                      | Histology                      |
|----|-----|-----|-----------------------------------|----------------------------------------------|---------------------------------|
| 18 | 48  | F   | Atypical chest pain               | Increased nuclear size, nucleoli, pleomorphic, spindling* |
| 19 | 33  | F   | EoE and dysphagia                 | Increased nuclear size                        | 2                               |
| 20 | 52  | M   | Varices                          | Mild spindling                                | 8                               |
| 21 | 68  | F   | Nausea                           | None                                          | 8                               |
| 22 | 53  | F   | Gastric bypass                   | Increased nuclear size, spindling             | 24                              |
| 23 | 50  | F   | Dysphagia                        | None                                          | 7                               |
| 24 | 56  | M   | Dysphagia and weight loss        | None                                          | 1                               |
| 25 | 57  | F   | Hematemesis                      | Increased nuclear size, spindling             | 14                              |
| 26 | 39  | F   | Odynophagia                      | None                                          | 1                               |
| 27 | 73  | F   | Anemia                           | None                                          | 0                               |
| 28 | 42  | F   | Gastric bypass                   | None                                          | 4                               |
| 29 | 52  | M   | Esophageal SCC                   | None                                          | 5                               |
| 30 | 57  | F   | Pain and anemia                  | Increased nuclear size, nucleoli, pleomorphic | 37                              |
| 31 | 44  | F   | chronic pancreatitis             | None                                          | 11                              |
| 32 | 48  | F   | Dysphagia                        | None                                          | 35                              |
| 33 | 30  | M   | Melena                           | None                                          | 0                               |
| 34 | 55  | F   | NA                               | None                                          | 4                               |
| 35 | 54  | F   | Esophageal stricture             | None                                          | 29                              |
| 36 | 55  | F   | Dysphagia and lichen planus      | None                                          | 1                               |
| 37 | 49  | F   | Anemia                           | None                                          | 0                               |
|   |   |   | Anemia | Increased nuclear size, nucleoli |   |   |   |
|---|---|---|---|---|---|---|---|
| 38 | 54 | M | Anemia | Increased nuclear size, nucleoli | 11 | 29 | NA |
| 39 | 48 | M | Dysphagia, prior GCT history | Increased nuclear size, nucleoli, pleomorphic, spindling | 12 | 51 | 0 |
| 40 | 47 | F | Dyspepsia and anemia | None | 0 | 0 | 0 |
| 41 | 51 | F | Dysphagia | Increased nuclear size | 3 | NA | 0 |
| 42 | 47 | F | Diarrhea, n/v, pain | Increased nuclear size, nucleoli, pleomorphic | 6 | 3 | 0 |
| 43 | 42 | F | Prior GCT history | None | 3 | 8 | 1 |
| 44 | 41 | F | Prior GCT history | Increased nuclear size, nucleoli | 2 | 1 | 0 |
| 45 | 55 | M | Dysphagia, dyspepsia and vomiting | None | 7 | 0 | 7 |

Abbreviations: F, female; M, male; NA, not available; n/v, nausea and vomiting; Eos, eosinophils.

*Goblet cell metaplasia*