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Association of mast cells with clinical, endoscopic, and histologic findings in adults with eosinophilic esophagitis

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To the editor

Eosinophilic esophagitis (EoE) presents with diverse features which can differ between children and adults, as well as among adults, but eosinophils alone do not account for this heterogeneity.(1, 2) Mast cells are involved in EoE pathogenesis, are highly increased in EoE compared to non-EoE controls, and mast cell-associated genes are upregulated in EoE.(2–5) Mast cells also produce the profibrotic factor TGF-β1 and promote smooth muscle contraction.(6) However, the extent to which mast cell presence correlates with clinical features of EoE is unknown. We aimed to determine if esophageal mast cell levels correlated with clinical symptoms, endoscopic findings, and histologic features in newly diagnosed adults with EoE.

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Dellon: project conception/design; data acquisition/analysis/interpretation; drafting of the article; critical revision

We performed a secondary analysis of data and biospecimens collected during a prospective cohort study of EoE cases, details of which have been previously described.(7) The parent study included adults (>18) undergoing outpatient endoscopy for symptoms of esophageal dysfunction. EoE was diagnosed by consensus guidelines.(8) This study was approved by the UNC Institutional Review Board. No authors have conflicts related to this study.

Data collection, biopsy procurement, symptom measures, full immunohistochemistry details, and statistical analyses are outlined in the Supplemental Materials. In brief, we used a mast cell tryptase antibody (#M7052, DAKO/Agilent, Santa Clara, CA) at 1:3000 dilution as previously described.(4, 5) Glass slides were digitized and the maximum density of tryptase-positive cells were quantified (cells/mm^2) in five non-overlapping high power fields of esophageal epithelium using the Aperio Positive Pixel Count Algorithm, version 9.1 (Aperio Technologies). For analysis, levels of mast cells were compared for EoE patients across demographic, endoscopic, and histologic characteristics, as well as for fibrostenotic vs inflammatory phenotypes. We also analyzed the mast cell to eosinophil ratio (a ratio >1 indicates more mast cells than eosinophils). For positive associations, we used linear regression to assess whether associations persisted after controlling for the eosinophil count.

We analyzed 96 EoE cases. Compared to patients with the lowest quartile of mast cells, patients with the highest quartile had significantly more furrows, higher eosinophil counts, and more eosinophil degranulation (Table 1). Notably, these findings persisted after regression analysis controlling for eosinophil counts. However, most of the clinical, endoscopic, and histologic features were similar regardless of mast cell quartile.

There was not a significant association between mast cells and clinical symptoms or atopic conditions (Figure 1A). Endoscopically, the mean level of mast cells was significantly increased in patients with the finding of furrows (279.9 ± 182.9 vs 139.6 ± 69.7; p=0.03), and there were weak trends towards an increase in patients with rings and exudates (Figure 1B). There was not as assocation between mast cell levels and the fibrostenotic or inflammatory phenotype. Histologically, eosinophil degranulation and spongiosis were weakly associated with mast cell density (Figure 1C). Eosinophil density was weakly correlated with mast cell infiltration (R=0.21, p=0.04) (Supplemental Figure 1). There was poor correlation between symptom severity and mast cells (Supplemental Figures 2A-C).

Twenty-four subjects (25%) had a mast cell to eosinophil ratio >1 (Table 1). These cases had significantly fewer exudates, eosinophil degranulation, microabscesses, and basal layer hyperplasia compared to those with ratio of ≤1. Mast cell to eosinophil ratio weakly correlated with reflux (R=0.23, p=0.03) but not with dysphagia or abdominal pain (Supplemental Figures 2D-F). There were no associations between mast cell to eosinophil ratio and clinical features (Figure 1D). On endoscopy, EoE cases with exudates had a significantly lower ratio than cases without exudates (Figure 1E). Mast cell to eosinophil ratios were significantly lower in patients with microabscesses (Figure 1F).

Several findings from our study were notable. First, we found that elevated levels of mast cells were associated with esophageal furrows and eosinophil degranulation independent of eosinophil counts. While little is known about the development of furrows in EoE, the same

association between mast cells and furrows has been preliminarily reported in a pediatric EoE cohort.(9) Furrows may represent areas of increased mucosal swelling, and mast cells could contribute by enhancing tissue contraction or edema.

Second, there was poor correlation between the degree of esophageal epithelial mast cell infiltration and dysphagia, heartburn, or abdominal pain symptom severity. One possible explanation could be that mast cell infiltration of deeper layers of the esophageal wall is more important to pathogenesis, and therefore would not been seen on our epithelial analysis.

Third, approximately a quarter of EoE cases who had higher levels of mast cells than eosinophils (mast cell to eosinophil ratio >1). Interestingly, this group did not have more allergic disease, but had fewer exudates endoscopically and microabscesses histologically. This novel metric may suggest a subset of EoE patients with a less severe phenotype in which mast cell directed therapies may be useful, but this is speculative and the hypothesis must be tested.

There are several limitations to note. We performed a secondary analysis of baseline samples from adult EoE patients, so further investigation in a primary study with correction for multiple testing is needed to confirm findings, evaluate children or post-treatment changes, though prior work shows mast cells decrease in EoE after successful treatment.(5) Differences in mast cell subtypes could not be distinguished with tryptase staining alone. We did not analyze extracellular tryptase or histamine deposition, were not able to assess cell-surface markers (KIT or IgE receptor) for information on mast cell activation, and our analysis was limited to the esophageal epithelium. However, the strengths of this study include: utilization of prospectively collected data and biospecimens linked to well characterized clinical, endoscopic, and histologic data; use of an autostainer and image analysis software to provide consistence in samples; and use of quantitative symptom scores.

In conclusion, the presence of furrows was significantly correlated with higher mast cell levels in patients with EoE. Despite this interesting finding, mast cell density did not seem to directly correlate with clinical symptoms or most endoscopic or histologic findings in patients with EoE. However, our study clearly identifies a subset of EoE cases with more mast cells than eosinophils, with differences in endoscopic and histologic features, potentially suggesting a role for mast cell directed therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Adare, Alivio, Allakos, AstraZeneca, Banner, Enumeral, Celgene/Receptos, GSK, Regeneron, Robarts, and Shire; and has received an educational grant from Banner and Holoclara. The other authors have no pertinent disclosures to report.

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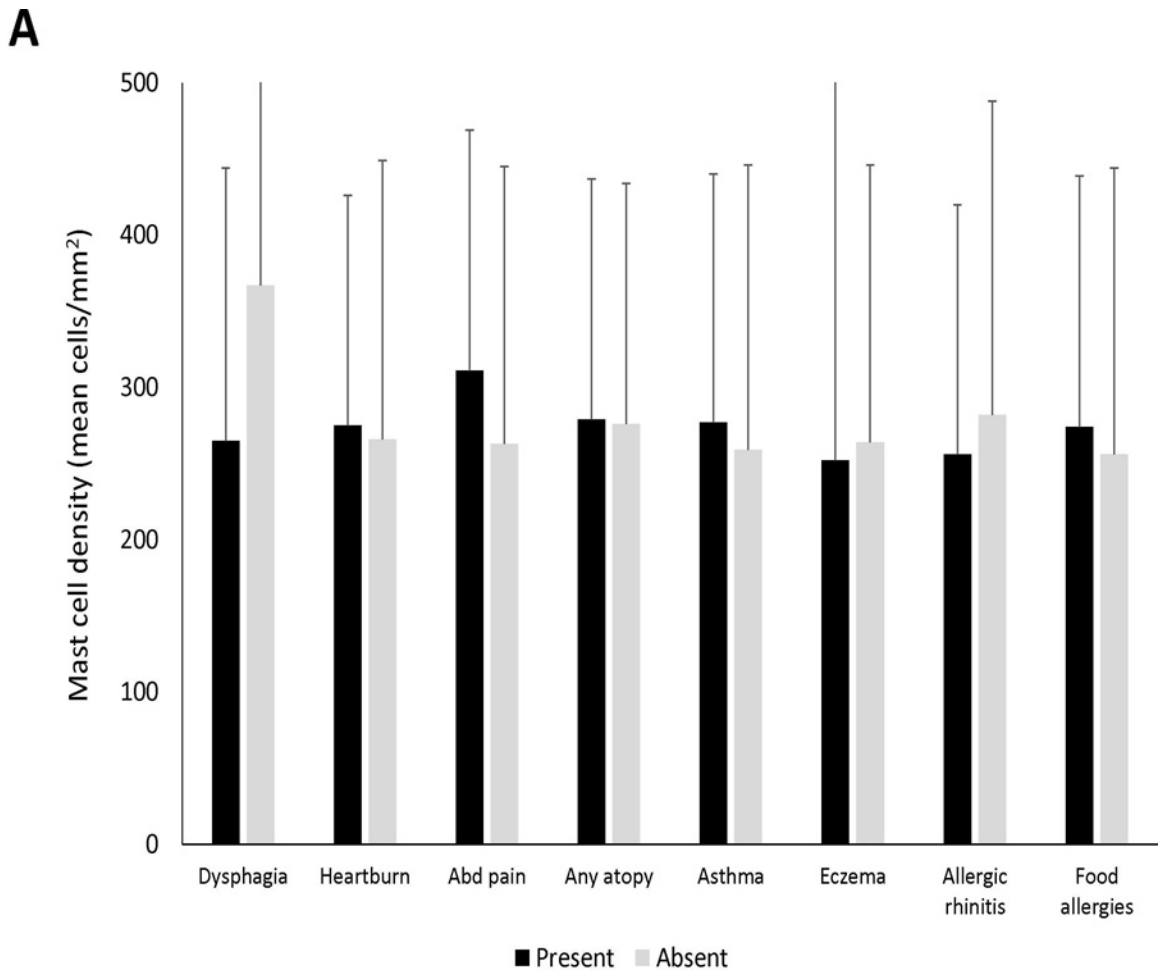

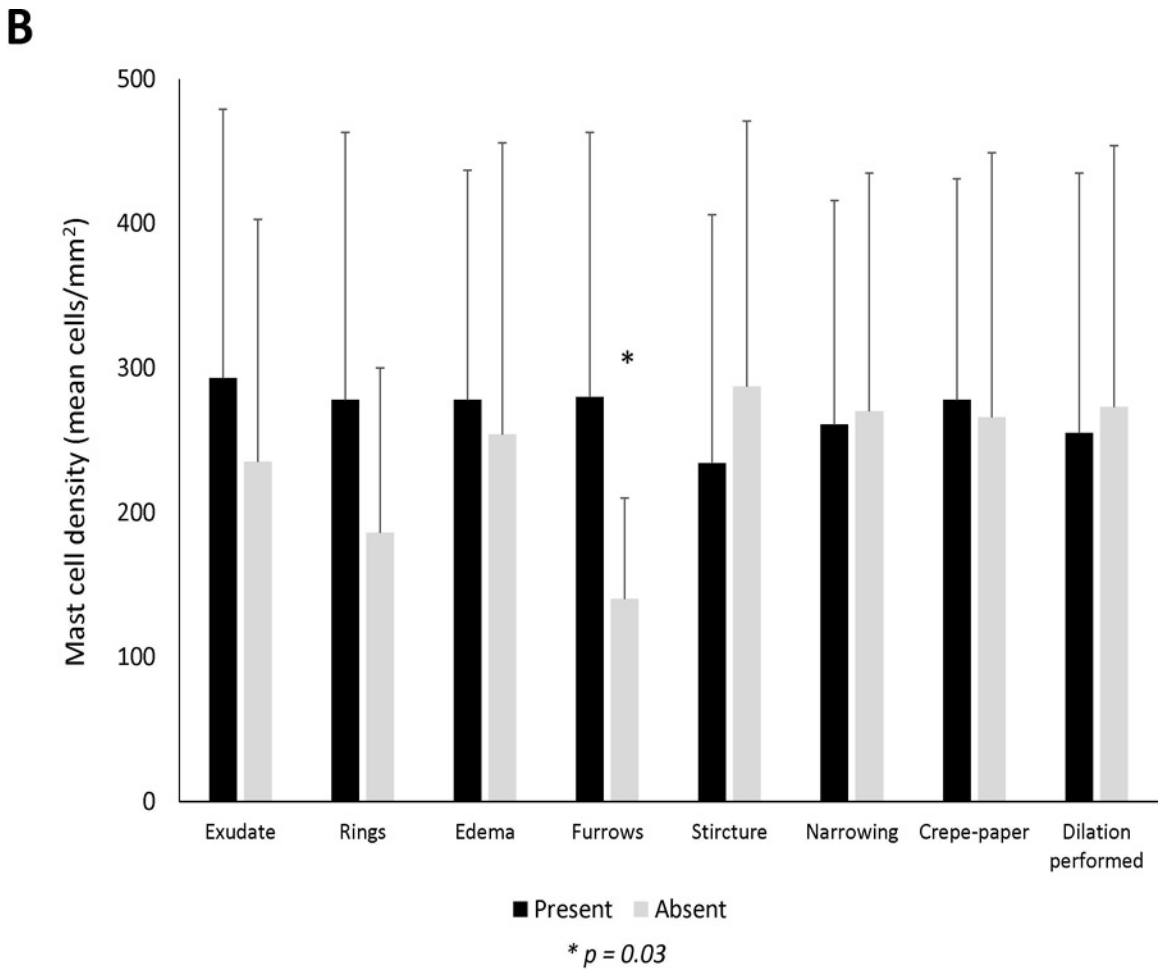

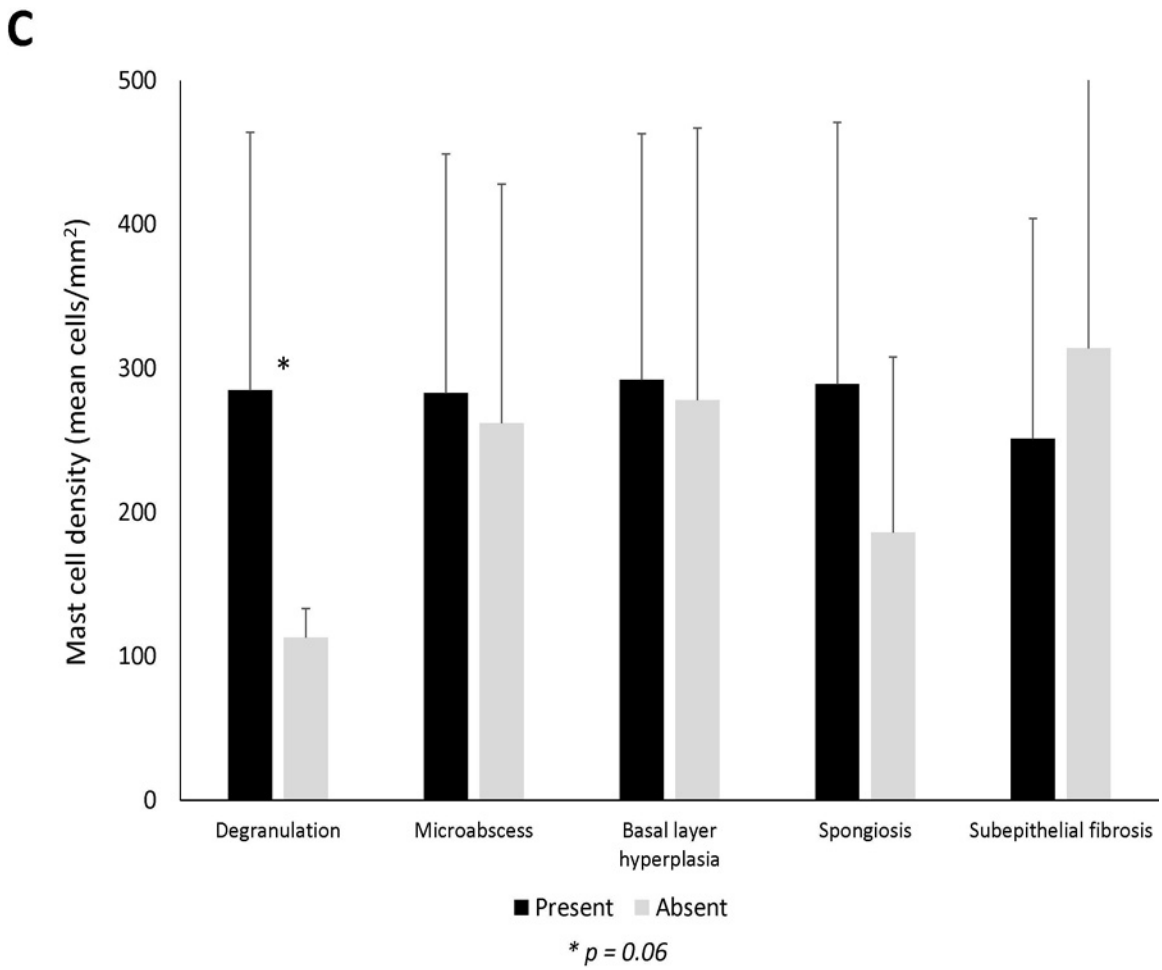

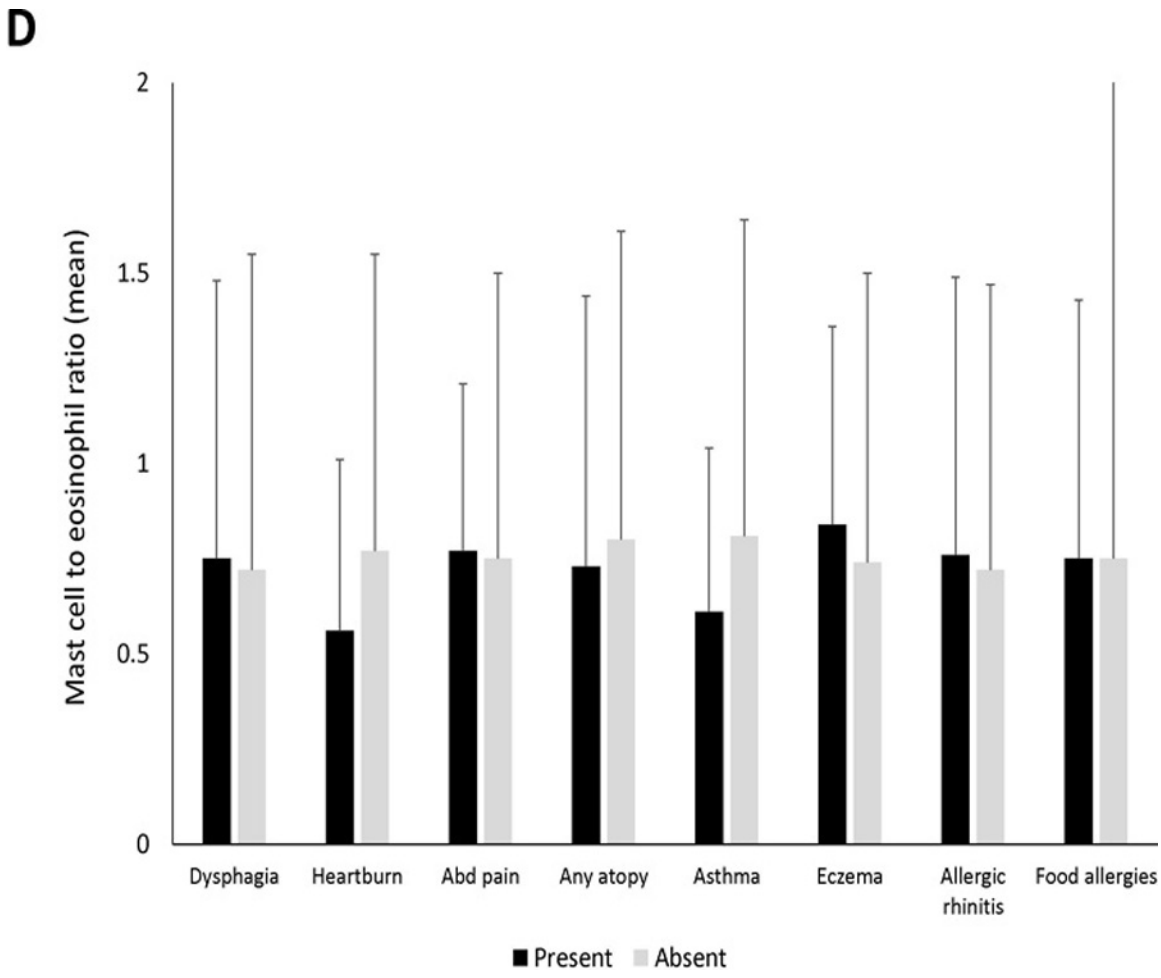

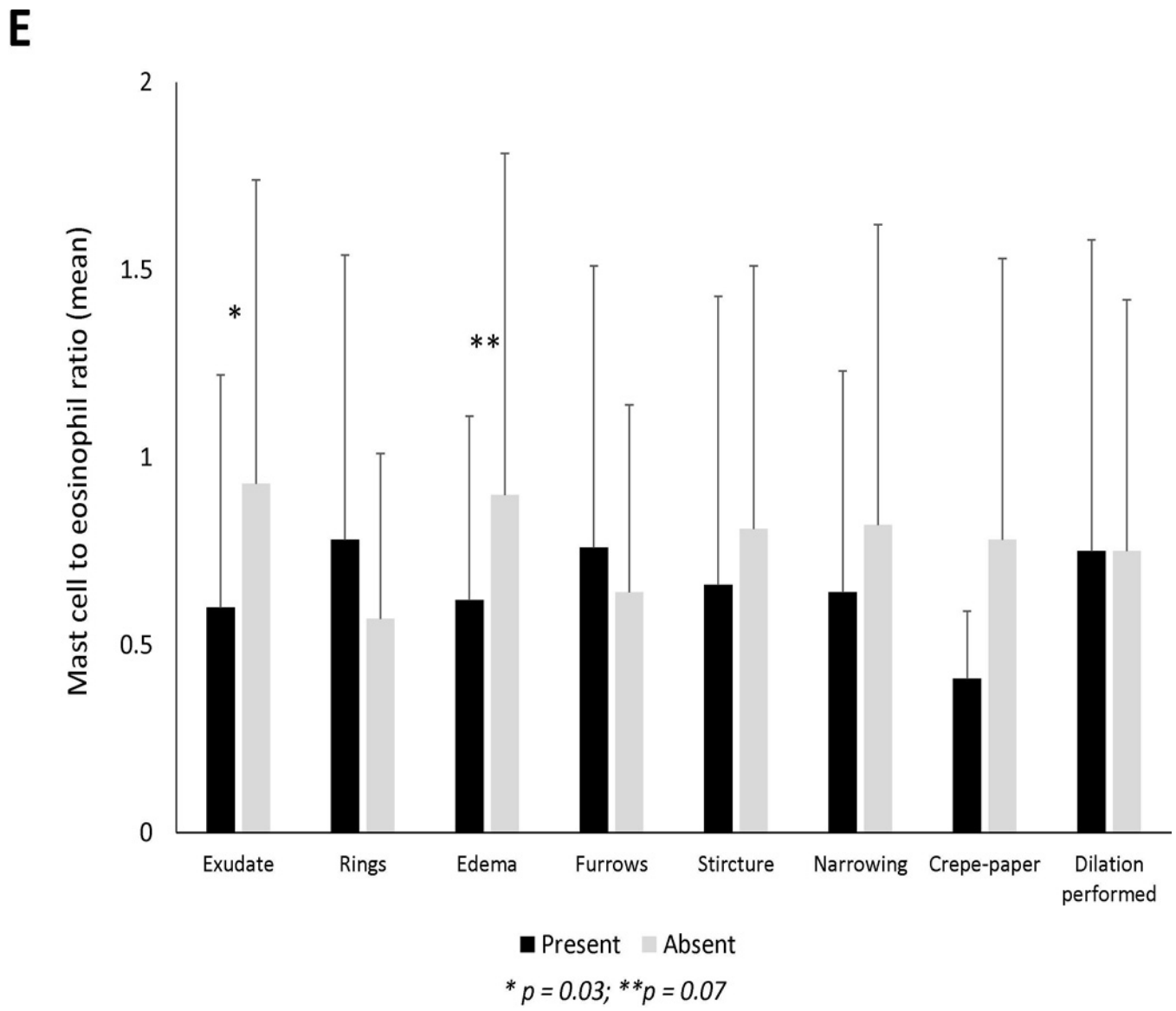

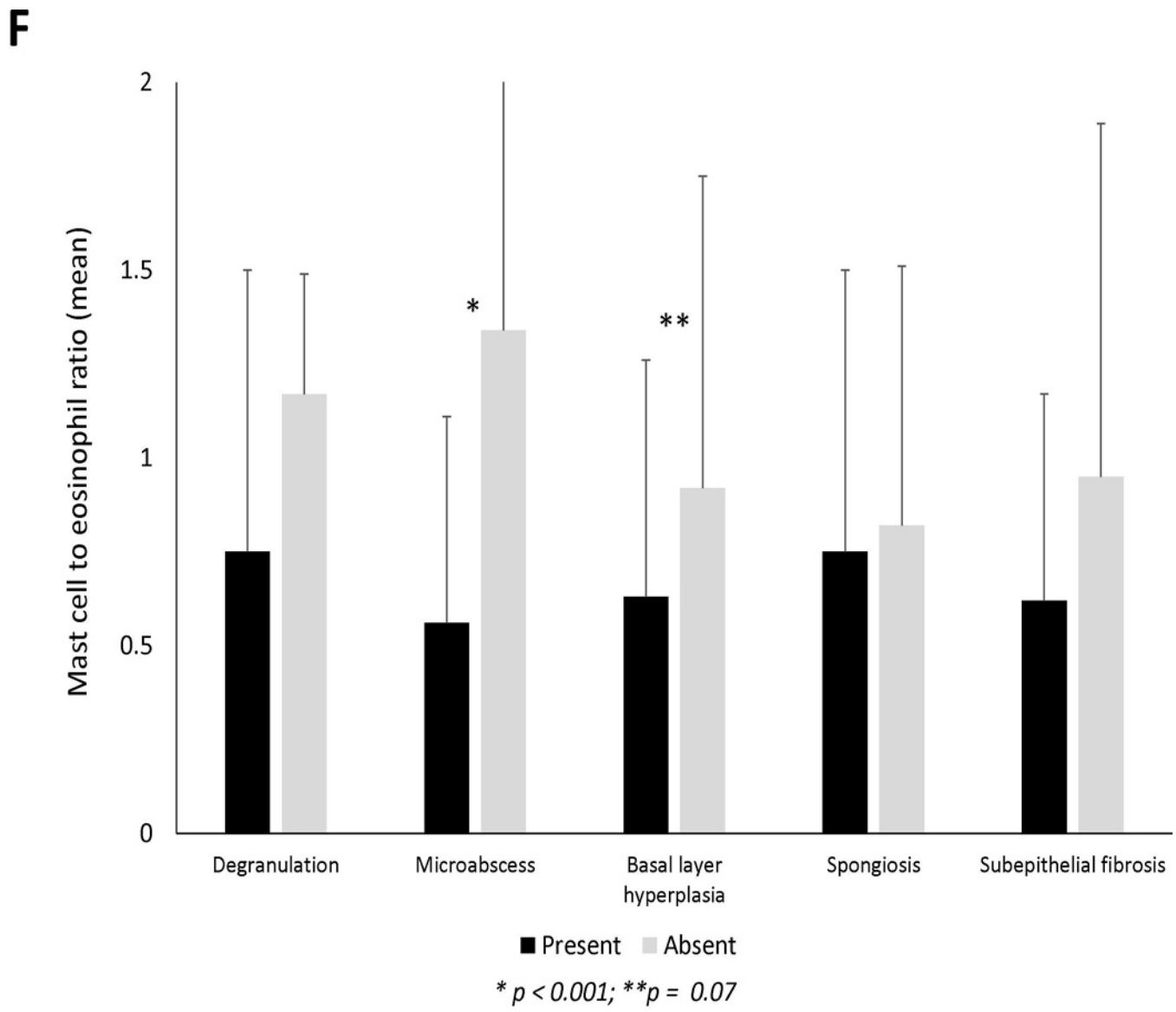

Figure 1.

Mean mast cell density in association with **(A)** clinical findings **(B)** endoscopic findings and **(C)** histologic findings of EoE. Black bars indicate the presence of the findings and gray bars indicated absence of the findings. Mean mast cell to eosinophil ratio in association with **(D)** clinical findings **(E)** endoscopic findings and **(F)** histologic findings of EoE. Black bars indicate the presence of the findings and gray bars indicated absence of the findings.

Table 1.

Patient Characteristic, and characteristics stratified by the highest and lowest mast cell quartile, and by mast cell to eosinophil ratios ≤1 and >1

Characteristic	Overall EoE population n=96)	Lowest mast cell quartile (n=24)	Highest mast cell quartile (n=24)	p	Mast cell to eos ratio ≤ 1 (n=72)	Mast cell to eos ratio > 1 (n=24)	p
Mast cell density (mean cells/mm^2 ± SD)	266.8 ± 180.0	88.7 ± 32.6	515.3 ± 157.4	--	235.1 ± 142.2	361.6 ± 242.6	0.002
Eosinophil density (eos/mm^2; mean ± SD)	555.9 ± 478.1	304.2 ± 212.0	717.5 ± 501.1	< 0.001	664.6 ± 498.8	229.8 ± 168.8	< 0.001
Age at diagnosis (mean ± SD)	37.2 ± 12.7	38.0 ± 14.2	38.4 ± 13.6	0.91	37.1 ± 12.6	37.6 ± 13.2	0.88
Male (n, %)	54 (56)	10 (42)	15 (63)	0.15	38 (53)	16 (67)	0.24
White (n, %)	91 (95)	23 (96)	24 (100)	0.31	68 (94)	23 (96)	0.79
Symptoms							
Dysphagia (n, %)	94 (98)	24 (100)	23 (96)	0.31	71 (99)	23 (96)	0.41
>5 yrs of dysphagia (n, %)	53 (60)	13 (56)	12 (55)	0.51	37 (57)	16 (70)	0.67
VAS * score (mean ± SD	3.5 ± 2.7	2.4 ± 1.9	3.6 ± 2.8	0.12	3.5 ± 2.6	3.5 ± 3.0	0.97
Heartburn (n, %)	8 (8)	1 (4)	2 (8)	0.55	7 (10)	1 (4)	0.39
GERD-Q † (mean ± SD)	4.7 ± 6.3	2.6 ± 3.9	4.5 ± 5.6	0.19	4.2 ± 6.3	6.2 ± 6.3	0.21
Abdominal pain (n, %)	7 (7)	0 (0)	1 (4)	0.31	5 (7)	2 (8)	0.82
SODA ≠ score (mean ± SD)	42.8 ± 12.5	39.1 ± 11.7	42.3 ± 12.8	0.51	43.3 ± 12.1	41.1 ± 13.9	0.58
Nausea/Vomiting (n, %)	0 (0)	0 (0)	0 (0)	--	0 (0)	0 (0)	--
Any atopic disorder (n, %)	69 (72)	11 (46)	16 (67)	0.31	44 (61)	15 (63)	0.65
Asthma	30 (32)	6 (25)	8 (33)	0.46	23 (32)	7 (29)	0.86
Atopic dermatitis	10 (11)	2 (8)	2 (8)	0.93	6 (8)	4 (17)	0.24
Allergic rhinitis/sinusitis	62 (66)	16 (67)	14 (58)	0.68	47 (65)	15 (63)	0.93
Food allergies	35 (37)	7 (29)	9 (38)	0.41	26 (36)	9 (38)	0.84
EGD findings (n, %)							
Normal	3 (3)	1 (4)	0 (0)	0.31	2 (3)	1 (4)	0.74
Rings	84 (88)	19 (79)	22 (92)	0.22	62 (86)	22 (92)	0.48
Strictures	37 (39)	11 (46)	6 (25)	0.13	30 (42)	7 (29)	0.28
Narrowing	36 (38)	7 (29)	8 (33)	0.76	29 (40)	7 (29)	0.33
Crepe paper mucosa	7 (7)	1 (4)	2 (8)	0.55	7 (10)	0 (0)	0.11

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Characteristic	Overall EoE population n=96)	Lowest mast cell quartile (n=24)	Highest mast cell quartile (n=24)	p	Mast cell to eos ratio ≤ 1 (n=72)	Mast cell to eos ratio > 1 (n=24)	p
Furrows	87 (91)	20 (83)	24 (100)	0.04	66 (92)	21 (88)	0.54
White plaques/exudates	53 (55)	11 (46)	17 (71)	0.08	45 (63)	8 (33)	0.01
Edema/decreased vascularity	51 (53)	9 (38)	14 (58)	0.15	42 (58)	9 (38)	0.08
Hiatal hernia	12 (13)	2 (8)	0 (0)	0.15	10 (14)	2 (8)	0.48
Dilation performed	34 (35)	9 (38)	6 (25)	0.35	27 (38)	7 (29)	0.46
Other histologic findings (n, %)[#]							
Eosinophil degranulation	86 (96)	16 (84)	24 (100)	0.04	67 (99)	19 (86)	0.02
Eosinophil microabscesses	67 (74)	13 (68)	20 (83)	0.25	59 (87)	8 (36)	< 0.001
Basal layer hyperplasia	42 (49)	7 (41)	13 (54)	0.41	36 (55)	6 (29)	0.03
Spongiosis	80 (89)	14 (74)	22 (92)	0.11	61 (90)	19 (86)	0.67
Lamina propria fibrosis	22 (37)	5 (36)	5 (29)	0.71	18 (43)	4 (24)	0.16

* VAS = visual analogue scale for dysphagia severity; data available for n = 79 overall, 42 in the quartile analysis, and 79 in the ratio analysis

† GERD-Q = Gastroesophageal reflux disease questionnaire; data available for 86 overall, 44 in the quartile analysis, and 86 in the ratio analysis

‡ Severity of Dyspepsia Assessment; data available for n = 54 overall, 27 in the quartile analysis, and 54 in the ratio analysis

Data available for n = 90 overall, 43 in the quartile analysis, and 90 in the ratio analysis