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血清嗜酸性粒细胞表达水平与鼻腔鼻窦内翻性乳头状瘤病理的相关性分析*

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摘要 目的：探讨血清嗜酸性粒细胞（EOS）表达水平与鼻腔鼻窦内翻性乳头状瘤（SNIP）病理的相关性。**方法**：选取我院2016年1月至2020年1月收治的63例SNIP患者作为研究对象，依照所有患者EOS水平将其分为低EOS组、中EOS组、高EOS组，对比三组患者的临床病理特征，并分析EOS表达水平与SNIP病理的相关性。行手术治疗后将63例患者分为预后不良组与预后良好组，对比两组患者的临床相关指标，并分析EOS表达水平对SNIP的预后预测价值。**结果**：三组患者临床分期、病理诊断对比差异显著（$P<0.05$）；以EOS表达水平进行分级：高水平：＞300个/μL，中水平：100-300个/μL，低水平：＜100个/μL。Spearman相关分析结果显示：性别、年龄、病灶位置与EOS表达水平无明显相关性（$P>0.05$），临床分期、病理诊断与EOS水平呈负相关（$P<0.05$）；预后良好组与预后不良组患者PLT水平对比无明显差异（$P>0.05$），预后两组患者L、EOS水平明显高于预后不良组，N、PLR、NLR低于预后不良组（$P<0.05$）；logistic回归分析结果表明：NLR、EOS为SNIP的预后独立预测因素（$P<0.05$）。**结论**：SNIP患者的临床分期、病理诊断与EOS表达水平呈负相关，且应用NLR和EOS可对SNIP术后复发情况进行预测，因此，可以考虑应用EOS表达水平对SNIP进行诊断与治疗效果判定。

关键词：嗜酸性粒细胞；鼻腔鼻窦内翻性乳头状瘤；临床分期；病理诊断

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Correlation between the Expression of Eosinophils in Serum and the Pathology of Inverted Papilloma of Nasal Cavity and Paranasal Sinuses*

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ABSTRACT Objective: To investigate the correlation between serum eosinophil (EOS) expression level and pathology of inverted papilloma in nasal cavity and sinuses (SNIP). **Methods:** 63 cases of patients with SNIP admitted to our hospital from January 2016 to January 2020 were selected as the research objects. According to the EOS level of all patients, they were divided into low EOS group, medium EOS group and high EOS group. The clinicopathological characteristics of the three groups were compared, and the correlation between EOS expression level and SNIP pathology was analyzed. After surgical treatment, 63 patients were divided into poor prognosis group and good prognosis group. The clinical related indexes of the two groups were compared, and the prognostic value of EOS expression level in SNIP was analyzed. **Results:** There was significant difference in clinical stage and pathological diagnosis among the three groups ($P<0.05$); According to the expression level of EOS, there were more than 300 eosinophils at high level/μL. Medium level: 100-300/μL. Low level:<100/μL. Spearman correlation analysis showed that there was no significant correlation between the expression level of the gender, age, lesion location and EOS ($P>0.05$), but negative correlation between the expression level of the clinical stage and pathological diagnosis and EOS ($P<0.05$); There was no significant difference in PLT between the two groups ($P>0.05$). The levels of L and EOS in the two groups were significantly higher than those in the poor prognosis group, and the levels of N, PLR and NLR in the two groups were lower than those in the poor prognosis group ($P<0.05$); Logistic regression analysis showed that NLR and EOS were independent prognostic factors of SNIP ($P<0.05$). **Conclusion:** The clinical stage and SNIP are negatively correlated with the expression level of EOS, and the application of NLR and EOS can predict the recurrence of SNIP. Therefore, the expression level of EOS can be considered to determine the diagnosis and treatment effect of SNIP.

Key words: Eosinophils; Inverted papilloma of nasal cavity and paranasal sinuses; Clinical stage; Pathological diagnosis

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前言

鼻腔鼻窦内翻性乳头状瘤(Inverted papilloma of nasal cavity and paranasal sinuses, SNIP)属于耳鼻喉科常见的一种上皮良性肿瘤,且术后易反复发作,易产生恶变与侵袭,对邻近组织结构造成破坏,属于交界性肿瘤的一种[1,2]。研究发现[3,4],SINP 术后复发率约为 15 %-20 %, 一般与手术切除不彻底有关。近 2 %-27 %的 SNIP 有恶变发生的可能, 且恶变的 SNIP 多为鳞状细胞癌,部分还会发展为腺癌[5]。当 SNIP 患者出现恶变,意味着预后不佳,有 63 %左右患者的生存率近仅为 3 年[6,7]。因此,鉴于 SNIP 术后易复发、易恶变、易误诊与漏诊现象,术前明确诊断以及判断肿瘤的良恶性情况, 对于 SNIP 的治疗与预后具有重要价值。但目前国内临床研究对于 SNIP 恶变的诊断依然缺乏相应的实验室指标与肿瘤标记物作为指导, 导致误诊率较高,临床诊断较困难[8]。随着临床医学发展,国外研究发现[9,10],恶性肿瘤会引发全身或局部炎症反应,对血小板、中性粒细胞与淋巴细胞比值(Neutrophil to lymphocyte ratio, NLR)以及血嗜酸性粒细胞(Blood eosinophils, EOS)表达程度产生影响。另有研究显示[11],对 EOS 的研究以往多集中在介导抗寄生从感染与超敏反应性疾病中,但在 120 多年前已有报道,发现癌症患者出现外周 EOS 升高现象。近年来, 陆续有报道发现 EOS 在多种肿瘤组织中存在浸润现象,但具体意义和发生机制尚无明确定论。因此,为了提升 SNIP 的诊断准确率,及时判定患者的病理情况,本研究探讨了 EOS 表达水平与 SNIP 病理的相关性,具体报告如下。

1 材料与方法

1.1 一般资料

选取我院 2016 年 1 月到 2020 年 1 月收治的 63 例鼻腔鼻窦内翻性乳头状瘤患者作为研究对象。63 例患者中男性 48 例,女性 15 例;年龄为 18-80 岁,平均年龄(55.35± 3.53)岁。

纳入标准: 所有患者均确诊为鼻腔鼻窦内翻性乳头状瘤;年龄≥ 18 岁;对本研究知情并签署同意书。本研究经我院伦理委员会批准。

排除标准:临床资料不全者;近期使用免疫抑制剂或糖皮质激素治疗者;合并其他肿瘤者;合并风湿免疫系统疾病或血液系统疾病者;合并泌尿、消化、呼吸系统感染者。

1.2 方法

对我院 2016 年 1 月至 2020 年 1 月收治的 63 例鼻腔鼻窦内翻性乳头状瘤患者进行回顾性分析, 依照所有患者 EOS 水平进行分组, 将＜100 个 /μL 的 18 例患者分为低 EOS 组,将 100-300 个 /μL 的 25 例患者分为中 EOS 组, 将＞300 个 /μL 的 20 例患者分为高 EOS 组。收集所有患者性别、年龄、病程、病灶位置、临床分期、病理诊断类型等一般资料,并收集所有患者血小板(Platelet, PLT)、淋巴细胞(Lymphocyte, L)、中性粒细胞计数(Neutrophil count, N)计数,并计算 PLT 与淋巴细胞比值(Platelet to lymphocyte ratio, PLR)和 NLR。

EOS 检测主要方法为:抽取患者静脉血 3 mL,应用直流检测方法,在全自动血细胞分析仪(希森美康,XN-9000)中进行样本检测,通过小孔样本产生的脉冲和自动界标法来进行计数。

1.3 统计学方法

本研究数据采取 SPSS 23.0 进行数据分析, 计数资料以(n/%)表示,进行 x^2 检验;计量资料以符合正态分布则用($\bar{x}\pm s$)表示,组间比较采用 F/t 检验;采用 Spearman 相关分析 EOS 表达水平与鼻腔鼻窦内翻性乳头状瘤病理的相关性;采用 logistic 回归分析分析上述指标与患者预后的关系; 以 P<0.05 为差异有统计学意义。

2 结果

2.1 三组患者临床病理特征对比分析

三组患者性别、年龄、病程、病灶位置等对比无明显差异(P＞0.05),三组患者临床分期、病理诊断对比差异显著(P＜0.05),如表 1 所示。

表 1 三组患者临床病理特征对比分析

Table 1 Comparative Analysis of clinicopathological characteristics of three groups of patients

Index	Low EOS group (n=18)	Medium EOS group (n=25)	High EOS group (n=20)	x^2/F	P
Gender(n)					
Male	11	16	11	0.380	0.826
Female	7	9	9		
Age(year)	55.35± 4.52	56.13± 3.24	54.25± 5.25	1.050	0.356
course of disease(year)	1.35± 0.35	1.36± 0.25	1.21± 0.36	1.446	0.244
Location of lesion					
Left nasal cavity	4	6	4	4.060	0.669
Right nasal cavity	3	7	8		
Bilateral nasal cavity	5	8	5		
Paranasal sinuses	6	4	3		
Clinical stages					
Ⅰ-Ⅱ	6	15	16	8.540	0.014

Ⅲ-Ⅳ	12	10	4		
Pathologic diagnosis					
Inverted papilloma	5	10	17	17.420	0.008
Low grade intraepithelial neoplasia	6	7	2		
High grade intraepithelial neoplasia	5	6	1		
Transitional cell carcinoma	4	2	0		

表 2 血清嗜酸性粒细胞表达水平与鼻腔鼻窦内翻性乳头状瘤病理的相关性

Table 2 Correlation between serum eosinophil expression level and pathology of inverted papilloma of nasal cavity and paranasal sinuses

Index	EOS	
	r	*P*
Gender	0.286	0.083
Age	0.245	0.109
Location of lesion	0.184	0.223
Clinical stages	-0.579	0.018
Pathologic diagnosis	-0.374	0.009

表 3 预后良好组与预后不良组患者临床相关指标对比分析($\bar{x}\pm s$)

Table 3 Comparative Analysis of clinical related indexes between patients with good prognosis and patients with poor prognosis ($\bar{x}\pm s$)

Category	Good prognosis group (n=42)	Poor prognosis group (n=21)	t	*P*
PLT(× 10^9/L)	207.24± 16.50	206.17± 21.52	0.219	0.827
L(× 10^9/L)	2.67± 0.28	1.52± 0.71	9.216	0.001
N(× 10^9/L)	8.24± 2.38	12.14± 3.32	5.357	0.001
PLR(%)	122.44± 45.30	175.17± 82.52	3.283	0.002
NLR(%)	4.12± 3.31	6.27± 2.08	2.715	0.009
EOS(n/μL)	432.30± 42.09	254.52± 29.73	17.288	0.001

表 4 血清嗜酸性粒细胞表达水平对鼻腔鼻窦内翻性乳头状瘤的预后预测价值

Table 4 The prognostic value of serum eosinophil expression level in nasal inverted papilloma

Factors	Parameter estimates	Standard error	Wald	*P*	OR	95% CI
L	-0.463	0.096	8.096	0.123	2.546	1.364~3.475
N	0.847	0.304	13.274	0.124	0.747	0.314~1.249
PLR	0.635	0.108	10.484	0.108	0.464	0.210~1.347
NLR	0.464	0.105	8.484	0.016	2.774	1.876~4.010
EOS	-0.457	0.089	8.145	0.030	2.458	1.359~3.257

2.2 血清嗜酸性粒细胞表达水平与鼻腔鼻窦内翻性乳头状瘤病理的相关性

以 EOS 表达水平进行分级：高水平：＞300 个 /μL，中水平：100-300 个 /μL，低水平：＜100 个 /μL。Spearman 相关分析结果显示：性别、年龄、病灶位置与 EOS 表达水平无明显相关性（P＞0.05），临床分期、病理诊断与 EOS 表达水平呈负相关（P＜0.05），如表 2 所示。

2.3 预后良好组与预后不良组患者临床相关指标对比分析

预后良好组与预后不良组患者 PLT 水平对比无明显差异（P＞0.05），预后两组患者 L、EOS 水平明显高于预后不良组，N、PLR、NLR 低于预后不良组（P＜0.05），如表 3 所示。

2.4 血清嗜酸性粒细胞表达水平对鼻腔鼻窦内翻性乳头状瘤的预后预测价值

logistic 回归分析结果表明：NLR、EOS 为鼻腔鼻窦内翻性乳头状瘤的预后独立预测因素（P＜0.05），如表 4 所示。

3 讨论

炎症反应是肿瘤的重要特征，包括局部及全身炎症反应[12]。

早在 1863 年,德国病理学家 Vichow 发现肿瘤常起源于慢性炎症部位,并在肿瘤组织中常可发现浸润的炎症细胞,提出了炎症致肿瘤假说。随着临床医学的发展,很多研究都证实了肿瘤和炎症的相关性,并出现了炎症促癌学说。鼻腔鼻窦内翻性乳头状瘤属于一种良性肿瘤,在临床极为常见。其症状一般表现为:流鼻涕、头部面部疼痛等[13,14]。EOS 在人体有毒蛋白颗粒损伤气道上皮之后会出现升高现象,所以气道上皮出现炎症反应,嗜酸性粒细胞会升高[15]。EOS 迁移活化颗粒导致毒性蛋白细胞因子释放,产生气道炎症反应与黏膜水肿,致使哮喘发病,因此 EOS 在气道阻塞中具有重要作用[16]。研究显示[17],EOS 升高与各种诱因导致的哮喘有着明显关系,且其水平决定了哮喘病情的严重程度。另有研究发现[18],鼻息肉的发生发展与 EOS 浸润、趋化因子、转化生长因子作用导致,且多以 EOS 浸润为主要特征。少数研究发现[19,20],EOS 与癌症和良性肿瘤的发生发展具有一定相关性,但具体机制尚无明确定论。

本研究结果表明,三组患者临床分期、病理诊断对比差异显著。与 Sek A C 等人[21]的研究相一致。Sek A C 等人[21]发现,外周血嗜酸粒细胞比例变化与 PD-1 抗体治疗晚期实体肿瘤的临床疗效具有一定相关性,与本研究结果相符。以上结果均表明,EOS 的表达水平与鼻腔鼻窦内翻性乳头状瘤临床分期与病理诊断具有一定关系。分析其原因为:EOS 能够在 CD8+T 细胞浸润过程血管正常化中发挥一定作用,具有免疫治疗效果,从而有益于于鼻腔鼻窦内翻性乳头状瘤的分期与诊断;以 EOS 表达水平进行分级:高水平:>300 个 /μL,中水平:100-300 个 /μL,低水平:<100 个 /μL。Spearman 相关分析结果显示:性别、年龄、病灶位置与 EOS 表达水平无明显相关性,但是临床分期、病理诊断与 EOS 表达水平呈负相关。本研究结果与 Makhsitaliev M 等[22]研究结果具有一致性。Makhsitaliev M 等发现,淋巴细胞减少、中性粒细胞增多、EOS 减少与肿瘤患者的的预后和临床分期具有密切关系。另有研究发现[23],鼻腔鼻窦内翻性乳头状瘤发生恶变时,全身炎症反应将会扩大与激活,与本研究结果相符。进一步推测可知,鼻腔鼻窦内翻性乳头状瘤的预后、临床分期与 EOS 息息相关;预后良好组与预后不良组患者 PLT 水平对比无明显差异,预后两组患者 L、EOS 水平明显高于预后不良组,N、PLR、NLR 低于预后不良组。由此证明,鼻腔鼻窦内翻性乳头状瘤患者术后复发情况与 L、EOS、N、PLR、NLR 表达具有一定关系。其原因可能为,鼻腔鼻窦内翻性乳头状瘤复发后,中性粒细胞在肿瘤部位聚集,而活化的中性粒细胞释放活性氧、细胞因子等导致炎症反应增加,使血小板聚集导致[24,25];logistic 回归分析结果表明:NLR、EOS 为鼻腔鼻窦内翻性乳头状瘤的预后独立预测因素。与 Cp A 等[26]研究相似,Cp A 等发现,当机体出现肿瘤时,肿瘤组织通过释放多种炎症介质募集大量中性粒细胞与 EOS,导致 EOS 和中性粒细胞进入到肿瘤组织中,激活全身性炎症反应,从而导致肿瘤的发生发展。进一步分析其机制可知,肿瘤组织中浸润着大量的中性粒细胞和 EOS,释放大量蛋白酶、趋化因子和细胞因子,促进肿瘤血管生成,最终导致肿瘤的转移和增殖[27,28]。Fulla M 的团队[29]发现,EOS 计数水平与结肠癌、食道癌以及宫颈癌等恶性肿瘤具有明显关系。淋巴细胞是机体发挥抗肿瘤作用的重要免疫细胞,而淋巴细胞的数量和机体免疫具有一定关系。外周血淋巴细胞计数下降,也代表患者机体处于免疫抑制状态,从而导致抗肿瘤能力下降[30]。但是以往研究中,并无将 EOS 应用于鼻腔鼻窦内翻性乳头状瘤患者预后情况进行判断,这也是本研究的创新之处,旨在希望为日后鼻腔鼻窦内翻性乳头状瘤的治疗与诊断提供参考意见。

综上所述,鼻腔鼻窦内翻性乳头状瘤患者的临床分期、病理诊断与 EOS 表达水平呈负相关,且应用 NLR 和 EOS 可有助于对鼻腔鼻窦内翻性乳头状瘤术后复发情况进行预测,因此,可以考虑应用 EOS 表达水平对鼻腔鼻窦内翻性乳头状瘤进行诊断与治疗效果判定。

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