头颈肿瘤专题 ●临床经验与技术交流●

涎腺分泌性癌 7 例临床病理分析*

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[摘要] **目的:** 探讨涎腺分泌性癌(mammary analogue secretory carcinoma,MASC)的临床病理特征、诊断标准及鉴别诊断。**方法:**收集我院 2011 年至 2018 年收治的 117 例涎腺恶性肿瘤,由两名高年资病理医师根据 2017 年版 WHO 头颈肿瘤分册中所描述 MASC 镜下形态学特征从中筛选出符合 MASC 形态特征的病例 7 例,分析其临床病理特点,运用免疫组化 EnVision 法检测 S-100、Vimentin、CK7、GATA-3、Mammaglobin、P63、Ki-67、CD117 及 DOG1 的表达情况。**结果:**7 例 MASC 病例中,发生于腮腺 6 例,颌下腺 1 例,女性 2 例,男性 5 例,发病年龄 21 ~ 63 岁,中位年龄为 44 岁,临床症状为颌下区缓慢增大的无痛性肿块,病程 2 周至 3 年;7 例均为单发结节,直径 1. 3 ~ 3. 5cm,平均直径(2. 77 ± 1. 33)cm,2 例结节界限清楚,5 例与周围涎腺分界不清;组织学形态显示肿瘤呈多结节状,结节被纤维组织分隔,肿瘤细胞排列成腺管状,微囊样及实性,2 例具有乳头状结构,腺腔及微囊内可见嗜酸性分泌物,类似甲状腺滤泡,肿瘤细胞呈圆形、卵圆形,细胞核圆,可见小核仁,胞浆嗜酸性或空亮,核分裂象少见;7 例病例均弥漫强阳性表达 CK7、Vimentin、Mammaglobin 及 S-100,强弱不等地表达 GATA-3,均不表达 P63、DOG1 及 CD117,Ki-67 增殖指数均较低(2% ~ 15%)。7 例病例,4 例获得随访资料,3 例失访,随访时间 8 ~ 43 个月,均未复发。**结论:**MASC 是临床罕见的低度恶性涎腺型肿瘤,易与涎腺腺泡细胞癌(acinic cell cancinoma,AciCC)混淆,结合组织学形态、免疫表型及基因检测可与 AciCC 鉴别。

[关键词] 涎腺肿瘤;分泌性癌;临床病理特征;鉴别诊断
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Mammary Analogue Secretory Carcinoma of Salivary Gland: Clinicopathological Features of 7 Cases

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[**Abstract**] **Objective**: To investigate the clinicopathologic features, diagnostic criteria and differential diagnosis of mammary analogue secretory carcinoma (MASC). **Methods**: Seven case of MASC were collected from our hospital from January 2011 to October 2018. Clinical data and pathological fea-

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tures of 7 cases of MASC were evaluated respectively. Microscopic examination and immunohistochemical study were performed with literature review. **Results**: The 7 patients comprised 5 men and 2 women, with a median and mean age of 44 and 45.1 years (21 – 63), respectively. All of the patients were treated with a slowly growing painless mass as the fist symptom, six occurred in the parotid and one in the submandibular gland. All of the tumors were solitary masses, and the mean diameter of the tumors was 2.77 cm (1.3 – 3.5 cm). Two neoplasms are well circumscribed, and the rest always invade the salivary glands; microscopic features showed multilobulated mass, subdivided into smaller segments by fibrous septa. These cells are arranged into microcystic, cribriform, tubular, papillary, follicular (thyroid like), or solid nests. Tumor cells have uniform round and vesicular nuclei with central nucleoli and eosinophilic pink vacuolated cytoplasm. The immunohistochemical features of 7 cases were positive for CK7, Vimetin, Mammaglobin and S-100, and negative for P63, DOG1 and CD117, Ki-67 positive rate ranged from 2% to 15%. Follow-up data were available for 4 patients, and follow-up period ranged from 8 to 43 months. The 4 patients remained well without recurrence. **Conclusion**: MASC is a rare low-grade malignant tumor of salivary glands, which was classified recently. The histopathologic, immunohistochemical, cytogenetic and molecular genetic features of MASC are helpful to distinct it with acinic cell cancinoma.

[**Key words**] Salivary gland neoplasms; Mammary analogue secretory carcinoma; Clinicopathological features; Differential diagnosis

涎腺分泌性癌(mammary analogue secretory carcinoma,MASC)是 2017 年世界卫生组织头颈肿瘤分册收录的新肿瘤类型[1],因其形态与原发于乳腺的分泌性癌类似,并同样具有特征性 *ETV6-NTRK3* 基因融合转录而得名。在被明确分类定义之前,这类肿瘤最常被诊断为涎腺腺泡细胞癌(acinic cell cancinoma,AciCC),其次为低级别非特异性癌、黏液表皮样癌等[2-4]。MASC 的发现者 Skálová 认为[5],MASC 与 AciCC 主要有三点不同:1). MASC 不存在胞浆内嗜碱性颗粒,而这是 AciCC 最重要的组织学特征;2). MASC 具有与 AciCC 完全相反的免疫表型,前者总是强阳性表达 S-100 蛋白和 Mammaglobin,不表达 DOG1;3). MASC 存在 *ETV6-NTRK3* 融合基因转录。因此,本研究通过回顾性收集我院 2011 年至 2018 年期间诊断的涎腺上皮源性恶性肿瘤 117 例,从中筛选出符合 MASC 组织学特征及免疫组化特点的病例 7 例,总结其临床病理特征,以减少误诊。

1 材料与方法

1.1 材料

回顾性收集我院病理科 2011 年 1 月至 2018 年 10 月诊断为涎腺上皮源恶性肿瘤的病例 117 例,其中腺泡细胞癌 25 例,腺样囊性癌 29 例,粘液表皮样癌 35 例,癌在多形性腺瘤中 11 例,涎腺导管癌 3 例,非特异性腺癌 4 例,肌上皮癌及上皮-肌上皮癌 10 例。

1.2 方法

标本均由 4% 中性甲醛固定,常规石蜡包埋及 HE 染色。117 例病例由两名高年资病理医师重新观察切片,严格根据 2017 年版 WHO 头颈肿瘤分册中所描述的 MASC 镜下形态学特征鉴别[1]:肿瘤细胞排列呈腺管状、微囊性、实体性、滤泡样和乳头状,并且胞浆嗜酸性、透明或泡沫状,从中筛选出 7 例病例(最初均被诊断为腺泡细胞癌),并对这 7 例病例采用 EnVision 二步法进行免疫组织化学染色,DAB 显色、苏木素对比染色。抗体包括 S-100、Vimentin、CK7、GATA-3、Mammaglobin、P63、Ki-67、CD117、DOG1,抗体均为北京中衫公司生产。

1.3 免疫组化结果判读

S-100 定位于细胞核和细胞质,CK7、Mammaglobin 与 Vimentin 定位于细胞质,P63、GATA-3 与 Ki-67 定位于细胞核,CD117 与 DOG1 定位于细胞质或细胞膜,阳性强度判读:1)在高倍镜(×400)下选取 10 个视野,计算细胞阳性率评分(阳性瘤细胞数/总瘤细胞数)×100%,0 分:阳性细胞数 <5%;1 分:5% ~25%;2 分:26% ~50% +;3 分: >50%;2)着色强度评分:0 分:无色;1 分:浅黄色;2 分:棕黄色;3 分:深棕色;3)阳性强度(细胞阳性率评分 + 着色强度评分):阴性:0 分;1 + :1 ~2 分;2 + :3 ~4 分;3 + :5 ~6 分。

2 结 果

2.1 临床资料

7 例患者详细资料见表 1,其中:1)性别和年龄:7 例 MASC 病例,女性 2 例,男性 5 例。发病年龄 21 ~63 岁,中位年龄 44 岁;2)发病部位:腮腺 6 例,颌下腺 1 例;3)临床表现:7 例病例均为自行发现的肿大包块,其中 1 例为外院手术后复发,术后病理诊断不详。病程 2 周至 3 年不等,包块缓慢增大;4)治疗和预后:7 例病例中 2 例行肿块及同侧腺叶 + 颈淋巴结清扫并术后放疗,其中 1 例颈部 IV 区淋

巴结见肿瘤转移,5 例因术前或术中冰冻未明确性质,仅行肿块及同侧腺叶切除术,术后未遵照医嘱返院治疗。7 例病例,4 例获得随访资料,3 例失访,随访时间 8 ~43 个月,均无肿瘤复发。

表 1　7 例 MASC 临床资料

Table 1. Clinical Data of 7 Cases of MASC

Case	Sex	Age	Location	Size (cm)	Clinial presentation	Original diagnosis	Stage	Treatment	Follow up
1	M	63	Right Parotid	3.5 ×2.5	Painless nodule for 1 year	AciCC	T2N0M0	RP + ND + RT	NED (10)
2	F	53	Right sub-mandi-bular	3.0 ×3.0	Slow growing, painless nodule for 3 years	Acicc with lymph node metastasis in right IV area	T2N0M0	RP + ND + RT	NED (8)
3	M	63	Right Parotid	3.2 ×2.6	Painless nodule for 2 weeks	AciCC	T2N0MO	RP	NED (27)
4	F	29	Left Parotid	3.0 ×3.0	Painless nodule for 2 years	AciCC	T2NOM0	RP	Lost
5	M	44	Left Parotid	1.3 ×1.1	Painless nodule for 1 month	AciCC	T1NOM0	RP	NED (43)
6	M	43	Right Parotid	2.6 ×1.8	Painless nodule for 1 year and postoperative recurrence for 2 months	AciCC	T2N0M0	RP	Lost
7	M	21	Right Parotid	2.5 ×1.7	Painless nodule in 6 months	AciCC	T2N0M0	RP	Lost

AciCC: acinic cell cancinoma; ND: neck dissection; RP: radical parotidectomy; RT: radiotherapy; NED: no evidence of disease.

2.2　病理学检查

大体观察:7 例病例均为单发结节,结节直径 1.3 ~3.5cm,平均直径(2.77 ±1.33)cm,2 例结节界限清楚,5 例与周围涎腺分界不清,肿块切面多为灰白色,质地偏软或中等硬度。组织学形态如图 1 所示:镜下显示 2 例病例具有薄包膜,5 例向周围涎腺组织浸润性生长,肿瘤呈多结节状,结节被纤维组织分隔(图 1A),其中 1 例间质富于淋巴细胞(图 1B),肿瘤细胞排列成腺管状,微囊样及实性(图 1C),腺腔及微囊内可见嗜酸性分泌物,类似甲状腺滤泡(图 1D),其中 2 例具有乳头状结构,乳头内细胞呈鞋钉状突起(图 1E),肿瘤细胞呈圆形、卵圆形,细胞核圆,可见小核仁,胞浆嗜酸性或空亮,核分裂少见(图 1F)。

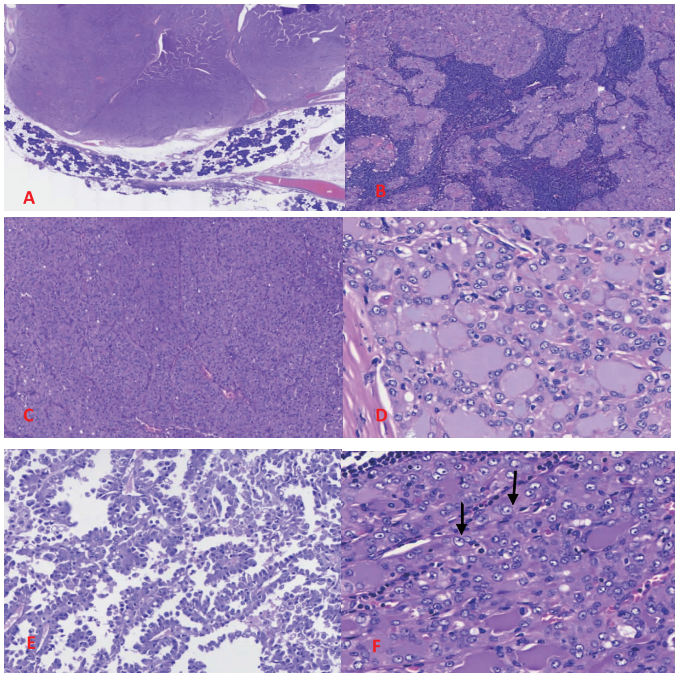

图 1　MASC 的组织学形态

Figure 1. Histopathology of MASC

A. All cases showed a mass divided by fibrous septa (40 ×); B. One case showed a background of abundant lymphocyte (200 ×); C. The tumors are composed of solid structures (200 ×); D. The tumors are composed of microcystic and tubular with abundant homogeneous secretion (200 ×); E. The tumors are composed of papillary structures (200 ×); F. The tumour cells have eosinophilic granular or vacuolated cytoplasm with small, uniform nuclei (400 ×).

2.3 免疫组化染色

7 例病例均弥漫强阳性表达 CK7(图 2A)、Vimetin(图 2B)、S-100(图 2C)及 Mammaglobin(图 2D),强弱不等地表达 GATA-3(图 2E),7 例均不表达 P63、DOG1(图 2F)及 CD117, Ki-67 增殖指数均较低(2%~15%)。详见表 2。

表 2 7 例 MASC 免疫组化结果

Table 2. Results of Immunohistochemical Study: 7 Cases of MASC

Case	Immunohistochemical marker								
	CK7	Vimentin	S-100	Mammaglobin	P63	GATA-3	DOG1	CD117	Ki-67
1	+ + +	+ + +	+ + +	+ + +	−	+	−	−	6%
2	+ + +	+ + +	+ + +	+ + +	−	+ +	−	−	2%
3	+ + +	+ + +	+ + +	+ + +	−	+ +	−	−	15%
4	+ + +	+ + +	+ + +	+ + +	−	+	−	−	10%
5	+ + +	+ + +	+ + +	+ + +	−	+ + +	−	−	10%
6	+ + +	+ + +	+ + +	+ + +	−	+ +	−	−	10%
7	+ + +	+ + +	+ + +	+ + +	−	+	−	−	8%

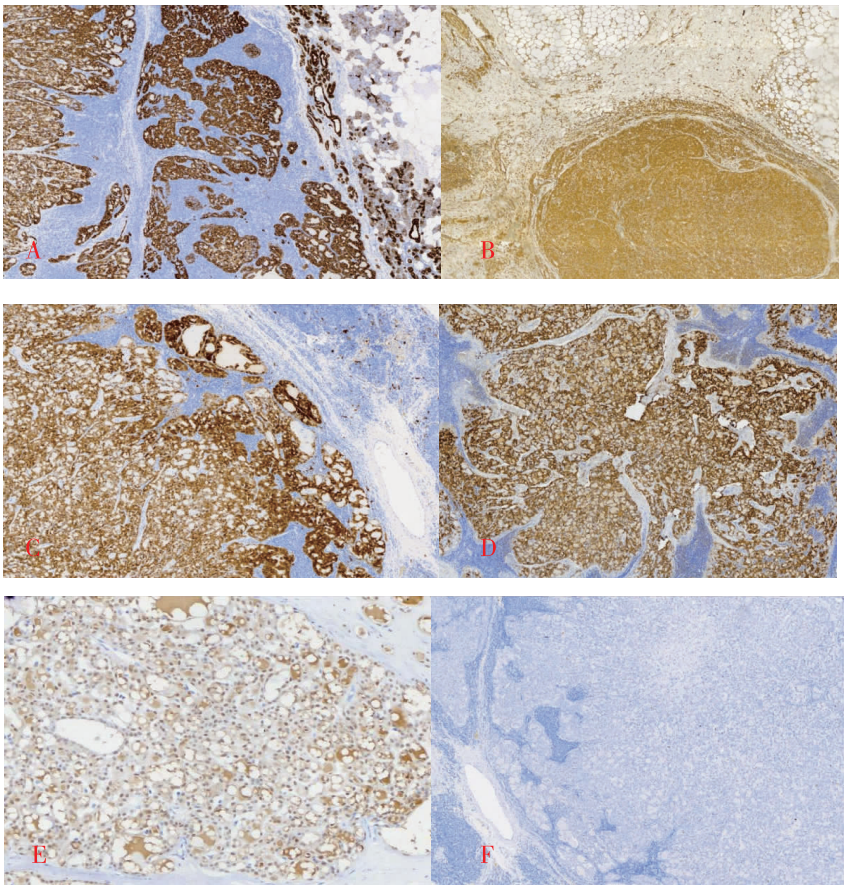

图 2 MASC 的免疫组织化学特征

Figure 2. Immunohistochemistry of MASC

A. Immunostaining for CK7 shows cytoplasmic positive results (100 ×). B. Immunostaining for Vimentin shows cytoplasmic positive results (100 ×). C. Immunostaining for S-100 shows strong, diffuse nuclear and cytoplasmic positive results (100 ×). D. Immunostaining for Mammaglobin shows cytoplasmic positive results (100 ×). E. Immunostaining for GATA-3 shows moderate nuclear positive results (200 ×). F. Immunostaining for DOG-1 shows negative results (100 ×).

3 讨 论

涎腺分泌性癌是新近命名的一种恶性涎腺型肿瘤,特征为存在 t(12;15)(p13;q25)特异性 *ETV6-NTRK3* 基因融合,在 2010 年由 Skálová 等首次报道[6]。他们发现了 16 例涎腺肿瘤具有与发生于乳

腺的分泌性癌一样的形态学特征，肿瘤呈分叶状生长方式，肿瘤细胞排列成微囊样和腺样，部分可呈实性及乳头状结构，腺腔及微囊内可见嗜酸性分泌物，细胞核卵圆形，异型性小，胞浆淡染或嗜伊红，核分裂及坏死少见；肿瘤细胞弥漫强阳性表达 CK7、CK8、CK18、S-100、Vimentin、EMA、STAT5、Mammaglobin，但是基底细胞/肌上皮细胞标记物 P63、calponin、CK14、SMA 和 CK5/6 不表达，Ki-67 阳性率不高（5% ~28%），并且 14 例病例中提取的 RNA 可满足 *ETV6-NTRK3* 融合基因转录分析，其中 13 例检测结果为阳性，具有 ETV6-NTRK3 融合转录。因此，他们认为这是一类有别于涎腺其他类型肿瘤的独立分类，将其命名为 MASC。随后，国内外多位学者对这类肿瘤进行了报道[6]，发现 MSAC 常发生于腮腺，少数可见于小涎腺[7]，男性多见，临床表现多为缓慢生长的肿物，病程 2 至 36 个月不等[8-9]。我们本组研究病例的中位年龄、性别比例、临床资料以及镜下表现及免疫组化表达特征均与文献报道一致。

在鉴别诊断中，最容易与 MASC 混淆的涎腺肿瘤为 AciCC[10]，并且目前研究报道的 MASC 大多都被诊断为 AciCC[11-12]。Connor 等[13]认为，S100、STAT5 和 Mamoglobin 是诊断 MASC 比较特异的标记物，而 CK7、CK8、CK18、CK19、GCDFP15 和 EMA 在涎腺的其他肿瘤中也会表达。MASC 的免疫表型特征证实了其来源与 AciCC 不同，前者来源于涎腺纹状管，而后者来源于腺泡细胞和润管。Bishop 等[14]认为，AciCC 具有明显的胞浆内颗粒，并且很少发生于腮腺以外的小涎腺，免疫组化能很好地区分两者，MASC 表达 Mammaglobin、S-100 和 Vimentin，不表达 DOG1，而 AciCC 表达刚好相反，两者的具体鉴别见表 3[15]。在我们的研究中，7 例 MASC 既往均被诊断为 AciCC，通过再次阅片，发现这 7 例病例肿瘤细胞胞浆均嗜酸性，胞浆内不能观察到酶原颗粒，由此可见并不符合 AciCC 的形态学特点，与文献报道一致，表达 Mammaglobin、S-100 及 Vimentin，不表达 DOG1 及 CD117。由于开展本研究时条件受限，未能获得适宜的标本，故未行基因检测。

表 3　AciCC 与 MASC 鉴别要点

Table 3. Clinicopathologic Differences between MASC and AciCC

Variable	AciCC	MASC
Site	95% present in parotid, minor salivary very rare	Both major and minor salivary
Sex distribution	Female predominance	Male predominance
Growth pattern	Composed of microcystic/solid, tubular, follicular, and papillary-cystic structures	Tubular and microcystic/solid predominant, follicular and papillary cystic common
Cell morphology	Acinar basophilic with granular PAS-positive cytoplasm	Eosinophilic granular or vacuolated cytoplasm
Cytoplasm	Zymogen granules present	No basophilic granularity in the cytoplasm, pale pink granular or acuolated cytoplasm.
Nuclei	Monomorphic	Uniform round and vesicular nuclei with central nucleoli and finely granular chromatin
Immunoprofile	S100 weak to negative, p63 and mammaglobin negative, DOG1 strong membranous and apical staining	S100, mammaglobin, GATA-3 positive, DOG1 and p63 negative
Molecular alteration	Unknown	t(12;15) ETV6-NTRK3 (95% ~98%); t(12;XX) ETV6-XX (2% ~5%)

MASC 大多数为低度恶性，生物学行为较惰性，但也可以局部复发和远处转移。据文献报道[16]，MASC 的无瘤生存时间从 71 至 115 个月不等，较 AciCC 短（92 至 148 个月），淋巴结转移率也比 AciCC 高。在本研究中，7 例病例 4 例获得随访资料，均无复发、死亡及远处转移。Connor 等[13]认为具有实性结构的 MSAC 比具有微囊结构的更具有侵袭性，少数高级别转化的病例可导致死亡[17]。在治疗方面，MASC 没有统一的治疗标准和特殊的治疗方法，和 AciCC 一样以手术切除为主，并进行术后放疗。据文献报道[18]，对于腮腺浅叶肿瘤及病理诊断为低级别的恶性肿瘤应行腮腺全切，腮腺全切是影响患者术后复发转移的独立因素。Drilon 等[19]报道了一例 MSAC 患者对酪氨酸激酶抑制剂恩曲替尼（Entritinib）治疗长期敏感；恩曲替尼主要针对携带 *NTRK*（*NTRK1*，*NTRK2* 和 *NTRK3*）、*ROS1* 或 *ALK* 基因融合的患者，但此患者最终因为 NTRK3 G623R 突变而耐药。

MASC 属于少见肿瘤，其全球发病率尚无文献报道。我们的研究中回顾了 117 例涎腺恶性肿瘤的病理切片，发现 MASC 占同期涎腺恶性肿瘤的 5.98%（7/117）。随着对其认识的深入，发病率可能会有所提高。由于这类肿瘤为新定义的肿瘤，并且易被误诊为 AciCC，故临床病理医生应在日常工

作中提高警惕加强对这类肿瘤诊断要点及鉴别诊断的认识,避免误诊及漏诊。

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