

doi: 10.3978/j.issn.2095-6959.2018.04.029

View this article at: <http://dx.doi.org/10.3978/j.issn.2095-6959.2018.04.029>

鼻咽部低级别乳头状腺癌诊断与治疗的研究进展

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[摘要] 鼻咽部低级别乳头状腺癌(low-grade nasopharyngeal papillary adenocarcinoma, LGNPPA)是发生在鼻咽部的十分罕见的以乳头状结构为主的低级别腺癌, 其病因不明。镜下肿瘤细胞呈乳头状及腺样结构排列, 免疫组织化学甲状腺转录因子-1(thyroid transcription factor-1, TTF-1; 也称甲状腺特异增强子结合蛋白)呈弥漫强阳性表达, 易与转移性乳头状癌等混淆, 因其惰性的生物学行为, 手术完整切除可治愈, 预后良好。本文将对LGNPPA的临床病理表现、诊断与鉴别诊断、发病机制及对该病的最新诊治共识进行阐述, 以提高对该病的认识。

[关键词] 鼻咽部低级别乳头状腺癌; 甲状腺转录因子-1; 诊断; 鉴别诊断; 治疗

Research progress in the diagnosis and treatment of low-grade nasopharyngeal papillary adenocarcinoma

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Abstract Low-grade nasopharyngeal papillary adenocarcinoma (LGNPPA) is very rare low-grade adenocarcinoma occurring in the nasopharynx and the main manifestation is papillary structure. The etiology is unclear. Microscopic tumor cells manifest as papillary and adenoid-like structure. Immunohistochemically, thyroid transcription factor-1 (TTF-1) was diffusely strong positive, which makes it easily confused with metastatic papillary carcinoma. Because of its inert biological behavior, complete surgical resection can be cured and the prognosis is good. This article will review clinical and pathological findings, diagnosis and differential diagnosis, pathogenesis and the latest consensus on diagnosis and treatment of LGNPPA, in order to raise awareness of the disease.

Keywords low-grade nasopharyngeal papillary adenocarcinoma; thyroid transcription factor-1; diagnosis; differential diagnosis; treatment

收稿日期 (Date of reception): 2018-01-24

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基金项目 (Foundation item): 国家自然科学基金青年科学基金 (81202092); 山东省重点研发计划项目 (2015GSF118015)。This work was supported by the National Natural Science Foundation Youth Science Fund Project (81202092) and the Shandong Province Key Research and Development Projects (2015GSF118015), China.

鼻咽部原发性腺癌约占鼻咽部恶性肿瘤的0.5%^[1],可分为普通型(又分为低度恶性和高度恶性)和涎腺型(包括腺样囊性癌、黏液表皮样癌等)两型,其中鼻咽部低级别乳头状腺癌(low-grade nasopharyngeal papillary adenocarcinoma, LGNPPA)属低度恶性普通型原发性腺癌的一种特殊类型。1988年Wenig等^[2]首次报道9例LGNPPA。随后2005年Carrizo等^[3]报道2例甲状腺转录因子-1(thyroid transcription factor 1, TTF-1;也称甲状腺特异增强子结合蛋白)阳性而甲状腺球蛋白(thyroglobulin, TG)阴性的LGNPPA,因其具有甲状腺乳头状癌的形态学特点(如乳头状结构、毛玻璃核、砂粒体及核沟等),将其命名为鼻咽部甲状腺样低级别乳头状腺癌(thyroid-like low-grade nasopharyngeal papillary adenocarcinoma, TL-LGNPPA)。2017年WHO^[4]在头颈部肿瘤分类中将鼻咽部乳头状腺癌定义为发生在鼻咽部的以乳头状结构为主的低级别腺癌,其同义词为鼻咽部甲状腺样LGNPPA。目前文献共报道42例^[3,5-27],其中英文文献报道26例^[3,5-17],中文报道16例^[18-27]。鉴于文献中多为个案报道,临床和病理医生尚缺乏对本病的认识,本文现对LGNPPA的诊治进展作一综述,以总结临床经验,减少误诊、误治率。

1 LGNPPA 的临床特点

LGNPPA是一种发生于鼻咽部的十分罕见的低度恶性上皮性肿瘤,属鼻咽部原发性腺癌的普通型。据文献^[3,5-27]报道:LGNPPA发病年龄9~68岁,平均年龄38岁,中位年龄36岁,其中男25例,女17例,男女比约为3:2;LGNPPA可发生在鼻咽部的任何部位,但以鼻咽的顶部后壁(18例,43%)最多见,其次可见于右侧壁(10例,24%)及鼻中隔后缘(7例,16%),其余病例未注明鼻咽部的具体部位;临床症状以鼻塞(16例,38%)和鼻出血(12例,29%)多见,其次可表现为鼻咽异物感(5例)和咽痛(3例),偶见头痛(2例)、不明原因发热(1例)及浆液性中耳炎(1例),其余2例为偶然发现,未见不适。此外,有研究^[28]报道1例LGNPPA伴有Turner综合征。由于该病病程从几周到几年不等,因此需借助内窥镜活检明确诊断。

2 LGNPPA 的病理学特点

肉眼观:肿瘤外观呈乳头状、息肉状或菜花状,部分带蒂,直径为0.5~4.0(平均2.5)cm,质软

或触之有砂砾感,部分易碎。肿瘤组织无或被覆部分包膜,部分呈侵袭性生长,常浸润周围组织。

镜下观:肿瘤细胞呈乳头状及腺样结构排列,乳头拥挤,呈微小的树枝状分支,间质为纤维血管轴心,部分伴显著玻璃样变性。部分乳头被挤压呈腺管样结构,腺管不规则,呈囊状或管状,部分区域呈背靠背或筛状结构。瘤细胞呈单层或假复层柱状被覆于乳头的表面,排列紧密,形态一致,相对温和,细胞核呈圆形或卵圆形,核仁小而不明显,可见核沟;细胞质少,呈嗜酸性,无核分裂象。可见坏死,乳头的纤维血管轴心内可见砂砾体,无血管、淋巴及神经浸润,大部分病例可见到肿瘤细胞与鼻咽部被覆的正常上皮相移行^[13,23,25]。肿瘤部分区域可见与乳头结构相移行的梭形片状区域以及腺管状结构^[25]。此外,约1/3的病例可见钙化^[4]。少数病例可伴有鳞化^[5,22]。

免疫组织化学染色对LGNPPA的诊断起重要作用。文献^[3,5-27]报道的所有病例肿瘤细胞TTF-1均呈弥漫强阳性表达,是诊断LGNPPA的有价值指标,但并非特异性指标。TTF-1属NKX2家族,选择性表达于胚胎发育过程中的甲状腺、肺和部分脑组织。研究^[29-31]显示:TTF-1除在肺和甲状腺来源的肿瘤中表达外,在肺外小细胞肿瘤、子宫内膜腺癌、胃肠癌及卵巢癌中也可呈阳性表达,其具体的表达机制和意义尚不清楚。此外,肿瘤细胞还可表达广谱细胞角蛋白pan(cytokeratin, CKpan),细胞角蛋白7(cytokeratin 7, CK7),细胞角蛋白19(cytokeratin 19, CK19),上皮膜抗原(epithelial membrane antigen, EMA),波形蛋白(vimentin),支持肿瘤起源于被覆上皮,部分病例CD117和P63呈弱阳性表达^[21-22];所有病例不表达可溶性蛋白-100(soluble protein-100, S100),细胞角蛋白5/6(cytokeratin 5/6, CK5/6),细胞角蛋白20(cytokeratin 20, CK20),钙调蛋白,抗平滑肌抗体(anti-smooth muscle antibody, SMA),胶质纤维酸性蛋白(glial fibrillary acidic protein, GFAP),结蛋白(desmin),提示肿瘤非肌上皮起源。绝大部分病例TG呈阴性,是其与甲状腺乳头状癌的鉴别诊断标志物之一。但Ozer等^[13]报道1例局灶TG阳性的病例,推测LGNPPA与甲状腺乳头状癌或许有相似之处,可能起源于异位或鼻咽部残存的甲状腺组织。所有病例Ki-67增殖指数均<5%,与其低度恶性的生物学行为相符。

特殊染色瘤细胞胞质内可见耐淀粉酶的PAS染色阳性物质,部分区域管腔和胞质可见灶状黏蛋白染色阳性的物质。

3 鉴别诊断

3.1 转移性甲状腺乳头状癌

LGNPPA与转移性甲状腺乳头状癌在形态学上十分相似,可出现甲状腺乳头状癌常见的细胞核特征,如毛玻璃核、核沟和核内包涵体,免疫表型TTF-1阳性更易使得二者混淆。但前者临床及影像学检查甲状腺无异常,镜下可见肿瘤细胞与周围正常上皮的过渡,免疫表型TG呈阴性。此外甲状腺乳头状癌CD15呈阳性表达,而LGNPPA CD15为阴性,有助于鉴别两者^[32]。必要时可行BRAF^{V600E}基因突变检测,甲状腺乳头状癌为阳性,LGNPPA常为阴性。

3.2 转移性腺癌

鼻咽部转移性腺癌较为罕见,肺、乳腺等部位的腺癌可转移到鼻咽部,尤其在腺癌呈乳头状生长时易与LGNPPA混淆。转移性肺腺癌患者年龄较大,有原发癌病史,影像学可见肺占位性肿块,瘤细胞异型性明显。转移性乳腺癌罕见,雌激素受体(estrogen receptor, ER),孕激素受体(progesterone receptor, PR)及人类表皮生长因子受体2(human epidermal growth factor receptor-2, HER2)等免疫表型阳性。

3.3 双相性滑膜肉瘤

部分研究^[15-16]报道:LGNPPA可伴有不同程度的梭形细胞成分,应与双相性滑膜肉瘤相鉴别。温和的细胞核、缺少核分裂及梭形细胞区细胞角蛋白(cytokeratin, CK)弥漫强阳性表达等特征在滑膜肉瘤中极其罕见,另外滑膜肉瘤B淋巴细胞瘤-2(B-cell lymphoma-2, BCL-2), CD99可呈阳性表达, TTF-1阴性有助于鉴别。

3.4 乳头状肠型腺癌

乳头状肠型腺癌主要发生在鼻腔或鼻窦,可延伸至鼻咽部,与暴露于木材粉尘等相关职业有关^[33]。乳头状肠型腺癌被覆高柱状杯状细胞和潘氏细胞,可见乳头状、腺管状、实性片状结构,乳头中还可可见分泌生长激素抑制素、胃泌素的散在内分泌细胞,并见充满黏液及扩张的腺腔,形成黏液湖,细胞异型性大,核分裂象易见,可伴局灶坏死。免疫组织化学染色CK20, CDX2和

MUC2呈阳性表达,一般不难鉴别。

3.5 鼻咽部多形性低度恶性腺癌

该肿瘤形态单一,核大小一致,但结构多样,可呈乳头状、实性巢状、筛孔状,也可见含有乳头的囊腔结构,肿瘤由腺上皮和肌上皮组成,与周围表面上皮无过渡,淋巴结转移常见。免疫标记肿瘤细胞表达CK, EMA, CEA, S100蛋白, SMA, Vimentin, 不表达P63。虽与LGNPPA在形态学和免疫表型方面均有部分重叠,但LGNPPA表达TTF-1, 不表达S100蛋白和SMA,可资鉴别。

4 LGNPPA 病因学及其发病机制

LGNPPA病因学尚不明确,无证据表明该病与吸烟或饮酒有关^[2]。鼻咽部恶性肿瘤大部分为上皮来源的或不伴角化的鳞状细胞癌,并与EB病毒(Epstein-Barr virus, EBV)相关。因此多项研究^[6,16,23,34]运用原位杂交和聚合酶链式反应(polymerase chain reaction, PCR)方法对LGNPPA肿瘤细胞中的EBV进行检测,结果均未发现EBV感染证据。Wu等^[34]应用PCR法检测肿瘤细胞的人乳头状瘤病毒(human papillomavirus, HPV),结果也为阴性。推测LGNPPA的发生可能与EBV, HPV感染无关。

因LGNPPA的组织学和免疫表型与甲状腺乳头状癌和肺的腺癌相似, Oide等^[5]利用PCR和荧光原位杂交(fluorescence in situ hybridization, FISH)检测BRAF, RAS, EGFR及ALK, 均未发现相关基因的突变,从分子层面上揭示LGNPPA与甲状腺乳头状癌无相关性。杜维等^[20]利用PCR检测BRAF基因1799位点15外显子(BRAF^{V600E})无突变; FISH检测t(X; 18)未见SYT-SSX1/SSX2融合。Pettersson等^[15]报道1例位于鼻中隔后端、伴有梭形细胞成分的LGNPPA, 并进行BRAF基因1799位点基因突变检测,结果为阴性,从基因水平进一步证明与甲状腺乳头状癌无相关性。但武迪等^[19]利用突变扩增系统(amplification refractory mutation system, ARMS)技术对3例LGNPPA行BRAF^{V600E}基因突变检测,其中1例为阳性,提示LGNPPA的发病机制可能与甲状腺乳头状癌有相似之处。因例数甚少,LGNPPA的发病机制仍有待进行更多病例的分子遗传学研究明确。

5 治疗与预后

LGNPPA具有惰性的生物学行为, 手术完整切除可治愈, 无潜在转移性, 预后良好。文献[3,5-27]报道的42例中, 获随访资料者39例, 失访3例, 随访时间最短为1个月, 最长达15年^[3], 均未见复发及转移。除Wenig等^[2]报道的3例手术后进行放疗之外, 其余均采用单纯手术切除, 未行其他术后辅助治疗。研究^[3,16,35]显示: 对于体积较小者可用内窥镜切除手术治疗, 较大且无法完全切除者, 行辅助放疗可预防复发。

6 结语

LGNPPA惰性的生物学行为和良好的预后对其与转移性乳头状癌等恶性肿瘤的鉴别诊断起重要作用, 可避免临床过度治疗, 提高患者生存质量。因目前报道的LGNPPA病例数有限, 未来仍需收集更多的病例并进行长期随访, 以进一步观察其生物学行为。

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本文引用: 吕蓓蓓, 徐嘉雯, 李加美, 王宏量. 鼻咽部低级别乳头状腺癌诊断与治疗的研究进展[J]. 临床与病理杂志, 2018, 38(4): 862-866. doi: 10.3978/j.issn.2095-6959.2018.04.029

Cite this article as: LÜ Beibei, XU Jiawen, LI Jiamei, WANG Hongliang. Research progress in the diagnosis and treatment of low-grade nasopharyngeal papillary adenocarcinoma[J]. Journal of Clinical and Pathological Research, 2018, 38(4): 862-866. doi: 10.3978/j.issn.2095-6959.2018.04.029