

乳腺分泌性癌 15 例临床病理特征及预后分析

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摘要: [目的] 探讨乳腺分泌性癌的临床病理特征、免疫组织化学表达特点及临床预后。[方法] 分析 15 例乳腺分泌性癌的临床表现及病理特征;采用 PAS、D-PAS 及阿辛蓝染色技术进行细胞分泌物染色,免疫组织化学检测 ER、PR、c-erbB-2、Ki-67、p53、EGFR 和 CK5/6 在肿瘤细胞中的表达,并对 11 例患者进行随访。[结果] 乳腺分泌性癌平均年龄 49 岁,女性患者占 93.3%。病理形态学主要特点为癌细胞异型性较小,出现微囊性结构,癌细胞能产生大量分泌物等,对 PAS/AB 及黏液卡红染色呈现阳性反应。20%患者伴有同侧腋窝淋巴结转移。中位随访 38.5 个月,未发现肿瘤复发转移和死亡病例。[结论] 乳腺分泌性癌为一种罕见的肿瘤,具有明显的组织病理学特征,预后良好。

关键词: 乳腺肿瘤;分泌性癌;临床病理特征;免疫组织化学;预后

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Clinicopathologic Feature and Prognostic Analysis of 15 Cases with Secretory Breast Carcinoma

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Abstract: [Purpose] To analyze the clinicopathological features and prognosis of patients with secretory breast carcinoma (SBC). [Methods] Clinical data and pathological characteristics of 15 patients with breast secretory carcinoma were collected and analyzed. Special staining of mucin carmine (MC), periodic acid-Schiff reaction (PAS) with and without diastase pretreatment and Alcian blue (AB), immunohistochemical staining (ABC method) of ER, PR, c-erbB-2, Ki-67, p53, EGFR and CK5/6 were performed. Eleven patients were followed up after various treatment. [Results] The average age of SBC patients was 49 years, and 14 were women (93.3%). The histopathological characteristics were mild atypia in carcinoma cells, prominent microcystic architecture and large amount of secretion in the cytoplasm and cysts positive for PAS/AB and MC staining. Ipsilateral axillary lymph node metastasis was found in 20% of patients. The median follow-up was 38.5 months, and no tumor recurrence, metastasis or death was observed. [Conclusion] SBC is a rare tumor with typical histopathological features and a favorable prognosis.

Subject words: breast neoplasms; secretory carcinoma; clinicopathologic feature; immunohistochemistry; prognosis

乳腺分泌性癌(secretory breast carcinoma, SBC)是非常少见的乳腺恶性上皮性肿瘤。Mcdivit 和 Stewart 首次报道的病例均为青少年,将其命名为幼年性乳癌^[1]。后来大多数病例报道发生于成人,故根据病理特征更名为分泌性乳腺癌。本文总结分析了

15 例 SBC 临床病理特征并结合文献复习,希望能为此型乳腺癌提供临床参考。

1 临床资料

1.1 一般资料

收集浙江省肿瘤医院和江苏省肿瘤医院 2004 年至 2016 年收治的 15 例乳腺分泌性癌的手术切除标本。15 例患者,男性 1 例,女性 14 例,年龄 15~82

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岁,中位年龄 49 岁。临床上均表现为无痛性肿物。病程从 3 天到 5 年不等。肿块局部切除 1 例,全乳切除 10 例,保乳术 4 例。20% 患者伴有腋窝淋巴结转移。截止至 2017 年 1 月 1 日,11 例患者获得随访,随访时间 4~70 个月,中位随访时间 38.5 个月,未发现肿瘤复发转移和死亡病例。

1.2 免疫组化方法

手术标本均经 10% 中性福尔马林固定、石蜡包埋及常规 HE 染色,免疫组化采用 EnVision 法,抗体 ER、PR、Ki-67、p53、Her-2、CK5/6、EGFR 及组织化学 PAS、AB-PAS 试剂购自 DAKO 及罗氏公司。

1.3 病理检查

肉眼观:肿物一般境界清楚,质地硬,无包膜。切面灰白色,如分泌物较多时可呈灰黄色,可在切面上

见暗黄色分泌物。

镜检:肿瘤细胞呈微囊状及管状排列,腔内有嗜酸性分泌物像甲状腺胶质,其中 5 例局部可见乳头状结构。肿瘤细胞异型性小,细胞核圆形或卵圆形,核分裂象少见,胞质嗜酸性或空泡状。间质广泛纤维化透明变性。无坏死和无神经或血管侵犯。肿瘤细胞异型性不明显,大致有两种类型,从而使肿瘤中出现不同的组织结构。(1)A 型细胞:即胞质内为均质性嗜酸性分泌物,由于分泌物量不同,致使癌细胞体积相差悬殊,较大的细胞酷似甲状腺滤泡,整个胞质充满分泌物,核被推向一侧,胞核较小,大小一致,规则,无明显异型性,常有清楚核仁,核分裂象罕见。(2)B 型细胞:肿瘤细胞胞质透明呈空泡状,细胞多呈圆形或多边形,核多居中,较 A 型细胞异型性明

显,偶见核分裂象,此型细胞主要形成实体巢状结构。间质广泛纤维化透明变性,有时可形成面积较大的硬化瘢痕(Figure 1)。

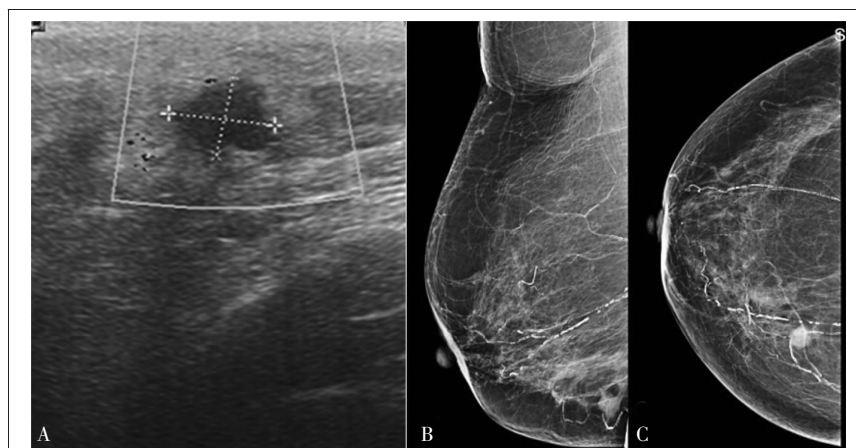
特殊染色:本组病例均有典型的组织学表现(Figure 2),均可见实性的巢片状、微囊状及囊泡状结构,部分区域可见与甲状腺滤泡相似的大空腔,腔内含嗜酸性分泌物,部分区域可见吸收空泡,部分区域浓缩呈小球状;肿瘤细胞异型性不明显;间质广泛纤维化透明变性(Figure 2D)。分泌物 PAS 及 AB-PAS 染色均呈阳性(Figure 2E)。

1.4 免疫表型

2009 年之前的病例缺少 Ki67、CK5/6 和 EGFR 检测,15 例患者中 14 例 ER、PR 阴性,Her-2 全部阴性,p53 大多阴性或仅局灶表达,Ki-67 弱表达,均未超过 10%,CK5/6 和 EGFR 绝大多数呈阳性(Figure 2F)。

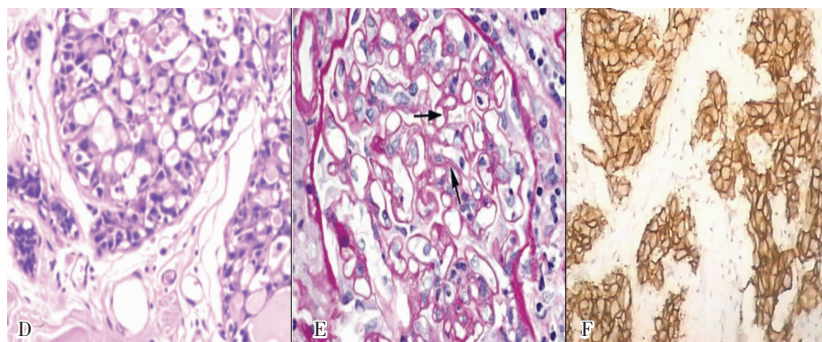
2 讨论

分泌性乳腺癌是一种罕见的,具有惰性的乳腺肿瘤。最初认为其



A: Breast ultrasound; a right breast hypoechoic nodule with irregular shape and unclear boundary, which blood flow signal is not obvious. B and C: Breast mammography; a nodule in the lower-inner quadrant of the right breast with regular shape and clear border.

Figure 1 Imaging findings of a breast secretory carcinoma



D: Eosinophilic secretions were seen, with absorption vacuoles in some areas and extensive fibrosis and hyaline degeneration in the stroma. E: The tumor cell secretion PSA was positive, PAS staining. F: Tumor cells C/K56 was positive.

Figure 2 The typical histopathologic features of breast secretory carcinoma (x400)

仅发生于青少年患者,后发现任何年龄段均可发病,有文献报道最小年龄3岁,最大年龄87岁^[2-3],儿童乳腺癌大多为SBC^[4]。大多数研究病例为年轻女性^[5],然而,Horowitz等^[2]报道的来自SEER数据库83例分泌性乳腺癌患者中位年龄为53岁。男性分泌性癌的发病年龄较早,中位年龄17岁^[6]。国内报道的分泌性癌患者年龄明显高于国外报道,提示可能存在人种差异。本研究15例患者平均年龄为49岁,与SEER数据库登记的患者年龄分布相似,以中年患者为主。

一般情况下,分泌性乳腺癌表现为乳房肿块,多位于乳晕周围,尤其是在男性和儿童患者,可单发或多发,也有血性乳头溢液伴或不伴有明显肿块。肿瘤生长缓慢,就诊时常已是发病很久,多因乳腺肿块而就诊。影像学上,分泌性乳腺癌多与良性病变相似,可呈类圆形或分叶状低回声或等回声肿块,与周围界限清楚^[7]。目前分泌性乳腺癌没有一个特定的影像学模式。临床疑似SBC,必须结合组织病理和免疫组织化学才能明确诊断^[8]。

分泌性乳腺癌细胞呈圆形或多边形,有双染或空泡状的细胞质,细胞核小,无明显异型,核分裂象罕见。细胞内和细胞外特征性分泌物表现为PAS及淀粉酶消化后PAS(D-PAS)或阿辛蓝染色均阳性。ER、PR通常阴性或仅有部分弱表达,提示该肿瘤多为非激素依赖性,Hre-2阴性或低表达,所以大多被归为三阴性乳腺癌,而CK5/6和EGFR通常阳性^[9-10]。增殖指数Ki67一般较低,提示分泌性癌是一种惰性肿瘤。90%以上SBC表达ETV6-NTRK3基因融合,其嵌合产物被认为是致癌蛋白的驱动因子^[11]。也有激素受体阳性分泌性癌的报道^[12]。本研究结果与上述报道基本一致。然而,Jacob等^[13]对来自美国国家癌症数据库中246例SBC回顾性分析发现,患者大多激素受体阳性。

因报道的SBC病例数量有限,还没有关于分泌性乳腺癌患者最佳治疗策略的共识。目前,手术切除是主要的治疗手段^[14]。Richard等^[15]认为年龄大于20岁且肿瘤直径大于2cm的患者,采用改良根治术其预后更好,建议行前哨淋巴结活检或腋窝淋巴结清扫来评估淋巴结状态^[6,16]。分泌性乳腺癌全身转移非常罕见,对化疗不敏感^[17]。辅助化疗和辅助放射治疗主要用于淋巴结阳性的患者,可改善患者的长期

生存^[2]。由于大多数分泌性肿瘤激素受体阴性,因此尚无内分泌治疗疗效的分析报道。本研究15例患者中,3例出现同侧腋窝淋巴结转移,占15%,2例出现3枚以上淋巴结转移,10例行改良根治手术,4例行保乳手术,1例行肿瘤局部切除术,3例行SLNB。淋巴结转移病例均行了术后辅助化疗及辅助放疗。

该肿瘤被认为是一种惰性疾病,10年疾病特异性生存率达90%以上^[2]。儿童和青少年SBC患者预后较好,成人相对较差。发病年龄<20岁、直径<2cm且边界清楚的SBC患者预后较好^[18]。青春期前SBC复发多出现在初次手术后20年,肿瘤复发常发生在术后15年^[19]。腋窝转移非常少见,尤其是肿瘤<2cm^[5]。3枚以上淋巴结转移预示存在远处转移风险和预后不良^[14]。也有SBC远处转移的报道,如Lian等^[20]报道了1例SBC肝转移。本研究中11例患者获得随访,中位随访时间38.5个月,均未发现肿瘤复发转移和死亡病例,可见SBC预后很好。尽管SBC侵袭性低,生长缓慢,仍不乏有复发及转移的病例报道,甚至术后20年出现转移。所以必须长期随访,如出现复发转移,及时给予积极治疗。

分泌性乳腺癌是一种非常罕见的疾病,具有较为独特的病理学特征。目前还没有最佳的治疗共识,治疗策略应根据患者的总体状况和疾病特征进行选择。

参考文献:

- [1] McDivitt RW, Stewart FW. Breast carcinoma in children [J]. JAMA, 1966, 195(5):388-390.
- [2] Horowitz DP, Sharma CS, Connolly E, et al. Secretory carcinoma of the breast: results from the survival, epidemiology and end results database [J]. Breast, 2012, 21(3):350-353.
- [3] Noh WC, Paik NS, Cho KJ, et al. Breast mass in a 3-year-old girl: differentiation of secretory carcinoma versus abnormal thelarche by fine needle aspiration biopsy [J]. Surgery, 2005, 137(1): 109-110.
- [4] Ghilli M, Mariniello MD, Scatena C, et al. Male secretory breast cancer: case in a 6-year-old boy with a peculiar gene duplication and review of the literature [J]. Breast Cancer Res Treat, 2018, 170(3):445-454.
- [5] Vasudev P, Onuma K. Secretory breast carcinoma: unique, triple-negative carcinoma with a favorable prognosis and characteristic molecular expression [J]. Arch Pathol Lab Med, 2011, 135(12):1606-1610.
- [6] Cadoo KA, McArdle O, O'Shea AM, et al. Management of

- unusual histological types of breast cancer[J]. *Oncologist*, 2012, 17(9):1135–1145.
- [7] Paeng MH, Choi HY, Sung SH, et al. Secretory carcinoma of the breast[J]. *J Clin Ultrasound*, 2003, 31(8):425–429.
 - [8] Benabu JC, Stoll F, Koch A, et al. De-escalating systemic therapy in triple negative breast cancer: the example of secretory carcinoma[J]. *J Gynecol Obstet Hum Reprod*, 2018, 47 (4):163–165.
 - [9] Lambros MB, Tan DS, Jones RL, et al. Genomic profile of a secretory breast cancer with an ETV6-NTRK3 duplication[J]. *J Clin Pathol*, 2009, 62(7):604–612.
 - [10] Liu XL, Chen H, Wang Q, et al. Secretory carcinoma of the breast: clinical histopathologic and biological behaviors[J]. *Zhonghua Yi Xue Za Zhi*, 2018, 98(30):2434–2437.
 - [11] Landman Y, Ilouze M, Neiman V, et al. Rapid response to larotrectinib (LOXO-101) in an adult chemotherapy-naïve patients with advanced triple-negative secretory breast cancer expressing ETV6-NTRK3 fusion[J]. *Clin Breast Cancer*, 2018, 18 (3):267–270.
 - [12] Sato T, Iwasaki A, Iwama T, et al. A rare case of extensive ductal carcinoma in situ of the breast with secretory features[J]. *Rare Tumors*, 2012, 4(4):e52.
 - [13] Jacob JD, Hodge C, Franko J, et al. Rare breast cancer: 246 invasive secretory carcinomas from the National Cancer Data Base[J]. *J Surg Oncol*, 2016, 113(7):721–725.
 - [14] Lombardi A, Maggi S, Bersigotti L, et al. Secretory breast cancer: case report[J]. *G Chir*, 2013, 34(4):125–127.
 - [15] Richard G, Hawk JC, Baker AS, et al. Multicentric adult secretory breast carcinoma: DNA flow cytometric findings, prognostic features, and review of the world literature (review)[J]. *J Surg Oncol*, 1990, 44(4):238–244.
 - [16] Pohlodek K, Mečiarová I, Grossmann P, et al. Secretory carcinoma of the breast: a case report[J]. *Int J Surg Case Rep*, 2019, 56:74–77.
 - [17] Herz H, Cooke B, Goldstein D. Metastatic secretory breast cancer. non- responsiveness to chemotherapy: case report and review of the literature [J]. *Ann Oncol*, 2000, 11(10):1343–1347.
 - [18] Din NU, Idrees R, Fatima S, et al. Secretory carcinoma of breast: clinicopathologic study of 8 cases[J]. *Ann Diagn Pathol*, 2013, 17(1):54–57.
 - [19] Sharma V, Anuragi G, Singh S, et al. Secretory carcinoma of the breast: report of two cases and review of the literature[J]. *Case Rep Oncol Med*, 2015, 2015:581892.
 - [20] Lian J, Wang XJ, Xu EW, et al. Secretory breast carcinoma with liver metastatic: report of a case [J]. *Zhonghua Bing Li Xue Za Zhi*, 2017, 46(2):124–125.