

doi: 10.3978/j.issn.2095-6959.2019.10.034

View this article at: <http://dx.doi.org/10.3978/j.issn.2095-6959.2019.10.034>

· 临床病例讨论 ·

## 乳腺原发性腺泡细胞癌的临床病理观察及文献复习

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**[摘要]** 探讨乳腺原发性腺泡细胞癌(acinic cell carcinoma, ACCA)的临床病理学特点、免疫表型、特殊染色特征及鉴别诊断。应用HE、免疫组织化学和特殊染色对1例乳腺原发性ACCA进行分析, 并复习相关文献。患者女, 41岁, 因左乳肿块就诊。镜下见肿瘤组织形态多样, 呈巢片状、腺泡状、小管状或微腺样等结构, 在周围的纤维脂肪组织中浸润性生长。巢片状分布的肿瘤组织中癌细胞有明显的异型性和高分裂活性, 细胞核级较高, 胞质呈粗颗粒状, 嗜碱性; 而呈腺泡状分化较好的肿瘤组织中癌细胞形态温和, 胞质为均一的细颗粒状, 较空亮。微腺样结构区域可见腔内的嗜酸性胶样分泌物, 类似于微腺型腺病。免疫组织化学显示: S-100, CK7, EMA均阳性, ER, PR, HER-2及肌上皮标志物CK5/6, p63, Calponin均阴性。PAS染色呈阳性。乳腺ACCA十分少见, 与涎腺的ACCA极其相似, 与三阴性非特殊类型的乳腺浸润性癌相比, 有比较好的预后, 但其组织学发生仍需要进一步的研究来阐明, 为更好的治疗方式提供策略。

**[关键词]** 乳腺癌; 腺泡细胞癌; 临床病理特征

## Clinicopathological observation and literature review of primary acinic cell carcinoma in breast

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**Abstract** To investigate the clinicopathological features, immunophenotype, special staining features and differential diagnosis of primary acinic cell carcinoma (ACCA) of the breast, a case of primary ACCA of the breast was analyzed by HE, immunohistochemistry and special staining, and the related literature was reviewed. The patient, a 41-year-old female, was treated for a mass in her left breast. Microscopically, the tumors had various morphologies, such as nest-like, alveolar, tubular or microadenoid structures, and infiltrated into the surrounding fibrous and adipose tissues. Tumor cells with nest-like patches had obvious atypia and high mitotic activity, with higher nuclear grade, coarse granular cytoplasm and basophilic cytoplasm, while those with better alveolar differentiation had

收稿日期 (Date of reception): 2019-01-24

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基金项目 (Foundation item): 武汉市科技计划项目 (2017060201010172)。This work was supported by the Science and Technology Planning Project of Wuhan, China (2017060201010172).

mild morphology and homogeneous granular cytoplasm. The eosinophilic colloidal secretions in the cavity can be seen in the area of microadenoid structure, which is similar to microadenopathy. Immunohistochemistry showed that S-100, CK7 and EMA were positive, while ER, PR, HER-2 and myoepithelial markers, such as CK5/6, p63 and Calponin were negative. PAS staining was positive. ACCA of the breast is very rare. It is very similar to ACCA of the salivary gland. Compared with triple negative invasive breast cancer, it has a better prognosis, but its histogenesis still needs further study to clarify and provide strategies for better treatment.

**Keywords** breast carcinoma; acinic cell carcinoma; clinicopathological features

乳腺与涎腺组织有着组织学和胚胎学上的相似性,腺泡细胞癌(acinic cell carcinoma, ACCA)是涎腺特有的一种肿瘤,同时也罕见发生于乳腺<sup>[1]</sup>。国外报道的乳腺ACCA仅几十例<sup>[2-27]</sup>,国内报道的病例较少<sup>[28-31]</sup>。本文报道了近期于武汉大学人民医院诊断的1例原发于乳腺的ACCA,通过文献回顾,对这种罕见乳腺癌的临床病理及免疫组织化学特征进行分析总结。

## 1 临床资料

患者,女,41岁,2个月前发现左乳肿块,无皮肤改变,无疼痛,患者未予以重视。2周前于外院行B超检查,示左乳2点钟方向距乳头6 cm可见大小为1.4 cm×1.3 cm低回声区,内可见强回声斑,边界尚可,提示左乳低回声病灶(BI-RADS 4a级),入院后行MRI(图1A),见左侧乳腺外上象限片状长T1、稍长T2信号,病灶范围约5.6 cm×2.3 cm×2.1 cm,动态增强扫描示病灶呈“速升-平台”型,内可见一结节状长T1、长T2信号,大小约1.1 cm×0.9 cm,动态增强扫描无强化,考虑为肿瘤性病变,乳腺癌可能性大。

手术切除标本经4%中性甲醛固定,常规脱水,石蜡包埋,4 μm厚切片,HE染色,光镜下观察。免疫组织化学采用EnVision法进行染色,所用抗体ER, PR, HER-2和AR购于美国Ventana公司;CK7, EMA, S-100, CK5/6, p63, Ki-67, Calponin和GCDFP-15购于丹麦DAKO公司,操作步骤和抗原修复按说明进行。

肉眼观见左乳肿物:脂肪样组织1块,大小

9.5 cm×7.0 cm×2.5 cm,书页状切开,切面可见一大小5.5 cm×3.5 cm×2.0 cm的灰白肿物,与周围组织界限不清,切面灰白,质中。左腋窝淋巴结:脂肪样组织6 cm×4 cm×2 cm一堆,其上可触及淋巴结数枚。

在低倍镜下,肿瘤细胞排列呈巢状、结节状、腺泡状或假球样,也可呈小管状或微腺样结构,甚至是分散的单个肿瘤细胞向周围的纤维脂肪组织中浸润性生长(图1B, 1C)。微腺样结构区域可见腔内的嗜酸性胶样分泌物,类似于微腺型腺病(图1D)。炎细胞浸润常见,特别是腺泡状结构区域。在高倍镜下,癌细胞的异型性与组织学结构相关,结节状和巢状分布的肿瘤组织中癌细胞有明显的异型性和高分裂活性,细胞核级较高,多形性明显,染色质粗,可以看到清晰的核仁,胞质呈粗颗粒状,嗜碱性(图1E);而呈腺泡状分化较好的肿瘤组织中癌细胞形态温和,核小而一致,染色质较细腻,核分裂也少见,胞质为均一的细颗粒状,较空亮(图1F)。呈小管状或分散的小细胞巢结构的肿瘤组织中癌细胞则表现为中级别的核特征。大部分肿瘤组织中肿瘤细胞的胞质染色不一,呈空泡状嗜酸性、粗颗粒状的嗜碱性或二者混合存在(图1G, 1H)。

免疫组织化学结果(图2)显示:S-100(图2A)、EMA(图2B)、CK7阳性,PR约1%细胞阳性,AR和GCDFP-15(图2C)呈灶状阳性,ER, HER-2, 肌上皮标志物CK5/6, p63, Calponin均阴性。特殊染色示具有嗜酸性胞质的细胞和胶样分泌物PAS阳性(图2D)。病理诊断:(左侧)乳腺ACCA。

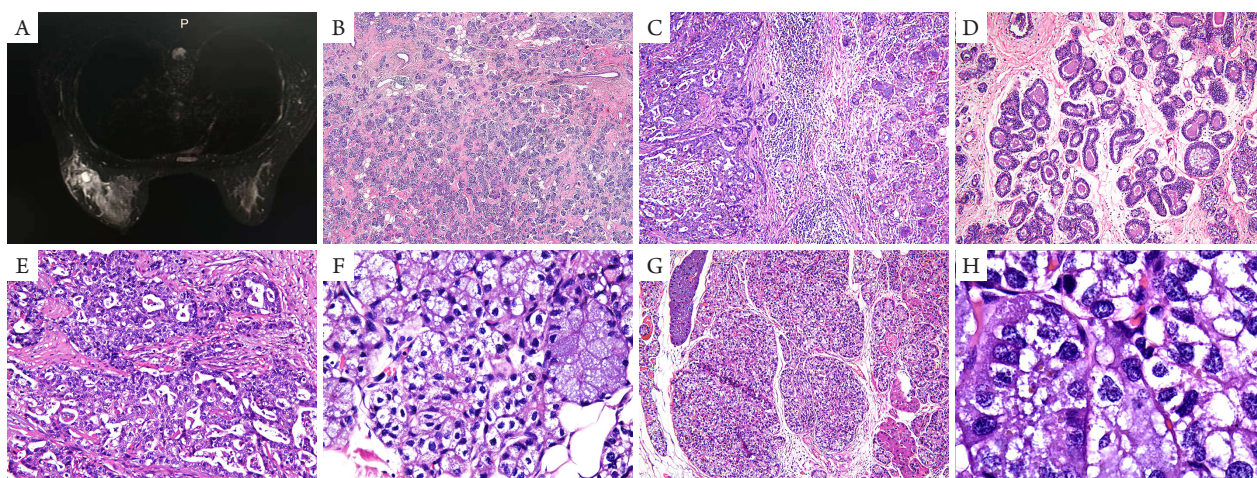


图1 乳腺原发性ACCA的病理学特征

Figure 1 Pathological features of primary acinic cell carcinoma of the breast

(A) MRI示左乳肿瘤性病灶; (B, C) 肿瘤组织形态多样, 呈巢片状、腺泡状、小管状或微腺样等结构, 在周围的纤维脂肪组织中浸润性生长(HE,  $\times 40$ ); (D) 微腺样结构区域可见腔内的嗜酸性胶样分泌物(HE,  $\times 100$ ); (E) 结节状和巢状分布的肿瘤组织中癌细胞有明显的异型性和高分裂活性(HE,  $\times 100$ ); (F) 呈腺泡状分化较好的肿瘤组织中癌细胞形态温和(HE,  $\times 200$ ); (G, H) 细胞的胞质染色不一, 呈空泡状嗜酸性、粗颗粒状的嗜碱性或二者混合存在(G: HE,  $\times 40$ ; H: HE,  $\times 400$ )。

(A) MRI showed tumorous lesions in the left breast; (B, C) Tumors had various histological forms, such as nested sheet, acinar, tubular or microadenoid structures, and infiltrated in the surrounding fibrous and adipose tissues (HE,  $\times 40$ ); (D) Eosinophilic colloidal secretions in the microadenoid areas (HE,  $\times 100$ ); (E) Nodular and nested tumors showed marked atypia and high mitotic activity (HE,  $\times 100$ ); (F) Tumor cells with good acinar differentiation were mild in shape (HE,  $\times 200$ ); (G, H) The cytoplasm of the cells is not uniformly stained, showing vacuolar eosinophilic, coarsely granular basophilic or a mixture of both (G: HE,  $\times 40$ ; H: HE,  $\times 400$ ).

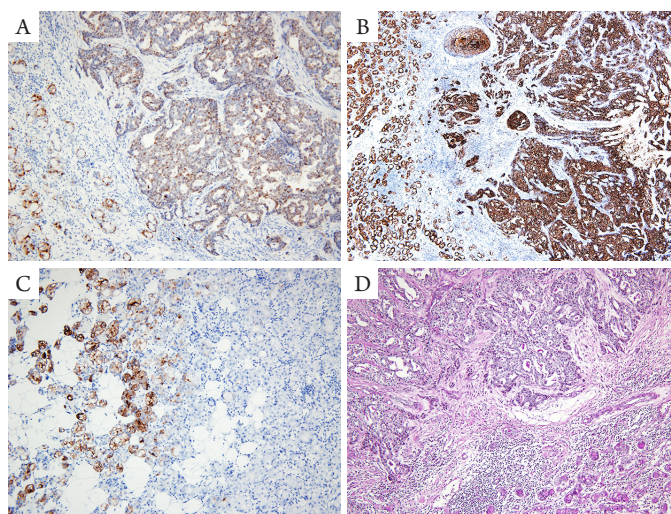


图2 乳腺原发性ACCA的免疫表型

Figure 2 Immunophenotype of primary acinic cell carcinoma of breast

(A) 肿瘤细胞阳性表达S-100(EnVision,  $\times 40$ ); (B) 肿瘤细胞阳性表达EMA(EnVision,  $\times 40$ ); (C) 肿瘤细胞灶状阳性表达GCDFP-15(EnVision,  $\times 40$ ); (D) 特殊染色PAS阳性(PAS,  $\times 40$ )。

(A) Positive expression of S-100 in tumor cells (EnVision,  $\times 40$ ); (B) Positive expression of EMA in tumor cells (EnVision,  $\times 40$ ); (C) Focal positive expression of GCDFP-15 in tumor cells (EnVision,  $\times 40$ ); (D) Positive expression of PAS by special staining (PAS,  $\times 40$ ).

## 2 讨论

乳腺是在胚胎学、组织学和功能上与其他分泌性器官(包括涎腺)相类似的器官,因此在涎腺中常见的肿瘤,如腺样囊腺瘤、多形性腺瘤、肌上皮瘤、腺肌上皮瘤、嗜酸细胞癌和黏液表皮样癌等也常发生于乳腺<sup>[32]</sup>。目前英文文献[2-27]中报道的乳腺ACCA有50例,中文文献[28-31]中报道的有5例,其中39例描述了详细的组织学特征。Shimao等<sup>[7]</sup>报道了唯一一例男性乳腺ACCA。乳腺原发性ACCA发病年龄为23~80岁,平均年龄为51岁,中位年龄为49岁。肿瘤大小1.3~5.5(平均3.2) cm<sup>[2-31]</sup>。

通过对国内外报道的55例ACCA进行文献复习,笔者发现所有报道的乳腺ACCA在组织学上具有一致性。大部分的病例形态学上呈结节状、巢状分布或小管和微腺样结构,具有多样性,其中具有嗜酸性胶样分泌物的腔样结构被部分学者描述为“微腺型腺病样结构”。在16例合并有浸润性导管癌(非特殊类型)患者中,除1例ER阳性外,剩余15例浸润性导管癌(非特殊类型)均为三阴性(ER/PR/HER2阴性)。在13例明确提及是否有淋巴管侵犯的病例中,有7例观察到了淋巴管侵犯;在31例明确提及是否有淋巴结转移的病例中,8例发生了淋巴结转移,这其中4例合并有低分化的浸润性导管癌(非特殊类型)。本例患者组织学上也表现为多样性,既有分化较好的腺泡样结构,也有分化较差的结节状或实性巢状结构,微腺样结构亦可见。中央腔内分泌嗜酸性胶样分泌物的区域免疫组织化学表达与其他部分相似,但并没有合并浸润性导管癌,未见淋巴管侵犯,20枚淋巴结均未见癌转移。

乳腺ACCA的免疫组织化学表达与涎腺ACCA类似,均表达S-100、溶菌酶、 $\alpha$ -糜蛋白酶、淀粉酶,特殊染色PAS阳性。大部分的浸润性乳腺癌在形态学上表现为“管状”结构,鲜有“腺泡状”或“分泌性”结构,几乎均不表达S-100和溶菌酶,即便是伴有顶浆分泌特征或起源微腺型腺病(microglandular adenosis, MGA)的肿瘤<sup>[3]</sup>。尽管大部分病例肿瘤细胞不表达性激素标志物,但少数肿瘤细胞可以表达ER或PR。而肌上皮的标志物如Calponin和p63在乳腺ACCA中为阴性,证实了肿瘤的浸润性生长模式。本例肿瘤细胞免疫组织化学检测结果中,除PR呈不高于1%的阳性表达外,其余标志物表达情况与文献报道一致。

大规模的基因学研究<sup>[33-34]</sup>表明:只有3个基因

在乳腺癌中的突变率超过了10%,即TP53(37%),PIK3CA(36%)和GATA3(11%),三阴性乳腺癌间的异质性更大,仅TP53呈高复发性突变(86%)。此外细胞周期检查点RB1和BRCA1, PTEN, INPP4B基因的缺失,可通过包括PIK3CA基因突变(9%)或扩增在内的途径激活PI3K通路,这是三阴性乳腺癌的主要特点。ACCA主要表现出基因扩增改变和高度重复的TP53突变的复杂模式,与常见三阴性乳腺癌的基因组图谱大致一致<sup>[31,33]</sup>。三阴性乳腺癌具有遗传学上BRCA1基因突变的乳腺癌相同的临床病理特征。Ripamonti等<sup>[16]</sup>曾报道过1例伴有BRCA1基因突变的乳腺ACCA。因乳腺ACCA与涎腺ACCA在免疫组织化学上有相似点,在三阴性乳腺癌中较为常见的基因突变是TP53和PIK3CA,而腮腺ACCA中TP53和PIK3CA的突变率分别是82%和10%<sup>[34]</sup>。由此可知,乳腺ACCA与三阴性乳腺癌在分子学上具有更多的相似点。FOXAI是一种与ER表达有关的转录因子,已被证实可以抑制与基底型乳腺癌相关基因的转录,在乳腺ACCA形成Luminal表型中起重要作用<sup>[35]</sup>。

乳腺ACCA具有特征性的组织学特征,一般不易被误诊,仅有微腺样结构时,与微腺型腺病或起源于微腺型腺病的癌类似,常有腔内嗜酸性胶样分泌物,但免疫组织化学EMA, S-100和淀粉酶阴性可与之鉴别。其他易与之误诊的疾病包括:1)分泌型癌。肿瘤由实性、微囊和管状结构构成,与ACCA类似,胞质常嗜酸性,组织学上有时难以鉴别,免疫组织化学EMA, S-100常阴性,特殊染色PAS阳性。2)大汗腺癌。肿瘤细胞较大,胞界清晰,胞质呈嗜酸性颗粒状,腺腔内常可见顶浆突起,免疫组织化学GCDFP-15一般为阳性, S-100阴性。3)腺样囊腺瘤。腺上皮细胞和肌上皮细胞组成的假腺腔结构内含有基底膜样物质和透明小体,与ACCA不难鉴别。4)富于糖原的透明细胞癌。胞质透亮的肿瘤细胞呈巢片状分布,少数可呈淡染嗜酸性颗粒状,免疫组织化学与浸润性导管癌类似。

国内外报道的55例病例<sup>[24]</sup>中,有29例进行了随访,随访周期3~185(平均29)个月,其中21例(72%)无复发,6例(21%)发生骨、肝或肺转移,2例(7%)死亡。早期的文献因报道较少,普遍认为乳腺ACCA预后很好<sup>[4]</sup>。但低分化的三阴性乳腺癌可与乳腺ACCA伴随,肿瘤也可复发和转移,甚至导致患者死亡<sup>[36]</sup>,因此需要更大量的数据来支持对这种罕见肿瘤的预后的判断,为乳腺ACCA的诊断和治疗提供依据。

## 参考文献

1. Limite G, Di Micco R, Esposito E, et al. Acinic cell carcinoma of the breast: review of the literature[J]. *Int J Surg*, 2014, 12(Suppl 1): S35-S39.
2. Roncaroli F, Lamovec J, Zidar A, et al. Acinic cell-like carcinoma of the breast[J]. *Virchows Arch*, 1996, 429(1): 69-74.
3. Huo L, Bell D, Qiu HM, et al. Paneth cell-like eosinophilic cytoplasmic granules in breast carcinoma[J]. *Ann Diagn Pathol*, 2011, 15(2): 84-92.
4. Damiani S, Pasquinelli G, Lamovec J, et al. Acinic cell carcinoma of the breast: an immunohistochemical and ultrastructural study[J]. *Virchows Arch*, 2000, 437(1): 74-81.
5. Coyne JD, Dervan PA. Primary acinic cell carcinoma of the breast[J]. *J Clin Pathol*, 2002, 55(7): 545-547.
6. Shimao K, Haga S, Shimizu T, et al. Acinic cell adenocarcinoma arising in the breast of a young male: a clinicopathological, immunohistochemical and ultrastructural study[J]. *Breast Cancer*, 1998, 5(1): 77-81.
7. Schmitt FC, Ribeiro CA, Alvarenga S, et al. Primary acinic cell-like carcinoma of the breast--a variant with good prognosis?[J]. *Histopathology*, 2000, 36(3): 286-289.
8. Elster EA, Markusic J, Ball R, et al. Primary acinic cell carcinoma of the breast[J]. *Am Surg*, 2002, 68(11): 993-995.
9. Kahn R, Holtveg H, Nissen F, et al. Are acinic cell carcinoma and microglandular carcinoma of the breast related lesions?[J]. *Histopathology*, 2003, 42(2): 195-196.
10. Peintinger F, Leibl S, Reitsamer R, et al. Primary acinic cell carcinoma of the breast: a case report with long-term follow-up and review of the literature[J]. *Histopathology*, 2004, 45(6): 645-648.
11. Tanahashi C, Yabuki S, Akamine N, et al. Pure acinic cell carcinoma of the breast in an 80-year-old Japanese woman[J]. *Pathol Int*, 2007, 57(1): 43-46.
12. Chang ED, Lee EJ, Lee AW, et al. Primary acinic cell carcinoma of the breast: a case report with an immunohistochemical and ultrastructural studies[J]. *J Breast Cancer*, 2011, 14(2): 160-164.
13. Choh CT, Komar V, Courtney SP. Primary acinic cell carcinoma of the breast: a rare lesion with good prognosis[J]. *Breast J*, 2012, 18(6): 610-611.
14. Shingu K, Ito T, Kaneko G, et al. Primary acinic cell carcinoma of the breast: a clinicopathological and immunohistochemical study[J]. *Case Rep Oncol Med*, 2013, 2013: 372947.
15. Ripamonti CB, Colombo M, Mondini P, et al. First description of an acinic cell carcinoma of the breast in a BRCA1 mutation carrier: a case report[J]. *BMC Cancer*, 2013, 13: 46.
16. Osako T, Takeuchi K, Horii R, et al. Secretory carcinoma of the breast and its histopathological mimics: value of markers for differential diagnosis[J]. *Histopathology*, 2013, 63(4): 509-519.
17. Sakuma T, Mimura A, Tanigawa N, et al. Fine needle aspiration cytology of acinic cell carcinoma of the breast[J]. *Cytopathology*, 2013, 24(6): 403-405.
18. Falletti J, Coletti G, Rispoli E, et al. Acinic cell carcinoma of the breast arising in microglandular adenosis[J]. *Case Rep Pathol*, 2013, 2013: 736048.
19. Winkler N, Morrell G, Factor RE. Invasive carcinoma with acinic cell-like features of the breast[J]. *Breast J*, 2013, 19(3): 334-335.
20. Zhao Y, Li W, Lang R, et al. Primary acinic cell carcinoma of the breast: a case report and review of the literature[J]. *Int J Surg Pathol*, 2014, 22(2): 177-181.
21. Limite G, Di Micco R, Esposito E, et al. The first case of acinic cell carcinoma of the breast within a fibroadenoma: case report[J]. *Int J Surg*, 2014, 12: S232-S235.
22. Reis-Filho JS, Natrajan R, Vatcheva R, et al. Is acinic cell carcinoma a variant of secretory carcinoma? A FISH study using ETV6 "Split apart" probes[J]. *Histopathology*, 2008, 52(7): 840-846.
23. Piscuoglio S, Hodi Z, Katabi N, et al. Are acinic cell carcinomas of the breast and salivary glands distinct diseases?[J]. *Histopathology*, 2015, 67(4): 529-537.
24. Sen R, Bhutani N, Kamboj J, et al. Primary acinic cell carcinoma of the breast: a case report with a clinicopathological and immunohistochemical study of a rare breast cancer subtype[J]. *Ann Med Surg (Lond)*, 2018, 35: 137-140.
25. Li H, Wang F, Shen P, et al. Pure acinic cell carcinoma of the breast: a case report and literature review[J]. *Medicine (Baltimore)*, 2017, 96(47): e8866.
26. Kawai H, Sugimoto R, Iga N, et al. A case of primary acinic cell carcinoma (ACC) of the breast[J]. *Gan To Kagaku Ryoho*, 2016, 43(12): 2019-2021.
27. Stolnicu S, Dohan M, Preda O, et al. Primary acinic cell carcinoma of the breast associated with an intraductal acinic cell component[J]. *Patologia*, 2010, 48(3): 204-207.
28. 刘永桥, 杨丽, 杨秀萍. 乳腺腺泡细胞癌1例[J]. *诊断病理学杂志*, 2011, 18(3): 236-237.  
LIU Yongqiao, YANG Li, YANG Xiuping. A case of acinar cell carcinoma of breast[J]. *Chinese Journal of Diagnostic Pathology*, 2011, 18(3): 236-237.
29. 赵冀安, 王占东, 张秋娜, 等. 乳腺原发性腺泡细胞癌2例分析并文献复习[J]. *实用肿瘤杂志*, 2010, 25(1): 81-84.  
ZHAO Yi'an, WANG Zhandong, ZHANG Qiuna, et al. Primary acinar cell carcinoma of breast: analysis of 2 cases and review of literature[J]. *Journal of Practical Oncology*, 2010, 25(1): 81-84.
30. 杨小兵, 王劲松. 乳腺原发性腺泡细胞癌临床病理分析[J]. *医药卫生(文摘版)*, 2018(38): 12-13.

- YANG Xiaobing, WANG Jinsong. Clinicopathological analysis of primary acinar cell carcinoma of breast[J]. Health Guide, 2018(38): 12-13.
31. Pia-Foschini M, Reis-Filho JS, Eusebi V, et al. Salivary gland-like tumours of the breast: surgical and molecular pathology[J]. J Clin Pathol, 2003, 56(7): 497-506.
32. 张和平, 解正新, 曹登峰, 等. 乳腺原发性腺泡细胞癌临床病理观察[J]. 诊断病理学杂志, 2014, 21(2): 76-79.
- ZHANG Heping, XIE Zhengxin, CAO Dengfeng, et al. Primary acinar cell carcinoma of the breast: a clinicopathological study[J]. Journal of Diagnostic Pathology, 2014, 21(2): 76-79.
33. Ng CKY, Schultheis AM, Bidard FC, et al. Breast cancer genomics from microarrays to massively parallel sequencing: paradigms and new insights[J]. J Natl Cancer Inst, 2015, 107(5): djv015.
34. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours[J]. Nature, 2012, 490(7418): 61-70.
35. Bernardo GM, Bebek G, Ginther CL, et al. FOXA1 represses the molecular phenotype of basal breast cancer cells[J]. Oncogene, 2013, 32(5): 554-563.
36. Lakhani SR, Ellis IO, Schnitt SJ, et al. WHO classification of tumours of the breast//WHO classification of tumours[M]. Lyon: International Agency for Research on Cancer, 2012.

**本文引用:** 吴娟, 何惠华, 余鑫鑫, 袁静萍. 乳腺原发性腺泡细胞癌的临床病理观察及文献复习[J]. 临床与病理杂志, 2019, 39(10): 2315-2320. doi: 10.3978/j.issn.2095-6959.2019.10.034

**Cite this article as:** WU Juan, HE Huihua, YU Xinxin, YUAN Jingping. Clinicopathological observation and literature review of primary acinic cell carcinoma in breast[J]. Journal of Clinical and Pathological Research, 2019, 39(10): 2315-2320. doi: 10.3978/j.issn.2095-6959.2019.10.034