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乳腺化生性癌合并大汗腺癌临床病理观察

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[摘　要]　报告1例乳腺化生性癌合并大汗腺癌患者，分析其临床表现、彩超、组织病理学、免疫表型和预后特点，并复习相关文献进行讨论。患者，女，62岁，临床表现为双侧乳腺肿物进行性增大。彩超示左侧乳腺局部腺体结构紊乱、回声减低，右侧乳腺实性包块伴钙化斑。行HE染色，显微镜镜下可见左侧乳腺组织导管内细胞核呈多形性，染色质粗大，核仁明显，核分裂象常见。右侧乳腺正常结构被破坏，囊腔内壁衬附具有不同程度核异形和多形性的鳞状细胞，部分肿瘤细胞由大汗腺癌细胞构成，细胞质丰富、颗粒状，呈强嗜酸性，细胞核大，核仁明显。免疫组织化学结果显示左侧乳腺肿瘤细胞P120(胞膜)，E-cadherin，ER，PR，HER-2均阳性表达，CK5/6阴性表达；右侧乳腺鳞状细胞癌成分ER，PR和HER-2均阴性表达，CK5/6和p63均阳性表达，Ki-67增殖指数约为40%。大汗腺癌细胞成分ER和PR阴性表达，AR，GCDFP-15，HER-2均阳性表达，Ki-67增殖指数约为40%。结合该患者临床资料、乳腺彩超、组织病理学特征及免疫组织化学结果确诊为左侧高级别导管原位癌(粉刺型)；右侧乳腺含有鳞状细胞癌分化的乳腺化生性癌合并大汗腺癌的特殊亚型乳腺癌。乳腺化生性癌是一组有异源性成分的癌，诊断依赖组织病理学特征和免疫表型，治疗上以手术切除为主。

[关键词]　乳腺肿瘤；乳腺化生性癌；鳞状细胞癌；大汗腺癌

Clinicopathological observation of metaplastic carcinoma combined with apocrine carcinoma of breast

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Abstract　To investigate the clinicopathological features, immunophenotypic characteristics, diagnosis and differential diagnosis of special subtype breast cancer containing metaplastic carcinoma and apocrine carcinoma, a case of metaplastic carcinoma combined with apocrine carcinoma of breast was collected. The clinical manifestations, Color Doppler ultrasound, histopathology, immunophenotype and prognosis characteristics were analyzed, and the relevant literatures were reviewed for discussion. The clinical manifestations of a 62-year-old female patient were progressive enlargement of bilateral breast masses. Color Doppler ultrasound showed local glandular

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structure disorder and echo reduction in the left breast, and solid mass in the right breast with calcified plaque. Microscopically, the luminal nucleus of the left breast tissue was pleomorphic, large chromatin and obvious nucleoli. Nuclear fission was common, and the normal structure of the right breast was destroyed. The inner wall of the cyst was lined with squamous cells with different degrees of nuclear abnormity and polymorphism. Some tumor cells were composed of cancer cells differentiated from apocrine glands. Microscopically, the cytoplasm was rich and had acidophilic granules, and tumor cells had large nuclei and obvious nucleoli. The results of immunohistochemistry showed that P120 (membrane), E-cadherin, ER, PR and HER-2 were positively expressed, and CK5/6 was negatively expressed in the left breast tumor cells; in the right breast tissue, squamous cell carcinoma was negative for ER, PR and HER-2, but positive for CK5/6 and p63. The proliferation index of Ki-67 was about 40%. The carcinomas with apocrine differentiation was negative for ER and PR, but positive for AR, GCDFP-15 and HER-2. The proliferation index of Ki-67 was about 40%. Combined with the clinical data, breast Color Doppler ultrasound, histopathological features and immunohistochemistry results of the patient, metaplastic carcinoma combined with apocrine carcinoma of breast was diagnosed. Metaplastic carcinoma of the breast is a group of cancers with heterogeneous components. The diagnosis depends on histopathological features and immunophenotype. The main treatment is surgical resection.

Keywords breast neoplasms; metaplastic breast cancer; squamous cell carcinoma; apocrine carcinoma

化生性乳腺癌是一组异质性肿瘤，其特征为肿瘤性上皮向鳞状细胞和/或间叶成分分化，包括但不局限于梭形细胞、软骨细胞、骨细胞和横纹肌细胞，肿瘤可完全由化生的成分构成，也可以由癌和化生的区域构成[1]。与非特殊型浸润性癌相比，化生性癌体积较大，淋巴结转移少见，远处转移较常见，90%以上病例的雌激素受体(estrogen receptor，ER)、孕激素受体(progesterone receptor，PR)及人表皮生长因子受体-2(human epidermal growth factor receptor 2，HER-2)阴性，并且预后较差[2-3]。研究[4-6]表明化生性癌的具体亚型与患者预后相关。因此，笔者报告1例乳腺化生性鳞状细胞癌合并大汗腺癌患者，并结合文献讨论其两种成分的临床特点、组织病理特征、免疫表型、鉴别诊断、治疗及预后，旨在提高临床医生对该病的认识及对患者预后的评估。

1 临床资料

该病例来自武汉大学人民医院2018年3月送检标本。临床病历信息及肉眼所见分别来自患者临床病历和标本电子记录信息，通过电话获取随访资料。标本来自乳腺全切手术，病理诊断根据2012年第4版WHO乳腺肿瘤分类，病理诊断经过2位病理学专家2次确诊。患者，女，62岁，因双侧乳腺肿物无痛性、进行性增大2月余，未予以任何治疗收住入院。体格检查：双侧乳腺对称，乳头无回缩及溢液，左乳11点可触及一大小约2.0 cm×1.0 cm的质韧肿块，边界清，活动度可；右乳12点可触及一大小约2.5 cm×1.0 cm的质硬肿块，界限尚清，活动尚可。双侧腋窝未触及肿大淋巴结。彩超示：左侧乳腺局部腺体结构紊乱、回声减低，右侧乳腺实性包块伴钙化斑(图1)。乳腺肿块穿刺结果示左侧乳腺导管原位癌；右侧乳腺浸润性癌。心、肺和腹部查体均无明显异常。实验室及生化检查指标无明显异常。结合病史、临床症状、体征及乳腺肿块穿刺检查结果，临床诊断考虑为左侧乳腺导管原位癌，右侧乳腺浸润性导管癌。为明确诊断，于2018年3月7日在我院行双侧乳腺切除术。

手术切除标本经常规4%甲醛固定24 h以上，脱水、石蜡包埋、4 μm厚连续切片及HE染色。选择具有代表性的蜡块进行EnVision免疫组织化学染色，光镜观察。所用一抗包括ER，PR，雄激素受体(androgen receptor，AR)，大囊肿病液体蛋白159(GCDFP-15)，细胞角蛋白5/6(CK5/6)，肿瘤蛋白(p63)，HER-2和Ki-67均购自丹麦Dako公司，其中HER-2，CK5/6，AR，GCDFP-15和p63为鼠单克隆抗体，ER，PR和Ki-67为兔单克隆抗体，设置阳性对照和阴性对照，实验步骤和抗原修复按照试剂盒说明书进行操作。

肉眼观：1)左乳乳腺肿块：灰黄乳腺组织一块，大小5 cm×4 cm×2 cm，切开切面可见一大小1.5 cm×1.5 cm的灰白质硬区，点状灰褐，边界不清。2)右乳乳腺肿块：灰黄乳腺组织2块大小合

约7.5 cm×6.5 cm×3.5 cm，切开其一乳腺组织可见一大小2.5 cm×2.0 cm×1.5 cm的肿物，切面均质灰白，质硬，边界清，无包膜，未见出血坏死及钙化；切开其二乳腺组织可见一大小1 cm×1 cm和2 cm×2 cm的灰白区，边界不清，未见出血坏死及钙化。

镜下观：左侧乳腺组织导管内细胞核呈多形性，极向差，染色质粗大，核仁明显，核分裂象常见。管腔内可见大量坏死样碎屑；右侧乳腺正常结构被破坏，可见大量囊性病变和不规则腔隙，囊腔内衬附具有不同程度核异形和多形性的鳞状细胞，表现为磷状细胞癌分化的特点(图2)。腔隙内被覆的鳞状细胞呈立方形，稍扁平，部分腔内可见大量的角化细胞、角质碎屑或角化细胞团(图3)。肿瘤细胞呈片状、条索状和巢状浸润至周围间质，并引起明显的间质反应，周围伴有炎细胞浸润(图4)。同时伴大汗腺癌组织成分，表现为肿瘤细胞大，胞界清楚，呈不规则圆形或矮柱状，细胞核大，核形态不一，有明显的核仁，部分肿瘤细胞核周围有空晕，细胞质丰富，呈颗粒状、强嗜酸性(图5)。

免疫表型：左侧乳腺肿瘤细胞P120(细胞膜)，E-cadherin，ER，PR，HER-2均阳性表达，CK5/6阴性表达。右侧乳腺鳞状细胞癌成分ER，PR和HER-2均阴性表达，CK5/6(图6)和p63(图7)均阳性表达，Ki-67增殖指数约为40%。大汗腺癌细胞成分ER和PR阴性表达，AR(图8)，GCDFP-15(图9)，HER-2(图10)均阳性表达，Ki-67增殖指数约为40%。

病理诊断：左侧乳腺高级别导管原位癌(粉刺型)；右侧乳腺化生性鳞状细胞癌合并大汗腺癌。

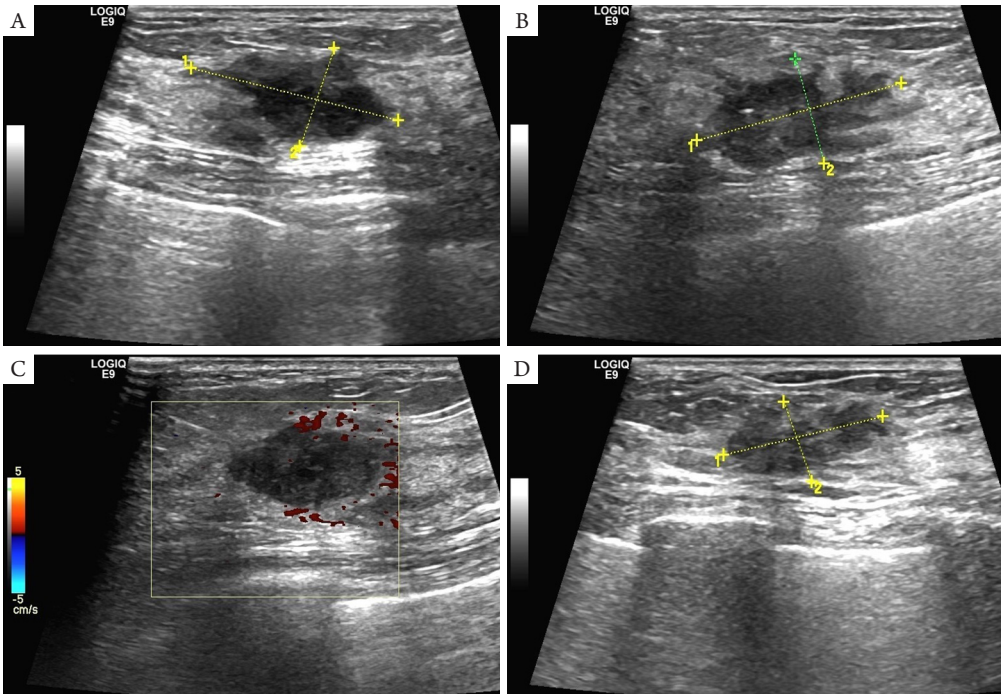

图1 双侧乳腺彩色超声多普勒检查结果

Figure 1 Color Doppler ultrasonography results of bilateral breast

(A，B)右侧乳腺12点钟方向可见2个大小分别为2.5 cm × 1.2 cm，2.5 cm × 1.3 cm低回声光团，形态不规则，边界清，边缘毛躁，内部回声不均，其内可见强回声光斑；(C)右侧乳腺光团内部及周边可见血流信号；(D)左侧乳腺11点钟方向局部腺体结构紊乱、回声减低，面积约1.9 cm × 1.0 cm。

(A, B) At the 12 o'clock position of the right mammary gland, two hypoechoic lesions of 2.5 cm × 1.2 cm and 2.5 cm × 1.3 cm were observed, with irregular shape, clear boundary, rough edge and uneven internal echo, and strong echo spot were seen inside; (C) Blood flow signal can be seen inside and around the light mass of the right breast; (D) The local glands at 11 o'clock position in the left breast are disordered in structure, and echo is reduced with the range of about 1.9 cm × 1.0 cm.

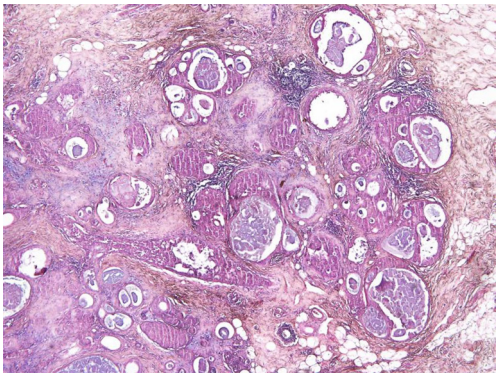

图2 鳞状细胞癌化生成分形成大量囊性病变和不规则腔隙(HE，×100)

Figure 2 Breast-mixed metaplastic carcinoma with squamous differentiation shows a large number of cystic lesions and irregular lacunae (HE, ×100)

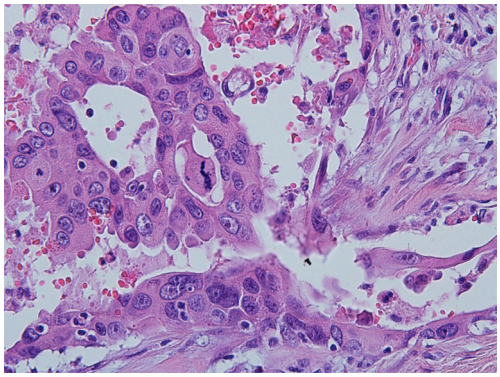

图5 大汗腺癌细胞胞质丰富、颗粒状，呈强嗜酸性，细胞核大，核仁明显(HE，×400)

Figure 5 Apocrine cancer cells show that the cytoplasm is rich and has basophilic granules, and tumor cells have large nuclei and obvious nucleoli (HE, ×400)

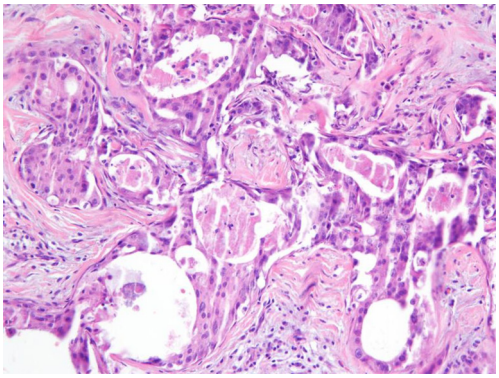

图3 腔隙内被覆的鳞状细胞呈立方形，部分腔内可见大量的角化细胞和角质碎屑(HE，×400)

Figure 3 Squamous cells covered in the lacuna are cuboidal, and a large number of keratinocytes and cuticle debris could be seen in part of the lacuna (HE, ×400)

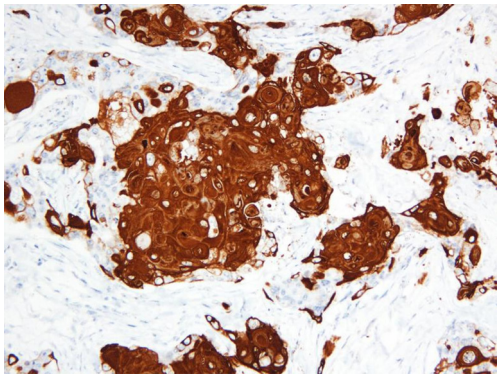

图6 鳞状细胞癌化生成分阳性表达CK5/6(EnVision，×400)

Figure 6 Positive expression of CK5/6 in squamous cell carcinoma (EnVision, ×400)

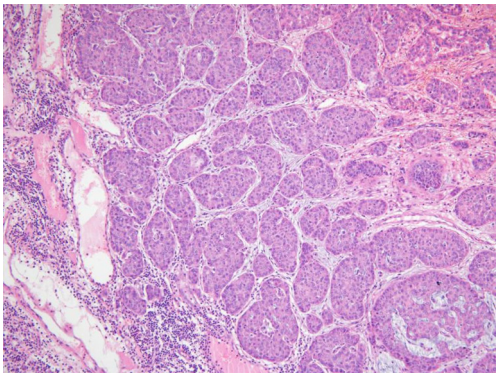

图4 肿瘤细胞呈片状、条索状和巢状浸润至周围间质，并引起明显的间质反应(HE，×200)

Figure 4 Tumor cells infiltrated into the surrounding stroma in a cord-like and nested manner, and caused obvious interstitial reaction (HE, ×200)

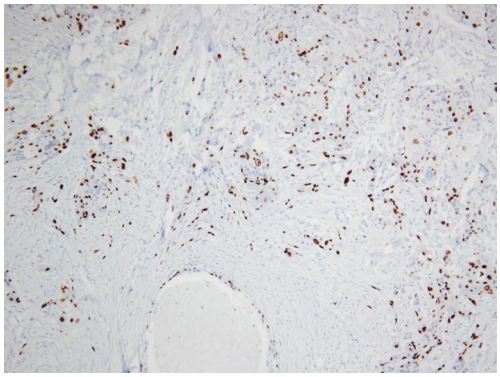

图7 鳞状细胞癌化生成分阳性表达p63 (EnVision，×100)

Figure 7 Positive expression of p63 in squamous cell carcinoma (EnVision, ×100)

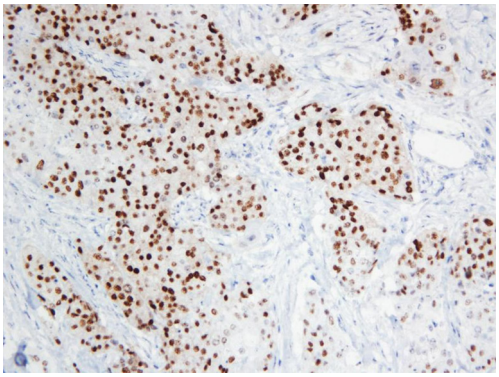

图8 大汗腺癌细胞成分阳性表达AR（EnVision，×200）

Figure 8 Positive expression of AR in apocrine cancer cells (EnVision, ×200)

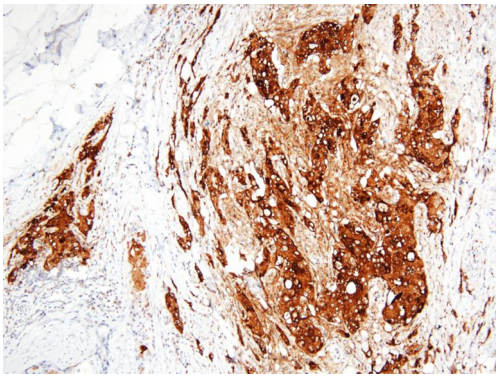

图9 大汗腺癌细胞成分阳性表达GCDFP-15（EnVision，×200）

Figure 9 Positive expression of GCDFP-15 in apocrine cancer cells (EnVision, ×200)

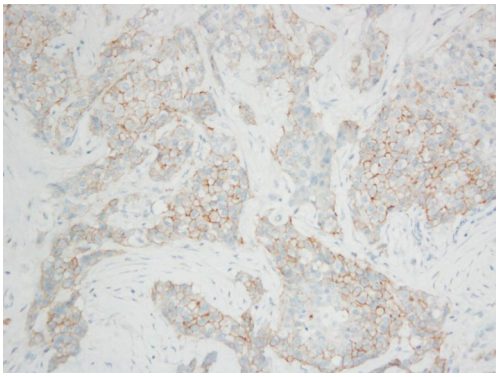

图10 大汗腺癌细胞成分阳性表达HER-2(EnVision，×200)

Figure 10 Positive expression of HER-2 in apocrine cancer cells (EnVision, ×200)

2 讨论

乳腺化生性癌是一类较罕见的特殊类型的浸润性乳腺癌，占所有浸润性乳腺癌的0.2%~5%[1]，且具有多样性的化生成分，不同的病理学亚型又可能与患者预后相关，因此这给病理医生的准确诊断带来了挑战。乳腺化生性癌的发病年龄与非特殊型浸润性癌相似，常发生于50岁以上的妇女[7]。其临床表现与一般乳腺癌相似，主要表现为乳房肿块，肿块活动度相对较好。与非特殊型乳腺癌相比，乳腺化生性癌生长速度较快，呈现进行性增大的趋势，且淋巴结转移率较低[6]。该例患者为女性，62岁，因乳腺肿块进行性增大入院，触诊肿块活动度尚可，无淋巴结转移，超声下肿块为实性回声，与文献[6]报道相符。

2012年WHO乳腺肿瘤分类标准中跟据肿瘤不同成分将化生性癌分为许多亚型，包括低级别腺鳞癌、纤维瘤病样化生性癌、鳞状细胞癌、梭形细胞癌、伴有间叶分化的癌。其中化生的鳞状细胞癌成分包括大细胞角化型、非角化型、梭形细胞型和棘层松解型，并且几种类型可以混合存在。大细胞角化型的镜下特点包括伴有嗜酸性玻璃状细胞质的多边形细胞、细胞间桥和丰富的角化珠，而非角化型缺乏细胞的角化，但细胞间桥清晰可见。梭形细胞型表现为间质浸润的鳞状细胞癌失去鳞状细胞的特征，变成梭形细胞，两者之间常有过渡，梭形细胞间可见散在分布的不规则形鳞状细胞团巢。棘层松解型镜下见不规则腔隙周围排列不典型鳞状细胞，呈假腺管样或假血管肉瘤样外观，腔隙被覆立方-钉突状细胞，类似于血管肉瘤，不规则腔隙内含有角化细胞和角质碎屑[1]。该例患者化生的鳞状细胞癌成分符合棘层松解型的诊断指南。大汗腺癌成分通常包含2种细胞：A型细胞具有丰富的颗粒状致密嗜酸性细胞质，细胞核呈空泡状有明显核仁；B型细胞也有丰富的细胞质，细胞质内有清楚而丰富的空泡，有时呈泡沫状，类似于组织细胞和皮脂腺细胞。该例患者部分肿瘤细胞胞质丰富，颗粒状、强嗜酸性，且细胞核大，有明显的核仁，具有A型细胞的组织学特点，说明该例患者不仅有鳞状细胞癌的化生成分同时还合并大汗腺癌成分。

研究[8-9]表明：90%以上含有鳞状细胞癌成分

的患者均呈现出ER，PR及HER-2阴性，仅少数患者的HER-2阳性表达。乳腺化生性鳞状细胞癌的上皮成分主要表现为高分子量角蛋白阳性表达，并且具有肌上皮样分化的特征，如p63阳性表达，其特异性和敏感性比较高[10-11]。在本例患者的免疫组织化学结果中显示鳞状细胞癌成分ER，PR和HER-2均阴性表达，CK5/6和p63均阳性表达，与上述文献描述相符。另外，大汗腺癌组织区域GCDFP-15常阳性表达[12]。Sapp等[13]报道称乳腺伴大汗腺癌通常不表达ER和PR，而常过表达AR。研究[14-15]表明：AR在大汗腺癌中的表达明显高于非大汗腺肿瘤。HER-2通常阳性表达，提示其与HER-2信号通路可能有关，但关于HER-2在大汗腺癌中过表达及其基因扩增的机制，目前尚未有详细的研究报道。在本例患者大汗腺癌细胞成分中，ER和PR阴性表达，AR，GCDFP-15，HER-2均阳性表达，这种免疫表型的肿瘤细胞具有典型的“大汗腺分子印记”特征，与上述文献相符。

乳腺化生性癌的化生成分复杂多样，发生率极低，在诊断上有一定的难度，因此，研究鉴别诊断具有重要的临床意义。在此例患者中，棘层松解型的鳞状细胞癌化生成分与血管肉瘤极易混淆，后者表现为内皮细胞常形成不规则的相互吻合的血管腔，形成乳头状，这种不规则腔隙结构与前者极其相似。免疫组织化学F-8，CD34及CD31前者表现为阴性，后者为阳性，可作为两者鉴别的依据。而该例患者大汗腺癌成分有时很难与乳腺非典型性大汗腺腺病相鉴别。后者相对前者来说，核仁较小，核膜较规则，染色质细腻，体积一般介于2~4 mm，仅包含1个小叶单位。

由于乳腺化生性癌的生物学行为和组织来源还不是十分清楚，目前临床上对于其治疗方案并未达成共识，大部分学者推荐行乳腺切除术加腋窝淋巴结清扫辅以术后放疗方案[16-17]。对于患者的预后文献报道出现2种截然相反的结论，大部分学者[18-20]认为乳腺化生性癌，恶性程度高，侵袭性强，易早期通过血道发生转移和复发，其预后比非特殊型浸润性导管癌更差，其中鳞状细胞癌亚型患者5年生存率较低。而乳腺伴大汗腺癌预后与非特殊型浸润性导管癌无明显差异[21]。本例患者正在定期随访中，其5年生存率将较差。

综上所述，由于乳腺化生性癌可同时伴有其他少见的特殊类型癌，要想对其进行有效的诊断及鉴别诊断，就需将整个乳腺肿块送检，多点广泛选材，结合典型病灶中组织病理学特征、免疫表型等结果。明确其生物学行为、组织来源、病理分型及预后因素等，对患者的治疗及预后具有重要的临床意义。

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