

## Borderline lesions of the breast: Current concept

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The term “borderline lesions” of the breast may be used for the lesions as follows. Some lesions are called as borderline because of several overlapped reasons:

- 1) Precursor lesions (precancerous lesions)
- 2) Lesions with uncertain malignant potential (lesions with difficulty to make differential diagnosis between benign and malignancy)
- 3) Risk lesions for developing carcinoma on both breast in the future

Not all the cases will be clearly defined, and some conceptual overlap may exist. In this issue, current concept of several borderline lesions will be discussed.

### Atypical ductal hyperplasia (ADH)

ADH is the most popular and classical borderline breast lesion. It is defined as the atypical intraductal epithelial proliferation, which mimics low-grade ductal carcinoma in situ (DCIS), and they are mostly small (less than 2mm).

The significance of ADH is its relative risk for developing invasive carcinomas on both breasts. Indeed, there are some breast carcinomas with peripheral ADH associations. For those cases, the area of peripheral ADH are recommended to be removed together with carcinoma, as they may be connected to the main lesion through the duct profiles. LOH analysis of peripheral ADH lesions are somewhat analogous to the invasive components at the central area of the tumor, so the peripheral area may be the front end

of carcinoma extension, or real precancerous area with well established carcinoma developed in the centre. So, ADH was originally defined as the risk lesions on both side of the breast regardless the location of it, some of the same morphology may have the real precancerous nature. There is one Japanese study concerning invasive carcinoma with previous biopsy on the same site. The average interval between initial biopsy and detection of invasive carcinoma was 78 months if the biopsy diagnosis was considered as ADH.

It is extremely difficult to diagnose ADH by fine needle aspiration cytology. Because of the size criteria, to extract epithelial cells from the area is not easy. The situation by core needle biopsy is similar. Even employing vacuum assisted procedure, the detection of ADH in a narrow sense will be the chance occurrence. More important recognition for diagnosing ADH within the core needle biopsy specimen is to see the distribution of the atypical lesions. If the ADH is widely distributed on the core needle biopsy specimen (ie. extending into several core, or extending into several duct profiles and lobules), frequently they may be up-graded as DCIS (or even invasive ductal carcinoma in few cases) on the subsequent surgical specimen.

Biologically, ADH is really neoplastic, and composed by monomorphous and monoclonal epithelial cell proliferation. It is classified into ductal intraepithelial neoplasia (DIN) 1B at the latest WHO classification, irrespective from usual ductal hyperplasia. In the practical sense, immunostains for high-molecular weight cytokeratins (HMW-CKs) may resolve the diagnosis of problematic intraductal lesions, as they are positive (mosaic fashion) for hyperplasia but negative for neoplastic lesions. The ADH is typically negative for HMW-CKs.

### **Flat epithelial atypia (FEA)**

FEA is a lesion with columnar and/or cuboidal epithelial lining within dilated terminal duct-lobular units with some degree of nuclear atypia. The many other technical terms had been employed for similar lesions: columnar cell lesion with atypia, atypical cystic duct (ACD), atypical cystic lobule (ACL), DIN1A, etc. The incidence to diagnose FEA might be increasing on

routine practice, according to the detection mammographically (as microcalcifications are frequently seen in FEA) and core needle biopsy performance in Japan.

Histologically, the low-power view of the lesion is similar to blunt duct adenosis, with accumulation of several dilated duct profiles. The cells are cuboidal to columnar with some nuclear overlapping. The nuclei are round, hyperchromatic, with some nucleoli. Mitoses are not frequently seen. Apical snouts are sometimes seen but the cytoplasm is not extensively eosinophilic. Typically, the lesions do not show any micropapillary/cribriform features. There is no good immunohistochemical marker to recognize and make differential diagnosis of FEA, but they are typically negative for HMW-CK and often strongly positive for ER/PR. However, as the recognition of “atypia” is not easy, especially on core needle specimen, several good immunohistochemical markers will be desired in the near future.

FEA is not infrequently associated with other low-grade neoplasia, such as ADH, DCIS, lobular neoplasia(LN; ALH/LCIS) and tubular carcinoma. Some of them are considered to have common genetic alterations.

### **Lobular neoplasia(LN)**

LN includes both atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS). They are continuous spectrum of the same neoplastic condition. Histologically, LN is originated from terminal duct-lobular units (TDLUs), which is the same origin with (intra-)ductal tumors. There is monotonous proliferation of uniform cells, with solid epithelial cell nests devoid of lumens. The tumor cells are less cohesive, and slit-like spaces exist between the individual cells. Sometimes, the tumor cells are extending into the ducts typically with Pagetoid features. So-called clover-leaf pattern is also evident. Immunohistochemically, LN is consistently E-cadherin negative.

Acini and terminal ducts are primary involved, and they are dilated in some degree. In LCIS, neoplastic cells expand TDLU, and the degree of expansion is lesser in ALH. There are no universal criteria to divide ALH from LCIS, but some authors consider that ALH involve less than 50% of

single TDLU area. Both lesions are clinically considered to have relative risk for developing invasive breast cancer on both breasts. The size criteria might be related to the degree of the risk, however, LCIS and ALH might be borderless. So the term LN may be more appropriate to employ rather than “carcinoma” (LCIS) and “(atypical) hyperplasia”(ALH).

Clinically, the LN has no specific features and usually found incidentally. As they are considered as risk lesions, there is no necessity to perform further excision even detected by core needle biopsy. If the lesion is classical type LN, it is unnecessary to re-excise, as it is a marker of a generalized increase of invasive carcinoma risk, and they may exist multicentric and/or bilateral. Close observation may be appropriate, but to reduce the relative risk, treatment by selective estrogen antagonists may be optional. However, additional excision may be desirable, if the LCIS is of pleomorphic variant, contains comedonecrosis, and/or combined with ductal carcinoma (mixed carcinoma in-situ).

Pleomorphic variant LCIS (PLCIS) is currently called as type B LCIS, in contrast to type A as classic LCIS (CLCIS). PLCIS shows uncohesive proliferation of neoplastic cells, like CLCIS, but the cells are characteristically larger (3-4 times of lymphocytes), more variable in size (pleomorphism), more atypical (prominent nucleoli) and more mitotically active. The cytoplasm is eosinophilic and abundant. PLCIS may be detected clinically by the mass formation or by microcalcification. Sometimes the lesion is widely distributed, and comedonecrosis and calcification are frequently seen. The lesion should be treated as DCIS, but still the tumor cells are negative for E-cadherin.

### **Atypical apocrine lesions**

Apocrine metaplasia is commonly seen in a wide variety of various breast lesions, including fibrocystic change (cyst, sclerosing adenosis), intraductal papilloma, fibroadenoma and/or some of the carcinomas. In general, its presence usually indicates benignity, especially if the area of apocrine features is focally distributed. However, diagnosis is not always straightforward, as some benign apocrine metaplastic cells show nuclear

enlargement and/or prominent nucleoli. The lesion with diffuse apocrine metaplastic change may be more particularly problematic. Apocrine sclerosing adenosis, especially those with some degree of nuclear atypia, and ductal adenoma with extensive apocrine metaplasia are the benign (or borderline) lesions, which often mimic carcinoma cytologically and histopathologically .

There is no way to clearly differentiate benign apocrine lesions from apocrine carcinoma either by histologically or by immunohistochemically. Ancillary features for atypia of apocrine cells are; necrosis, cellular dyscohesion and mitoses. Nuclear stratification, loss of basal location of the nuclei, pallor or vacuolization of the cytoplasm, enlargement of nuclei/nucleoli are the features to recognize atypia in apocrine differentiated epithelium. In addition, there is no distinct category for the borderline apocrine lesions, although the borderline categories may have a relative risk for developing breast cancer.

We examined various apocrine lesions, and found that expression of p53 and a high Ki-67 index (more than 10%) may be markers of apocrine carcinoma (either in-situ or invasive), but there has been no additional study to confirm this postulation. Another study reported that intermediate to high grade DCIS shows high Ki-67 and e-c-erbB-2 expression, but there was no data presented for the differential diagnosis between low-grade apocrine DCIS and benign apocrine lesions. Further investigations will be necessary to resolve the problem.

### **Special conditions**

1. Mucocele-like lesions (tumors) (MLT/MLL): It is characterized by dilated duct-lobular profiles filled by mucin, and the mucin is extracting into the stroma by the disrupted involved duct profile. It is originally considered as benign, but one third to half of the cases may accompany atypical hyperplasia or low-grade carcinoma.
2. Cystic hypersecretory hyperplasia and carcinoma (CHH/CHC): The rare lesions with hypersecreted proteinaceous materials within the dilated ducts. The cytoplasm of the epithelial cells may show vacuolar alteration,

which indicates hypersecretion. The similar conditions are divided into benign (CHH) and malignant (CHC, a variant of DCIS). Atypical and/or borderline lesions may be categorized but extremely rare.

3. Microglandular adenosis (MGA): It is a kind of adenosis and is basically benign, but it lacks myoepithelial cell layers and the glands are haphazardly distributed within the breast parenchyma. Although the lesion had been categorized as a special variant of adenosis, MGA sometimes recur, frequently associated with carcinoma by its follow-up, and is characteristically triple negative (ER -ve, PR -ve, HER2 -ve).
4. Radial sclerosing lesions (RSL)(Radial scar): It is a benign condition and is not borderline lesion essentially. It has the relative risk for developing breast carcinoma, but RSL itself may not extending into carcinoma. It is not required to re-excise the lesion, even if the area is partly removed on core needle biopsy specimen. Again RSL is a worrisome lesion but not precancerous (so may not be fit to this session) .

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