

Nerve Invasion by Epithelial Cells in Benign Breast Diseases

Yu-Jan Chan^{1*}, Shan-Long Chen²

Departments of ¹Pathology, Tamshui, and ²General Surgery, Taitung, Mackay Memorial Hospital, Taiwan, R.O.C.

Nerve invasion by glandular epithelial cells in a lesion is usually regarded as invasive carcinoma. However, some benign conditions in the pancreas, prostate, breast and other organs may show involvement of nerve bundles by benign epithelial cells. We report an 18-year-old female with nerve invasion in benign breast disease. The lesion in her right breast revealed fibrocystic changes with ductal hyperplasia and stromal sclerosis. Perineural and intraneural involvement by bland-looking small ducts lined by 2 layers of cells including an outer layer of myoepithelial cells were found, suggestive of benign nerve invasion. There was no evidence of malignant cells in any of the sections. The patient remains well after 31 months of follow-up. About 44 cases of nerve invasion in benign breast diseases have been reported in the literature. It is necessary to carefully evaluate nerve involvement in breast lesions to avoid over-diagnosis and inappropriate operation. [*J Chin Med Assoc* 2009;72(3):150–152]

Key Words: benign breast diseases, nerve invasion

Introduction

The neoplastic cells of invasive carcinomas in most organs may invade to adjacent lymph nodes, blood vessels and nerves. Epithelial cells in nerves are usually considered malignant. However, epithelial cells may be found in the nerve bundles in some benign conditions in a variety of organs including the pancreas,¹ prostate,² gallbladder,^{3,4} skin,^{5,6} and breast.^{7–14} We report a case showing fibrocystic changes with epithelial hyperplasia, stromal sclerosis and benign nerve invasion by epithelial cells in the right breast of an 18-year-old female.

Case Report

The patient was an 18-year-old female who visited our outpatient department with the chief complaint of painless nodular lesions in bilateral breasts. She had a past history of left breast fibroadenoma removed 17 months before this admission. After admission, excision of the nodules from bilateral breasts was performed. Sections of the lesion from the left breast showed a well-defined fibroadenoma with morphology similar

to the previous tumor in the patient's left breast. Two pieces of tissue from her right breast were submitted fresh for intraoperative frozen section, and 5 subsequent pieces were received in formalin for pathology examination. The breast tissue was firm, with no tumor mass identified grossly. Histology of the lesion from the right breast revealed fibrocystic changes with ductal epithelial hyperplasia and stromal sclerosis (Figure 1). Most impressive of all was the presence of perineural and intraneural invasion by small groups or ductules lined by 2 layers of bland-looking epithelial cells (Figures 2 and 3).

Both layers of cells were cytokeratin (AE1/AE3)-positive. The outer layer of cells was smooth muscle actin- and p63-positive myoepithelial cells (Figure 4), which represented benign ductal proliferation. No diagnostic malignant cells were found in the tissue sections. After excision of bilateral breast lesions, the patient was well after 31 months of follow-up.

Discussion

Nerve invasion by epithelial cells in a lesion usually represents invasion of malignant cells to the nerve



*Correspondence to: Dr Yu-Jan Chan, Department of Pathology, Mackay Memorial Hospital, 45, Minsheng Road, Tamshui 251, Taiwan, R.O.C.
E-mail: yjc@ms1.mmh.org.tw • Received: March 25, 2008 • Accepted: October 27, 2008

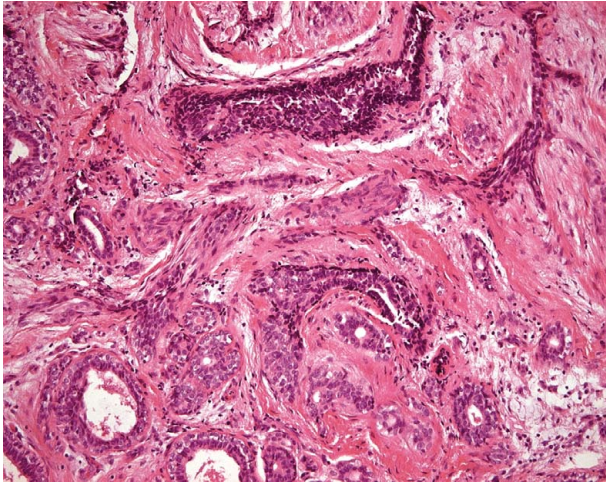


Figure 1. Ductal epithelial hyperplasia with sclerotic stroma in the right breast (hematoxylin & eosin, 100×).

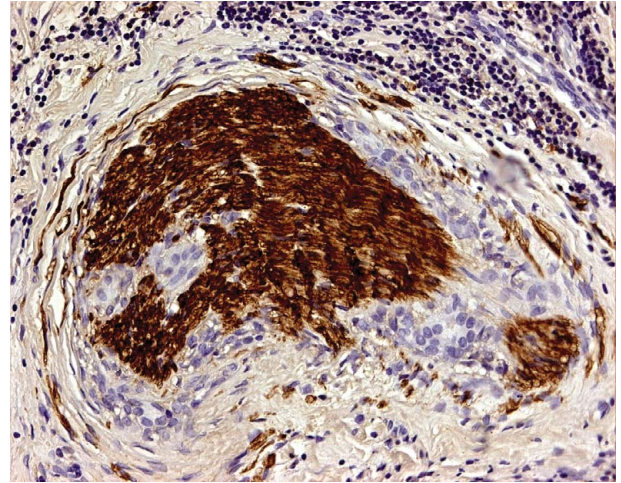


Figure 3. An S100-positive nerve bundle with perineural and intraneural invasion by S100-negative epithelial cells (S100 immunostain, 200×).

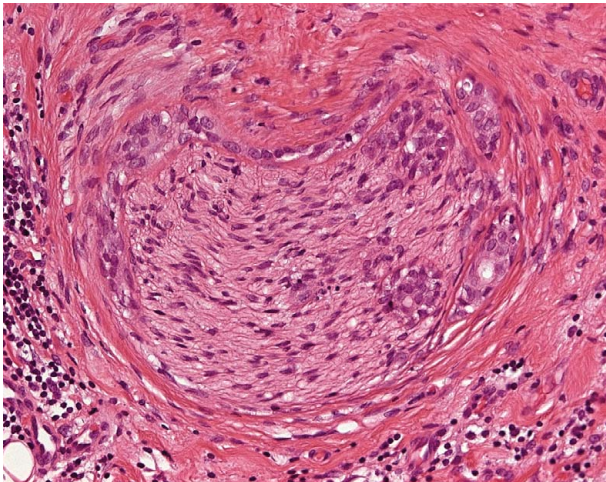


Figure 2. Bland-looking epithelial cells around and inside a nerve bundle located at the center of the field (hematoxylin & eosin, 200×).

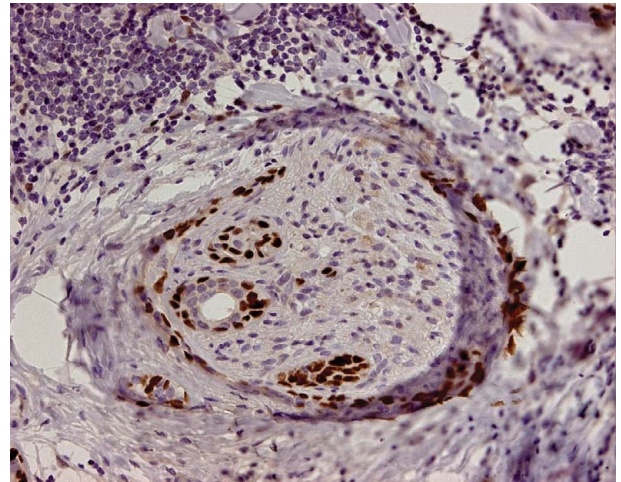


Figure 4. P63-positive myoepithelial cells around and inside the nerve bundle (P63 immunostain, 200×).

bundles adjacent to carcinomas. In some cancers, nerve invasion is one of the prognostic factors.¹⁵ Occasionally, a variety of benign conditions in different organs may show nerve invasion, such as chronic pancreatitis,¹ benign prostate,² hyperplastic or metaplastic glands of gallbladder,^{3,4} cellular capillary hemangiomas and reactive lesions of the skin,^{5,6} and benign diseases of the breast.⁷⁻¹⁴

The first reported case of nerve invasion in a benign breast lesion was by Ackerman in 1957.⁷ Ten years later, Taylor and Norris reported 20 cases out of 1,000 consecutive breast biopsies showing epithelial invasion of nerves in benign diseases of the breast, including fibrocystic disease, sclerosing adenosis and intraductal papillomatosis.⁸ Seventeen patients received

only biopsy and 3 had radical mastectomy. All patients were alive and well, with a median follow-up interval of 7 years. Since then, about 23 cases have been reported in the literature (Table 1).⁹⁻¹⁴ The breast lesions in these 23 cases were cysts, adenosis, papillomatosis, oncocytic metaplasia, periductal inflammation, radial scars, atypical ductal hyperplasia, florid hyperplasia and ductal adenoma with epithelial cells involving nerve bundles. The percentage of nerve invasion in these reports ranged from 0.14% to 3.2%.

The etiology of nerve invasion in benign diseases is uncertain. A small number of cases had previous trauma or excision at the same site.^{6,8} The association of ductal hyperplasia and papillomatosis suggests active growth of benign epithelium around or into the nerve bundles.

Table 1. Number of cases with nerve invasion in benign breast diseases and ductal carcinoma *in situ* reported in the literature

Authors, Year [Ref]	Benign disease	DCIS	Cases reviewed	Percent
Ackerman, 1957 [7]	1			
Taylor & Norris, 1967 [8]	20		1,000	2
Davies, 1973 [9]	4		316	1.3
Gould et al, 1975 [10]	2			
Tsang & Chan, 1992 [16]		1		
Cerilli & Fechner, 2000 [11]	1			
Gobbi et al, 2001 [12]	11	3	10,000	0.14
Doyle et al, 2007 [13]	4		125	3.2
Fellegara & Kuhn, 2007 [14]	1			
Total	44	4	11,441	

The presence of nerve invasion by bland-looking glands in breast diseases does not necessarily indicate invasive carcinoma. Further immunostaining is helpful to identify the 2 types of epithelial cells, including myoepithelial cells within the nerve, to confirm the benign nature of the lesion. Beside benign breast diseases, 4 cases of ductal carcinoma *in situ* (DCIS) associated with neural invasion were also reported (Table 1).^{12,16} The epithelial cells surrounding or in the nerve bundles were similar to adjacent DCIS with myoepithelial cells at the edge. These neural-invasive DCIS did not represent invasive carcinoma.

In conclusion, nerve invasion by bland epithelial cells in breast lesions without diagnostic malignant cells should be evaluated carefully to avoid over-diagnosis and inappropriate operation.

References

- Bockman DE, Buchler M, Malfertheliner P, Berger HG. Analysis of nerves in chronic pancreatitis. *Gastroenterology* 1988;94:1459–69.
- Ali TZ, Epstein JI. Perineural involvement by benign prostatic glands on needle biopsy. *Am J Surg Pathol* 2005;29:1159–63.
- Albores-Saavedra J, Henson DE. Adenomyomatous hyperplasia of the gallbladder with perineural invasion. *Arch Pathol Lab Med* 1995;119:1173–6.
- Albores-Saavedra J, Henson DE. Pyloric gland metaplasia with perineural invasion of the gallbladder: a lesion that can be confused with adenocarcinoma. *Cancer* 1999;86:2625–31.
- Calonje E, Mentzel T, Fletcher CDM. Pseudomalignant perineurial invasion in cellular ('infantile') capillary haemangiomas. *Histopathology* 1995;26:159–64.
- Chen KTK. Reactive neuroepithelial aggregates of the skin. *Int J Surg Pathol* 2003;11:205–10.
- Ackerman LV. Seminar on lesions of the breast. In: *Proceedings of the Twenty-Second Seminar of the American Society of Clinical Pathologists*. Chicago, IL: American Society of Clinical Pathologists, 1957.
- Taylor HB, Norris HJ. Epithelial invasion of nerves in benign diseases of the breast. *Cancer* 1967;20:2245–9.
- Davies JD. Neural invasion in benign mammary dysplasia. *J Pathol* 1973;109:225–31.
- Gould VE, Rogers DR, Sommers SC. Epithelial–nerve intermingling in benign breast lesions. *Arch Pathol* 1975;99:596–8.
- Cerilli LA, Fechner RE. Benign intraneural epithelium in the breast. *Arch Pathol Lab Med* 2000;124:465.
- Gobbi H, Jensen RA, Simpson JF, Olson SJ, Page DL. Atypical ductal hyperplasia and ductal carcinoma *in situ* of the breast associated with perineural invasion. *Hum Pathol* 2001;32:785–90.
- Doyle EM, Banville N, Quinn CM, Flanagan F, O'Doherty A, Hill AD, Kerin MJ, et al. Radial scars/complex sclerosing lesions and malignancy in a screening programme: incidence and histological features revisited. *Histopathology* 2007;50:607–14.
- Fellegara G, Kuhn E. Perineural and intraneural "invasion" in benign proliferative breast disease. *Int J Surg Pathol* 2007;15:286–7.
- Knudsen JB, Nilsson T, Sprechler M, Johansen A, Christensen N. Venous and nerve invasion as prognostic factors in postoperative survival of patients with respectable cancer of the rectum. *Dis Colon Rectum* 1983;26:613–7.
- Tsang WY, Chan JK. Neural invasion in intraductal carcinoma of the breast. *Hum Pathol* 1992;23:202–4.