Pathology - Research and Practice 215 (2019) 152624

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Case report

Perineural and intraneural involvement in ductal carcinoma in-situ of breast: Case report

Osama Elfituri, Rajyasree Emmadi

University of Illinois at Chicago, 1740W. Taylor St., Chicago, IL, United States

ARTICLE INFO

Keywords:
Breast
Ductal carcinoma in situ
Perineural invasion
p63
Calponin

ABSTRACT

Invasion of peripheral nerves by epithelial cells has been traditionally regarded as a feature diagnostic of malignancy, its presence therefore being often sought to document a diagnosis of carcinoma, particularly in the breast. Perineural involvement (PNI) by benign breast disease is not often seen and the etiology is uncertain. The first reported case of nerve invasion in a benign breast lesion was by Ackerman in 1957. Subsequent reports have further confirmed this finding in the breast. The most challenging observation is when the glands involving nerves show cytologic and architectural features of the adjacent atypical duct hyperplasia (ADH) or ductal carcinoma in situ (DCIS). Here, we describe a case of ductal carcinoma in situ grade 2 with nerve involvement in a lumpectomy specimen in a 59-year-old woman. To the best of our knowledge, only five cases of atypical duct hyperplasia by Gobbi et al. and four cases of ductal carcinoma in situ, 3 by Gobi et al. and 1 by Tsang and Chan, associated with nerve involvement, have been reported in English medical literature. Two layers of epithelial cells with the immunohistochemical demonstration of the preservation of a continuous myoepithelial layer in the mammary ducts within the nearby small nerves, is the main clue to confirm the in-situ nature of the inclusions. It is necessary to be aware of this phenomenon in breast lesions to avoid over-diagnosis and inappropriate surgery.

1. Introduction

Perineural invasion defined as the presence of viable tumor cells in the perineural space, and intra-neural invasion defined as the presence of perineural invasion with tumor cells invading into and/or with irregular destruction of the axon of the nerve bundles [1]. It is common in head and neck cancer, prostate cancer and colorectal cancer and is one of the established prognostic factors in different carcinomas. Nerve involvement may occur in some benign proliferative conditions as well. Here, we describe a case of mammary duct carcinoma in situ with nerve involvement in a lumpectomy specimen.

2. Case report

The patient first came for a screening mammogram that showed suspicious calcifications in the left breast. She also had some dark brown nipple discharge at the same time. She denied any associated palpable mass, pain, or tenderness. She had an image-guided biopsy that showed DCIS grade 2 cribriform and micropapillary patterns. Immunohistochemical studies for breast tumor marker were performed and showed greater than 95% strong estrogen receptor, while PR and HER-2/neu were negative. She underwent left breast lumpectomy with sentinel lymph node biopsy.

3. Pathologic finding

A lumpectomy tissue was received from her measuring 4.6 × 3.9 × 2.4 cm. The breast tissue was firm, with no tumor mass identified grossly. Histology of the lesion revealed two foci of grade 2 DCIS, cribriform, papillary and micropapillary types with microcalcification and focal necrosis, measuring 2.4 and 1.2 cm in greatest dimension were present, with negative resection margins. Non-neoplastic mammary tissue showed atypical ductal hyperplasia, ductal hyperplasia of usual type, columnar alterations, fibrocystic change with apocrine metaplasia and dense nodular stromal fibrosis. Adjacent small nerves showed ductal inclusions (Fig. 1a). These inclusions were 5 mm away from the closest resection margin. The epithelial cells surrounding or in the nerve bundles were similar to adjacent DCIS highlighted by the AE1/AE3 immunohistochemical stain (Fig. 1b) with myoepithelial cells at the edge highlighted by calponin immunohistochemical stain (Fig. 1c). Two sentinel lymph nodes were negative for metastatic tumor. After excision of breast lesions, the patient was well after 20 months of follow-up.

E-mail address: oelfitur@uic.edu (O. Elfituri).

https://doi.org/10.1016/j.prp.2019.152624
Received 19 July 2019; Received in revised form 24 August 2019; Accepted 5 September 2019

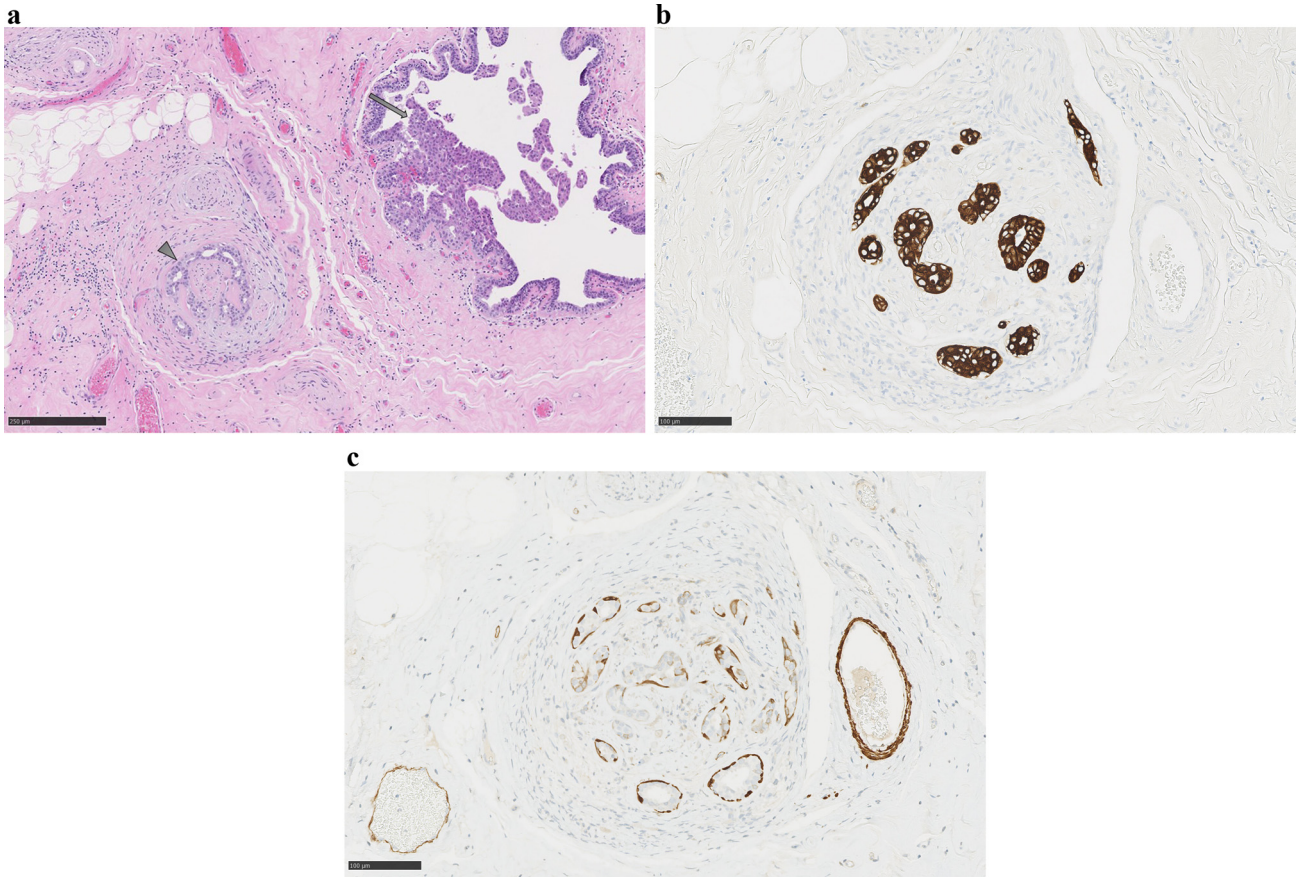

Fig. 1. Section from breast lumpectomy showing ductal carcinoma in-situ grade 2 (arrow). The epithelial cells surrounding or in the nerve bundles are similar to adjacent DCIS (arrowhead) (1a, orig mag 100 ×) and highlighted by AE1/AE3 (1b, org mag 200 ×). The myoepithelial cells are highlighted by calponin (1c, orig mag 200 ×).

4. Discussion

Invasion of peripheral nerves by epithelial cells has been traditionally regarded as a feature diagnostic of malignancy, its presence therefore being often sought to document a diagnosis of carcinoma, particularly in breast. Perineural involvement (PNI) by benign breast disease is not often seen and the etiology is uncertain. The first reported case of nerve invasion in a benign breast lesion was by Ackerman in 1957 [2]. The phenomenon was fully documented later by Taylor and Norris, who encountered it in 20 cases studied after reviewing 1000 consecutive slides of breast biopsies at the Armed Forced Institute of Pathology. All patients survived with a 7-year follow-up. Also, Davies had documented 4 cases with PNI found in 316 benign breast lesions (1.3%). Subsequent reports further confirmed this finding in the breast (Table 1) [3]. Most of these studies have shown the associated breast pathology to be cysts, adenosis, papillomatosis, oncocytic metaplasia, periductal inflammation, radial scars, atypical ductal hyperplasia, florid hyperplasia and ductal adenoma with epithelial cells involving nerve bundles [3–9] with a higher propensity in papillomatosis and sclerosing adenosis [4,5]. The presence of nerve invasion by bland-looking epithelium of mammary glands or ducts with benign appearance of the background process makes the etiopathogenesis uncertain. A small number of cases had previous trauma or surgical intervention at the same site resulting in mechanical implantation. [3,11] Also, an incorporation of epithelial and neural tissue during embryogenesis may be one explanation of the pathogenesis [3]. Two layers of bland-looking

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

Authors, Year (Ref)	Benign disease	DCIS	ADH	Specimen type	IHC	Follow up
Ackerman, 1957 [2]	1			–	–	–
Taylor & Norris, 1967 [3]	20			17 biopsies, 3 radical mastectomy		LW* median 7 years
Davies, 1973 [4]	4			Biopsies	–	LW median 23 months
Gould et al., 1975 [5]	2			–	–	–
Tsang & Chan, 1992 [10]		1		Radical mastectomy	MSA	–
Cerilli & Fechner, 2000 [6]	1			Mass Excision	–	LW 5 months
Gobbi et al., 2001 [7]	6	3	5	Biopsies	PGP, SMA	–
Doyle et al., 2007 [8]	4			Mass Excision	–	–
Fellegara & Kuhn, 2007 [9]	1			Mass Excision	p63, SMA	–
Chan & Chen 2009 [14]	1			Mass Excision	AE1/AE3, SMA, p63	LW 31 months
Total	40	4	5			

Abbreviations: IHC, immunohistochemical stains, PGP, protein gene product, SMA, smooth muscle actin, MSA, muscle specific actin.
* "LW" indicates patient living and well at stated interval following treatment.

epithelial cells with the immunohistochemical demonstration of the preservation of a continuous myoepithelial layer in the mammary ducts within the nearby small nerves, is the main clue to confirm the benign nature of the inclusions. It is necessary to be aware of this phenomenon in breast lesions to avoid over-diagnosis and inappropriate surgery. The most challenging observation is when the glands involving the nerves show cytologic and architectural features of the adjacent atypical duct hyperplasia (ADH) or ductal carcinoma in situ (DCIS). To the best of our knowledge, only five cases of ADH by Gobbi et al. and four cases of DCIS; 3 by Gobi et al. and 1 by Tsang and Chan (Table 1) had been reported in English medical literature. DCIS is defined as a clonal proliferation of epithelial cells confined to the ductal-lobular system without evidence of invasion through the basement membrane into the surrounding stroma. Up to 80% of invasive ductal breast carcinomas show at least small foci of DCIS. About 5 to 20% of breast tumors present as pure DCIS without any detectable invasive tumor at the time of diagnosis [12]. The mechanism of transition from carcinoma in situ to invasive carcinoma is not yet fully understood. It may be due to loss of function of normal supporting cells and stromal cells rather than gain of function of tumor cells. The spread of breast adenocarcinoma to the nerves is by direct infiltration of the nerves, i.e., direct perineural spread. The pathogenesis of presence of atypical glands with intact myoepithelial layer within the nerves in case of adjacent DCIS has not been fully explained. It could be suggested as part of a complex sclerosing lesion with nerve extension followed by monoclonal proliferation of tumor cells within the ducts [8]. Another explanation, could be a cancerization theory as DCIS extends to adjacent ducts including the ones in the nerves. Perineural invasion associated with DCIS and ADH is probably likely to have minimal clinical implications. This assumption is supported by results of studies showing that perineural invasion did not affect clinical consequence [15]. Also, previous studies have shown that the presence of perineural invasion did not affect the clinical outcome in invasive mammary carcinomas [13].

We suggest using term “involvement” rather than “invasion” in cases of benign breast diseases, ADH and DCIS.

5. Conclusion

Intimate intermingling of benign ductal epithelium and nerves is an uncommon finding in breast diseases. The mechanisms proposed for PNI have not been well understood, and further studies seem to be necessary. This article is aimed at adding to the sparse data on this phenomenon, to help the surgical pathologist arrive at the correct diagnosis and thus avoid unnecessary surgeries, extended resections, and large fields of irradiation.

References

[1] Amit Moran, et al., International collaborative validation of intraneural invasion as a prognostic marker in adenoid cystic carcinoma of the head and neck, Head Neck 37 (7) (2014) 1038–1045, https://doi.org/10.1002/hed.23710.
[2] L.V. Ackerman, Seminar on lesions of the breast, Proceedings of the Twenty-Second Seminar of the American Society of Clinical Pathologists, American Society of Clinical Pathologists, Chicago, IL, 1957.
[3] H.B. Taylor, H.J. Norris, Epithelial invasion of nerves in benign diseases of the breast, Cancer 20 (1967) 2245–2249.
[4] J.D. Davies, Neural invasion in benign mammary dysplasia, J. Pathol. 109 (1973) 225–231.
[5] V.E. Gould, D.R. Rogers, S.C. Sommers, Epithelial–nerve intermingling in benign breast lesions, Arch. Pathol. 99 (1975) 596–598.
[6] L.A. Cerilli, R.E. Fechner, Benign intraneural epithelium in the breast, Arch. Pathol. Lab. Med. 124 (2000) 465.
[7] H. Gobbi, R.A. Jensen, J.F. Simpson, S.J. Olson, D.L. Page, Atypical ductal hyperplasia and ductal carcinoma in situ of the breast associated with perineural invasion, Hum. Pathol. 32 (2001) 785–790.
[8] E.M. Doyle, N. Banville, C.M. Quinn, F. Flanagan, A. O’Doherty, A.D. Hill, M.J. Kerin, et al., Radial scars/complex sclerosing lesions and malignancy in a screening programme: incidence and histological features revisited, Histopathology 50 (2007) 607–614.
[9] G. Fellegara, E. Kuhn, Perineural and intraneural “invasion” in benign proliferative breast disease, Int. J. Surg. Pathol. 15 (2007) 286–287.
[10] W.Y. Tsang, J.K. Chan, Neural invasion in intraductal carcinoma of the breast, Hum. Pathol. 23 (1992) 202–204.
[11] K.T.K. Chen, Reactive neuroepithelial aggregates of the skin, Int. J. Surg. Pathol. 11 (2003) 205–210.
[12] WHO, Tumors of the breast, in: F.A. Tavassoli, P. Devilee (Eds.), World Health Organisation Classification of Tumors: Pathology and Genetics of Tumours of the Breast and Female Genital Organs, IARC Press, Lyon, 2003, pp. 9–112.
[13] T.P. Mate, D. Carter, D.B. Fischer, et al., A clinical and histopathologic analysis of the results of conservation surgery and radiation therapy in stage I and II breast carcinoma, Cancer 58 (1986) 1995–2002.
[14] Y.J. Chan, S.L. Chen, Nerve invasion by epithelial cells in benign breast diseases, J. Chin. Med. Assoc. (2009).
[15] T.P. Mate, D. Carter, D.B. Fischer, et al., A clinical and his-topathologic analysis of the results of conservation surgery and radi-ation therapy in stage I and II breast carcinoma, Cancer 58 (1986) 1995–2002.