ATIPIA EPITELIAL PLANA (FEA). Una lesión problemática para los programas de cribado de cáncer de mama.

Dra. Concepción de Miguel

Complejo hospitalario de Navarra B.

Pamplona

- Los programas de cribado de cáncer de mama ha conferido **carácter de entidad patológica a esta lesión** debido a la tendencia a calcificarse.

- La identificación de esta lesión como la causa de calcificaciones es importante en la evaluación de la **patología detectada en los programas de cribado.**

- Su significado biológico es incierto, pero la coexistencia con lesiones más avanzadas y estudios genéticos e IHQ sugieren que **representa una forma muy precoz de cambio maligno**.

- La distinción histológica entre **LCC sin atipia y con atipia (FEA) es problemática.**

Historia

- Adenosis de conductos terminales (BDA). Foote y Stewart (1945)
- Metaplasia columnar. Bonser (1961)
- Carcinoma intraductal "clinging" monomorfo de Azzopardi. (1979)
- Programas poblacionales de cribado: BIOPSIAS DE MICROCALCIFICACIONES
- CAPSS: Alteraciones columnares con "snouts" apicales y secrecciones. Fraser (1998)
- ELUCA: Unidades túbulo-lobulillares agrandadas con altraciones columnares. Kasami (2004)
- Cambios columnares sin atipia/adenosis de conductos terminales (BDA)
- Cambios columnares con atipia : **ATIPIA EPITELIAL PLANA** (OMS) (2003)

Table 5.1. Classification of **intraductal proliferative lesions** according to traditional and alternative (DIN) terminologies;World Health Organization classification. (2003)

Traditional terminology	**Alternative terminology**
Usual ductal hyperplasia	Usual ductal hyperplasia
Flat epithelial atypia	**DIN grade 1a (DIN1a)**
Atypical ductal hyperplasia	DIN grade 1b (DIN 1b)
DCIS, low grade (G1)	DIN grade 1c (DIN1c)
DCIS, intermediate grade (G2)	DIN grade 2 (DIN2)
DCIS, high grade (G3)	DIN grade 3 (DIN3)0

FEA (OMS)

Lesiones englobadas y reemplazadas:

- Carcinoma “clinging” monomorfo
- Lóbulos quísticos atípicos
- Cambios columnares con atipia
- DIN1a
- Hiperplasia pretubular (Rosen)

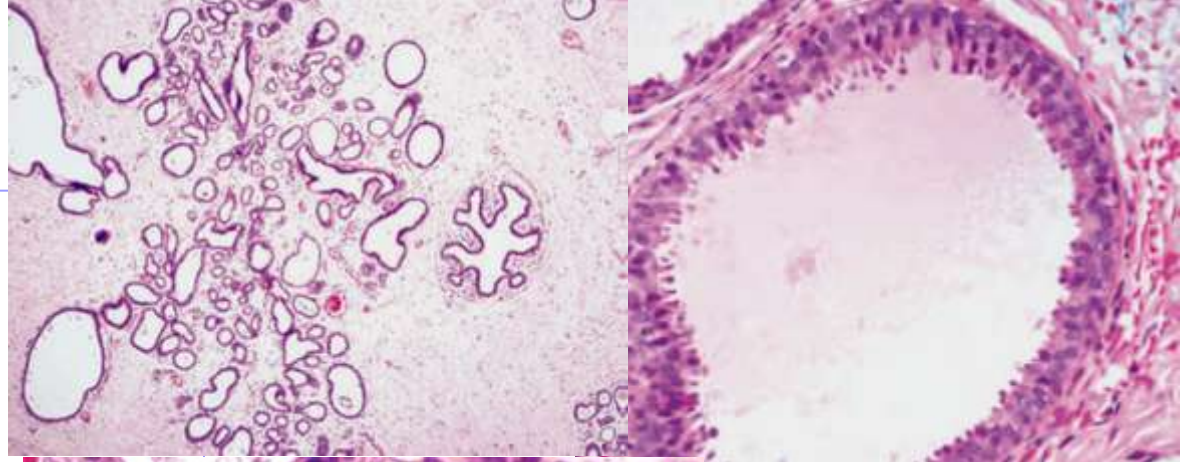
Definición

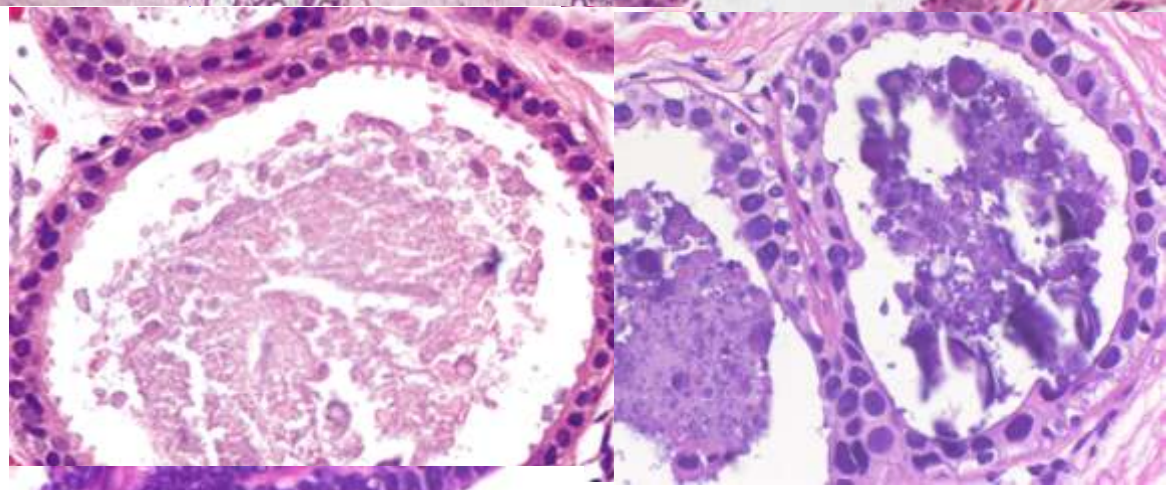
- Alteración de la unidad ducto-lobulillar terminal.

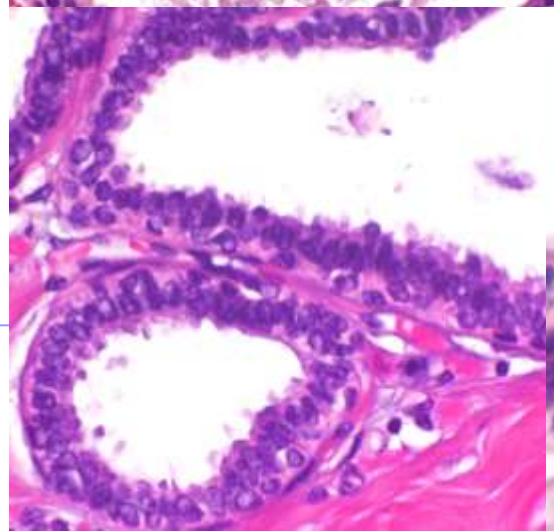
Dilatación rígida de unidades

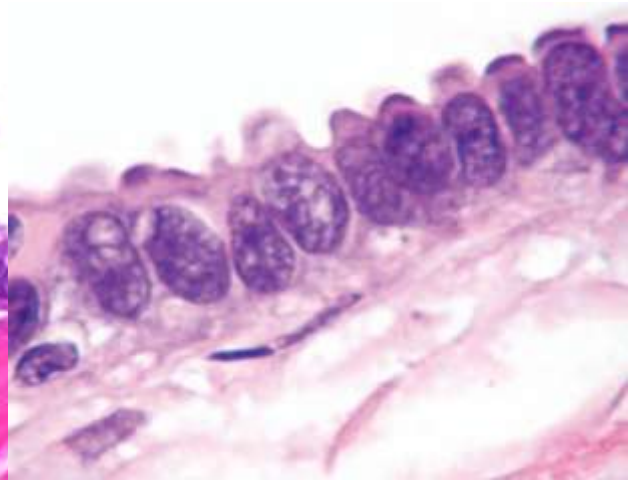
- terminales.
- **No proliferación intraluminal**: Una o dos capas de células cilíndricas/cúbicas
- Proyecciones citoplasmáticas apicales “ snouts”
- Material granular intraluminal: calcificaciones
- **Atipia citológica leve del epitelio**

- Localización de la lesión: A bajo aumento
- Diagnóstico de la lesión: A gran aumento.



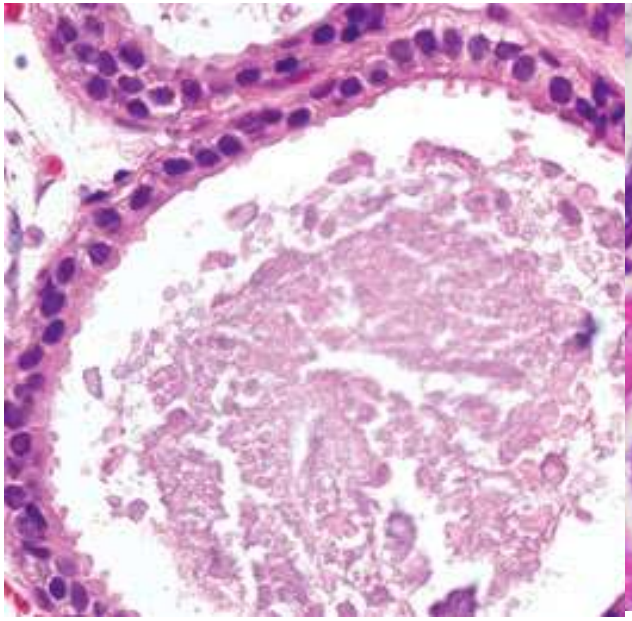


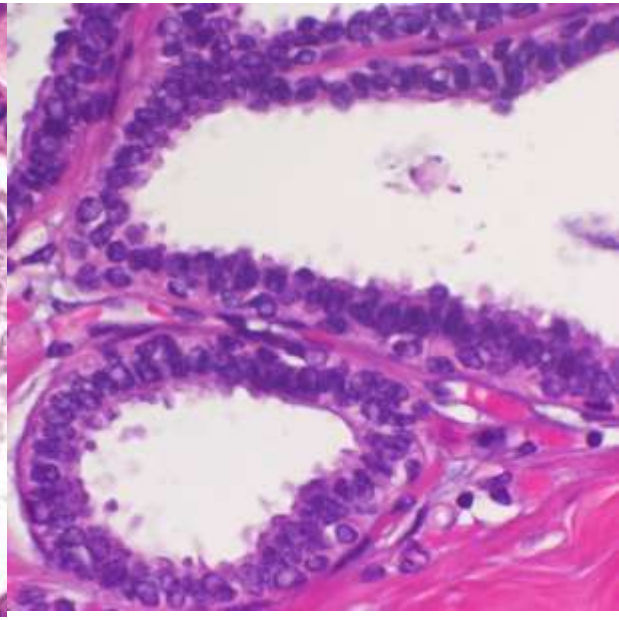


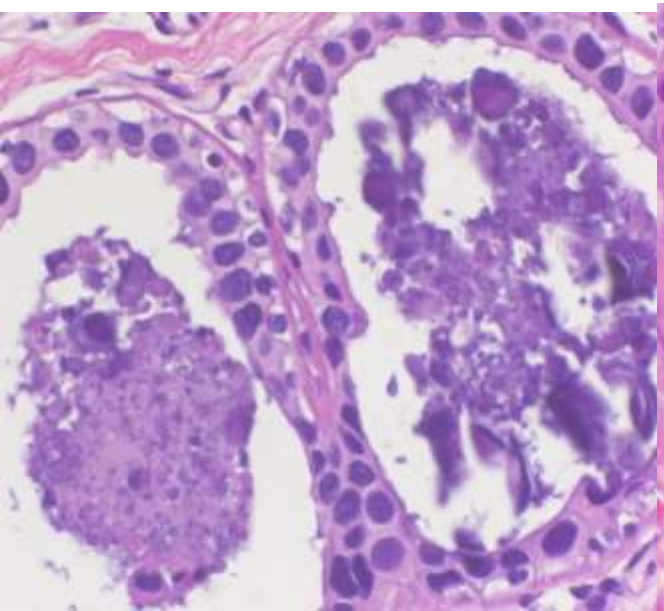


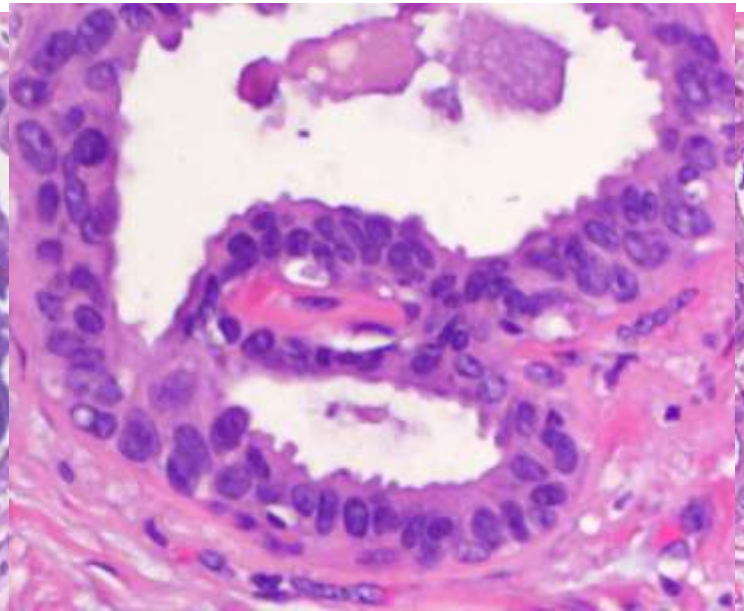
FEA: Atipia citológica leve

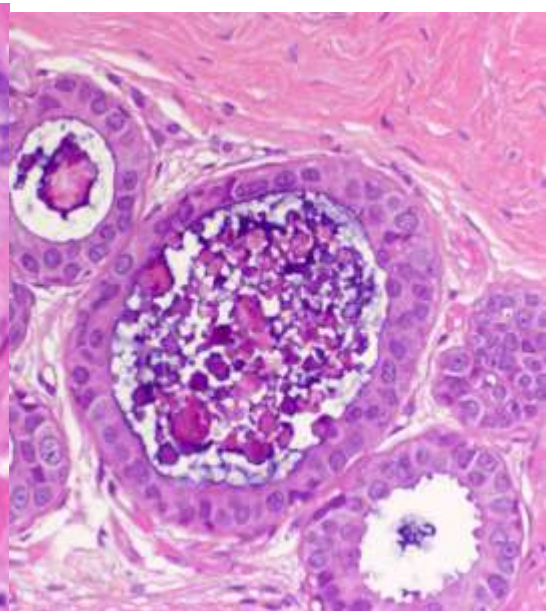
- Núcleos redondos más que ovoides
- Pérdida de la perpendicularidad
- Nucleolos
- Mitosis ocasionales



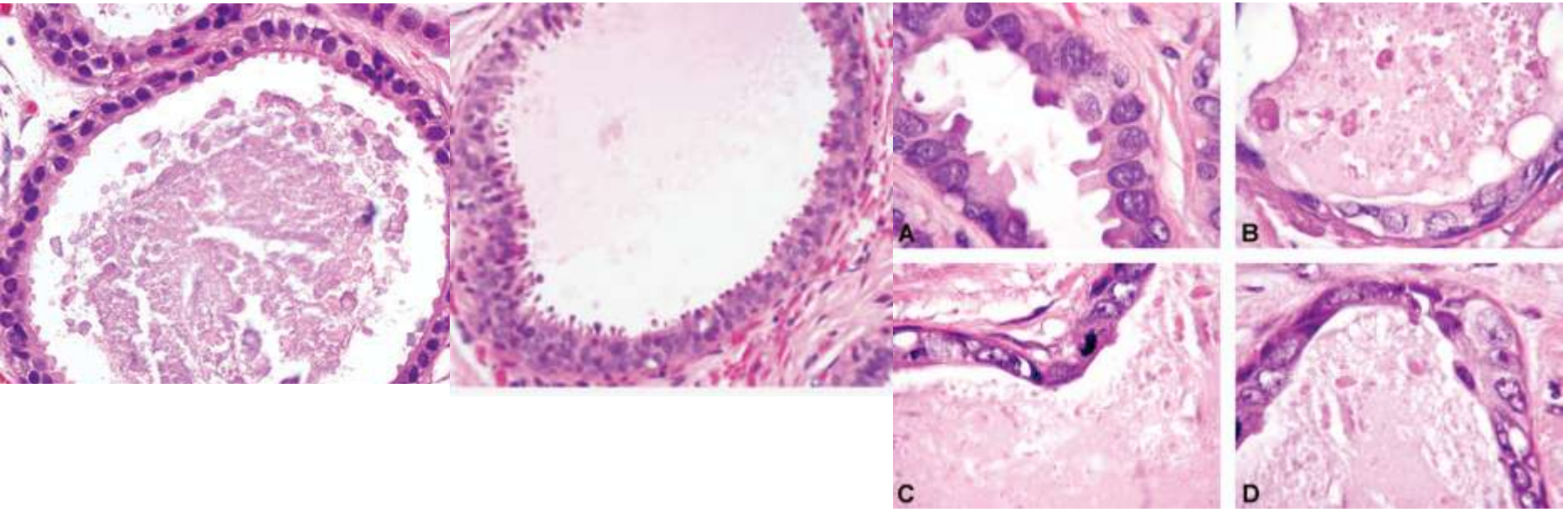


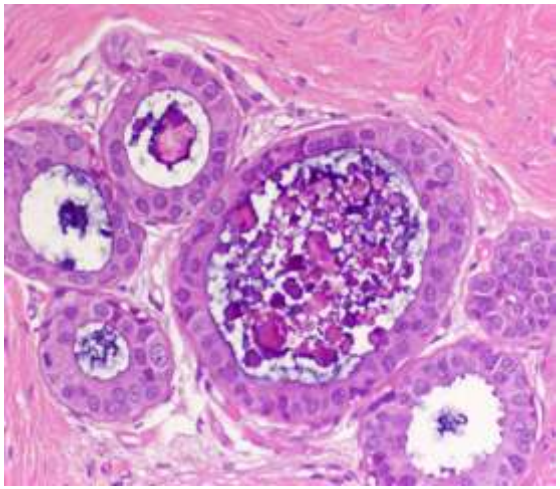


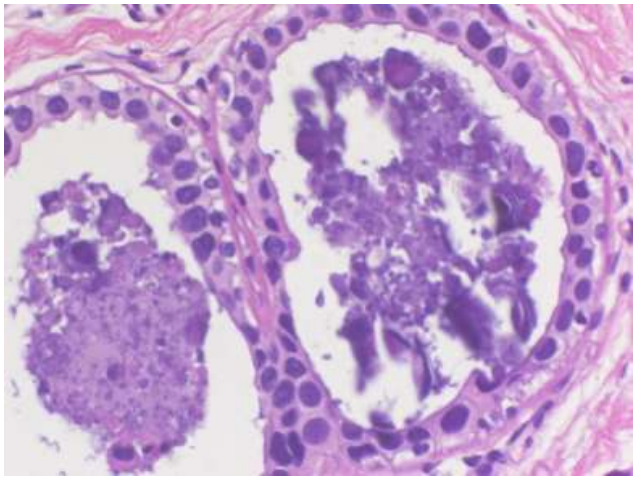


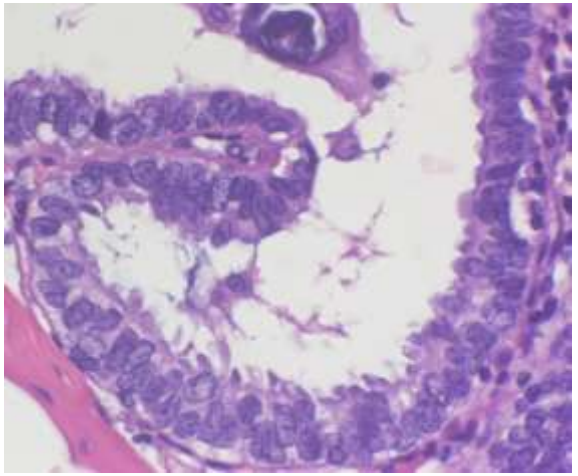


Atipia citológica de alto grado monocapa es un CID de alto grado



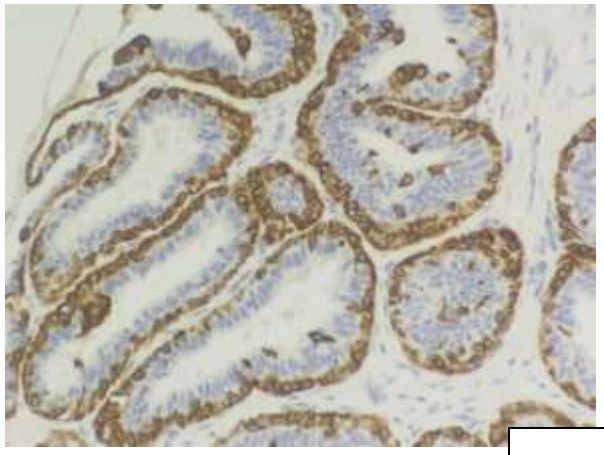


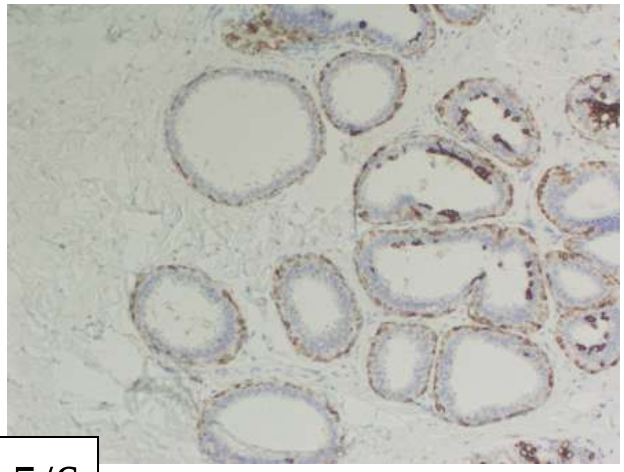




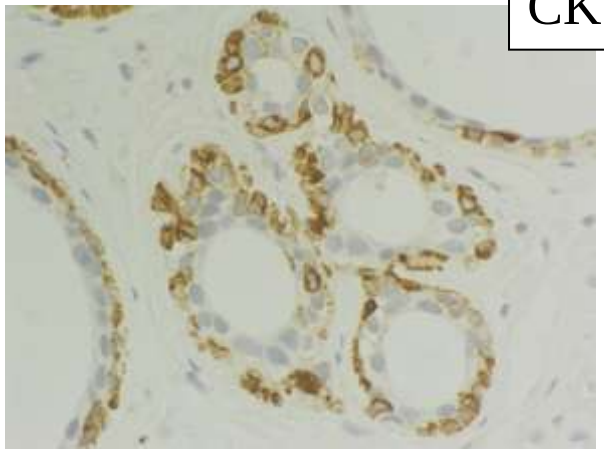
FEA: IHQ

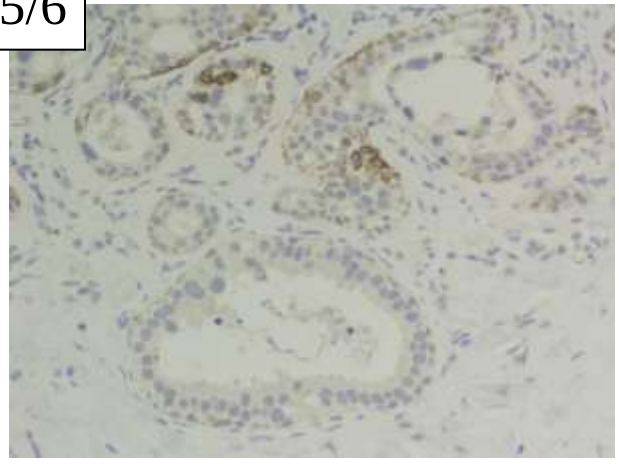
- Similar a CID bajo grado
- Negativa CK 5/6
- RE y RP positivos
- Her2 negativo
- E-cadherina negativa
- Ki-67 bajo (<10%)

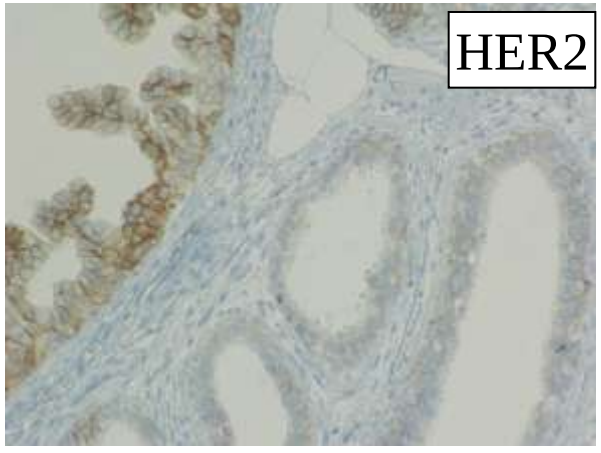




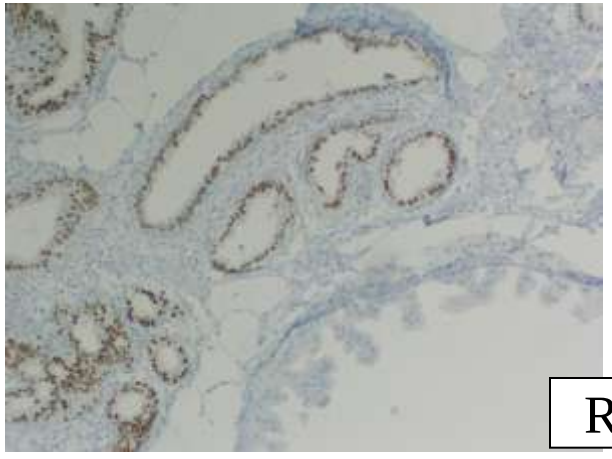
CK 5/6

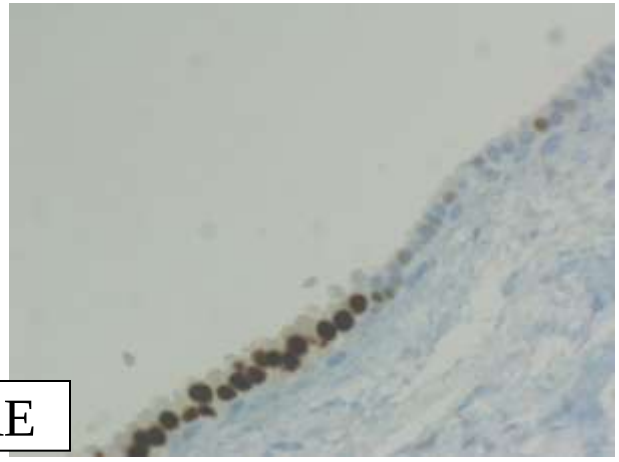






HER2

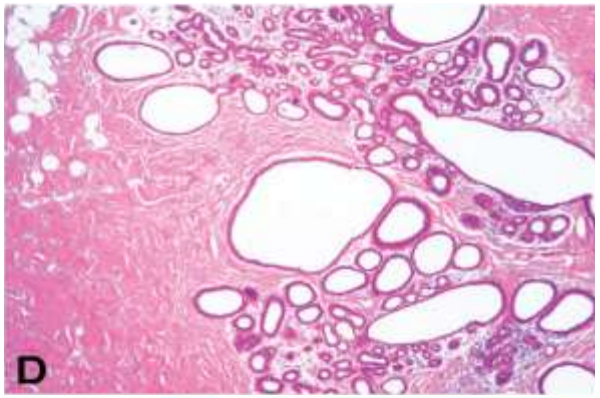


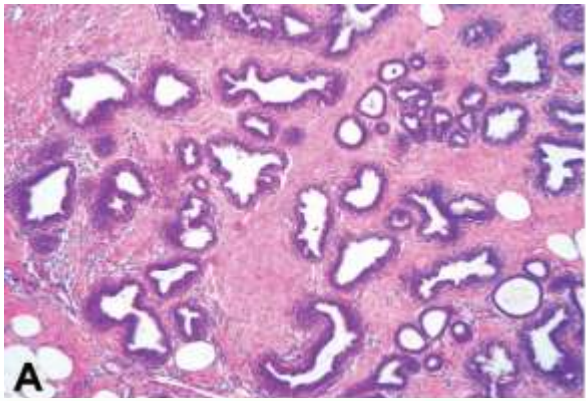


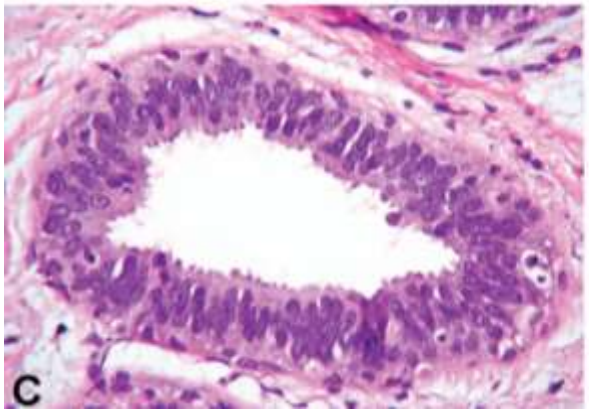
RE

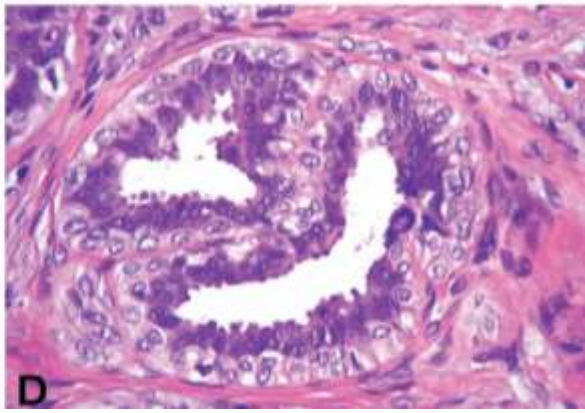
DD: Cambios columnares sin atipia/Adenosis de conductos terminales (BDA)

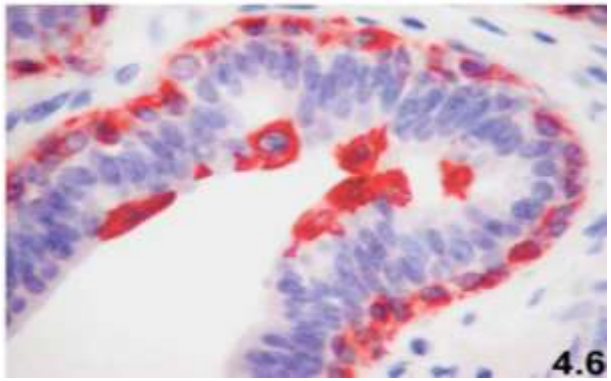
- Unidad terminal
- Patrón organoide a bajo aumento
- **Hipertrofia de células epiteliales y mioepiteliales**
- Atipia en zonas:similar
- Snouts: prominentes en ambas
- **CK 5/6** positiva en BDA y negativa en FEA

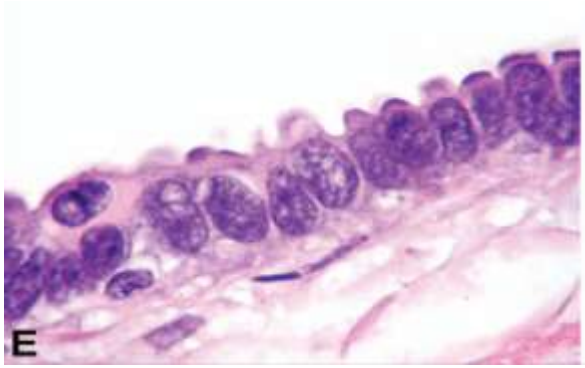


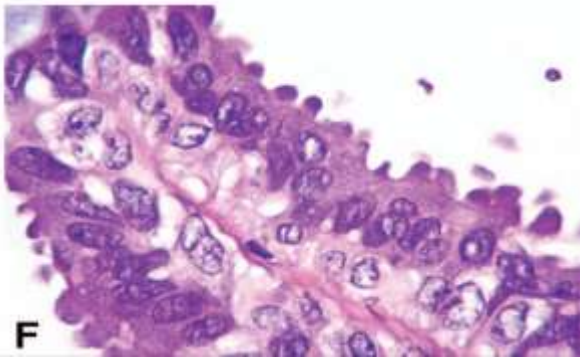


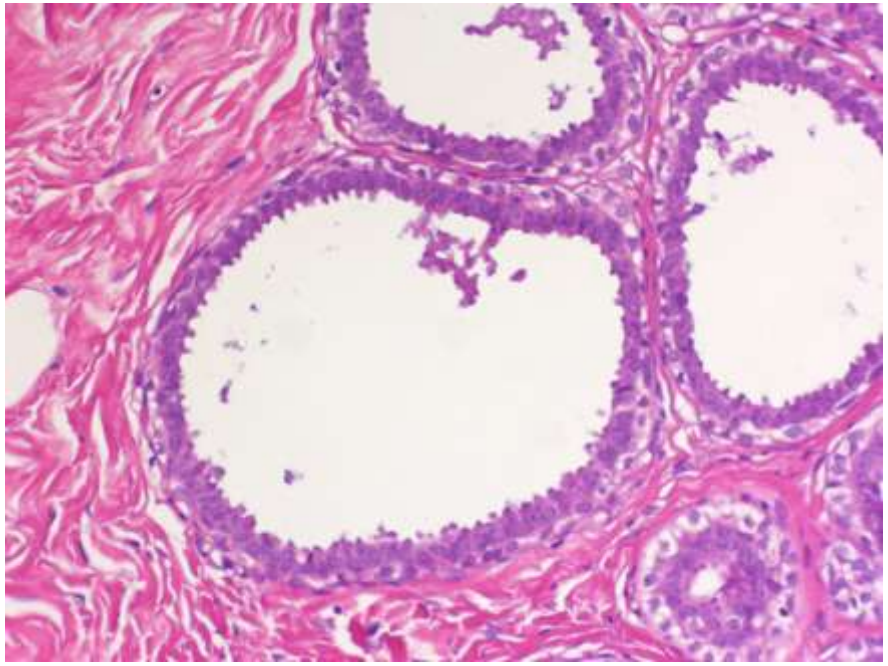


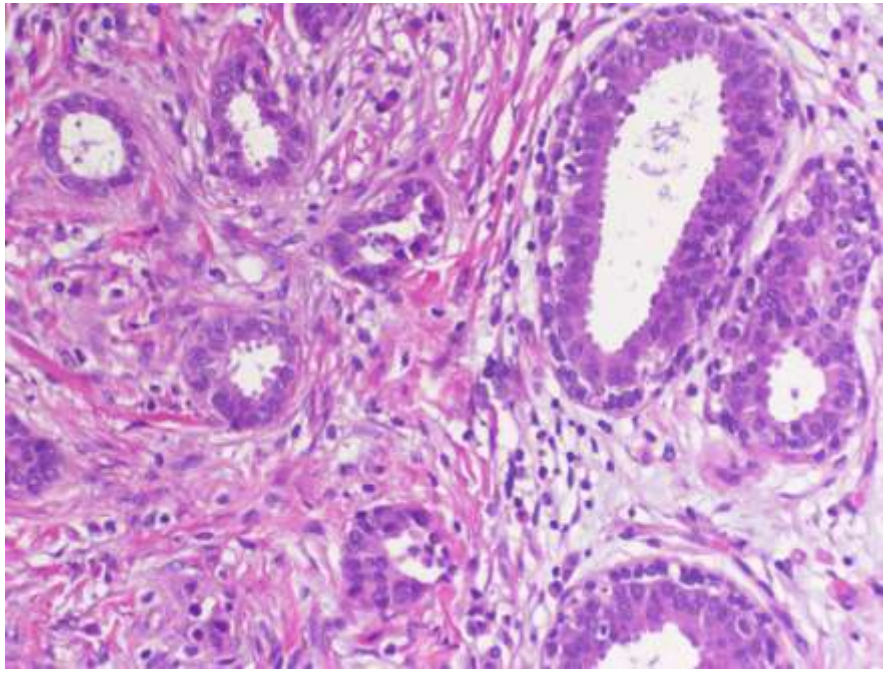


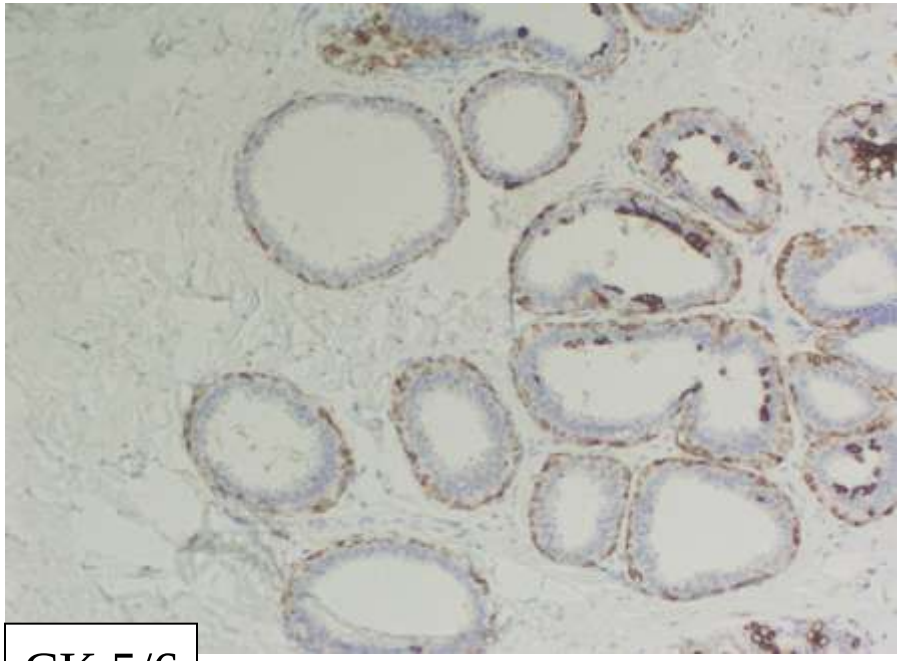




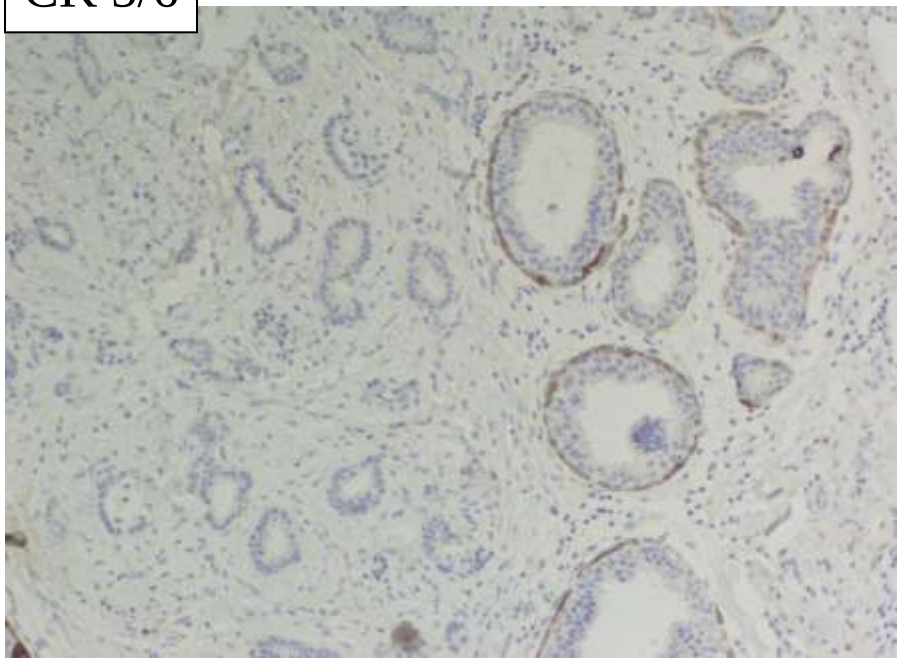






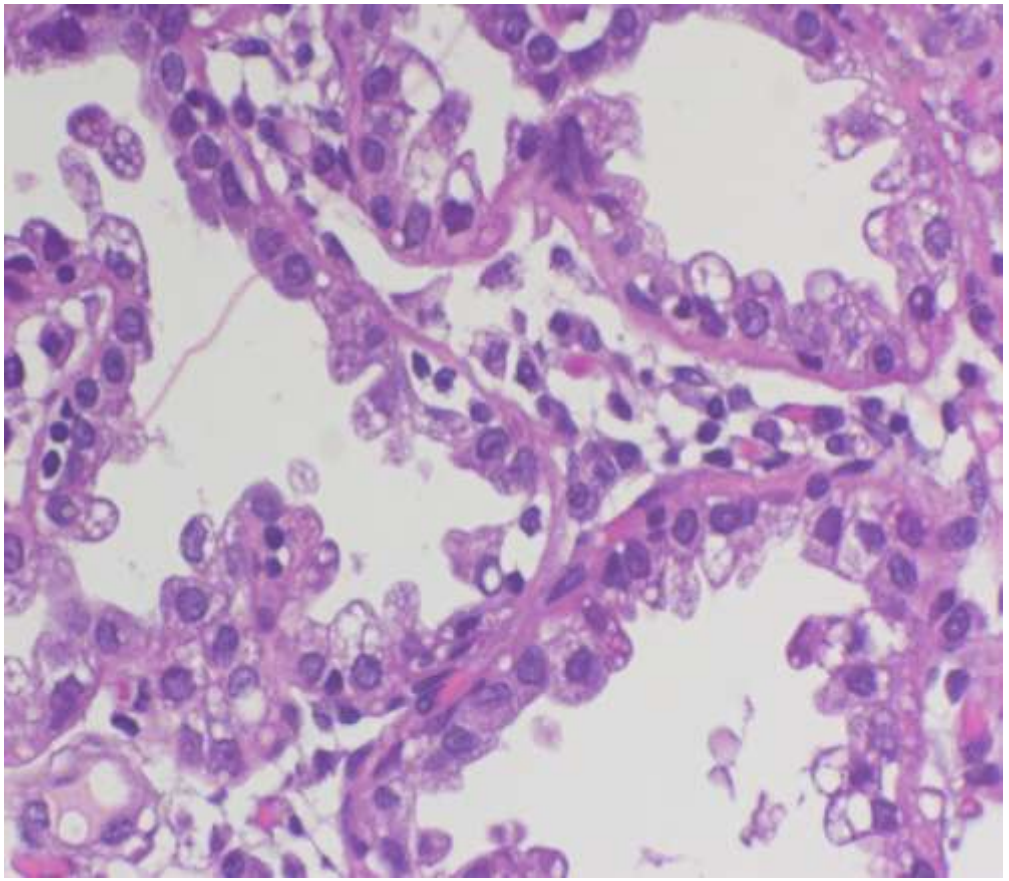


CK 5/6



DD. Cambios secretores tipo mama lactante

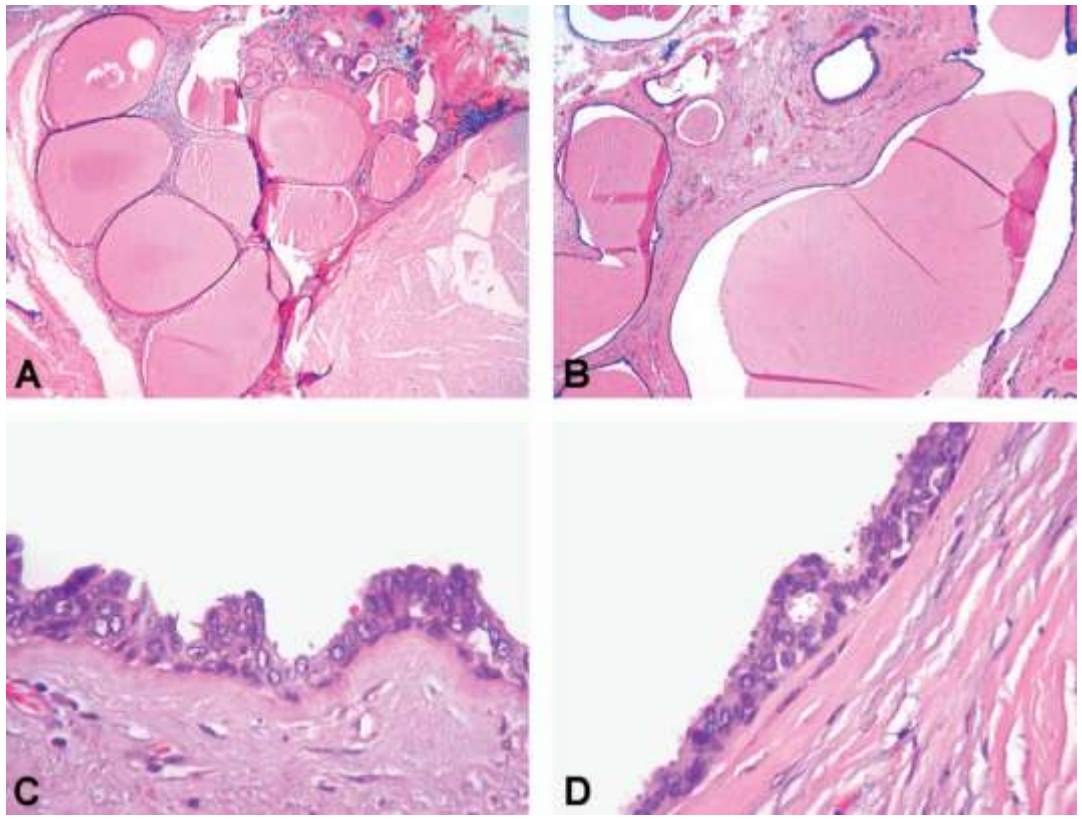
- Unidades terminales dilatadas
- “snouts” apicales
- Citoplasmas amplios y claros
- Secrecciones luminales y calcificaciones laminadas.



DD: Hiperplasia quística hipersecretora

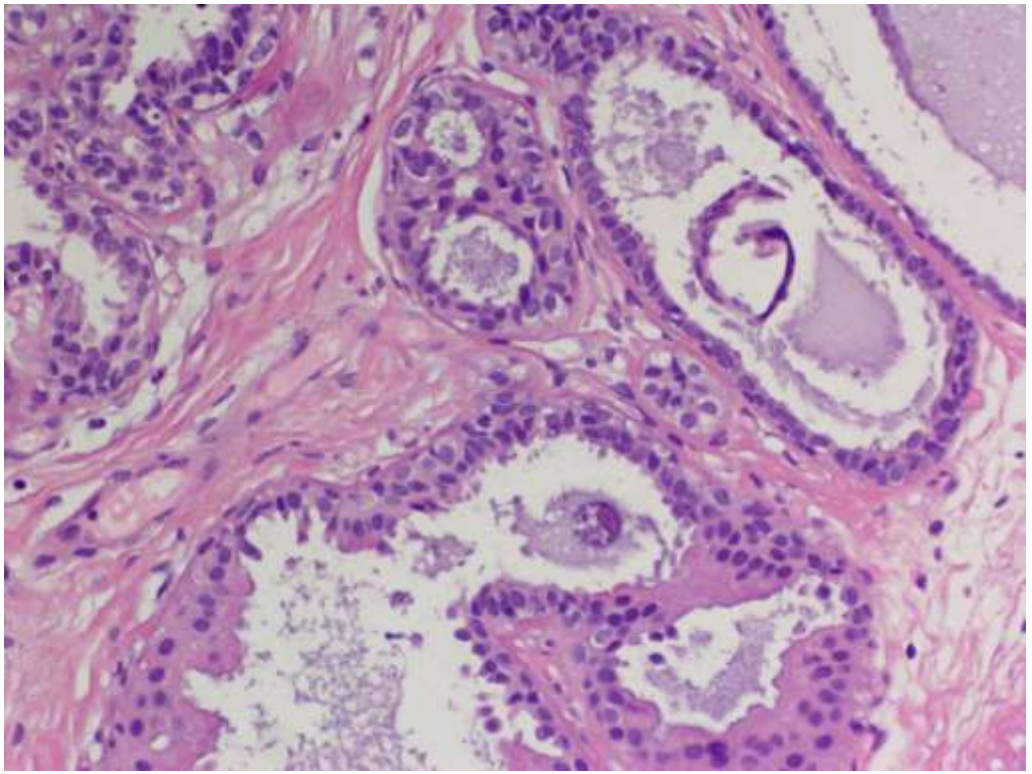
- Acinos quísticos dilatados
- Material tipo coloide intraluminal
- Epitelio columnar aplanado
- Calcificaciones raras

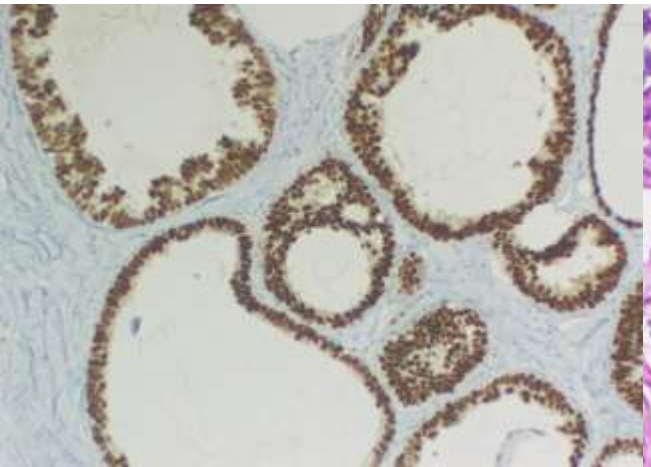
- Si epitelio atípico o varias capas y puentes o papilas: FEA variante quística hipersecretora

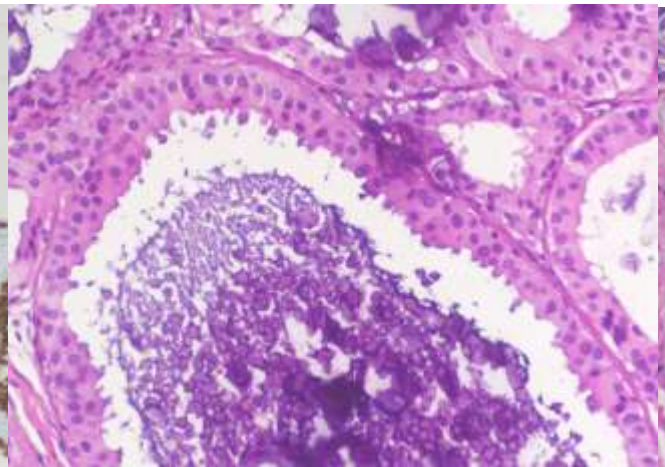


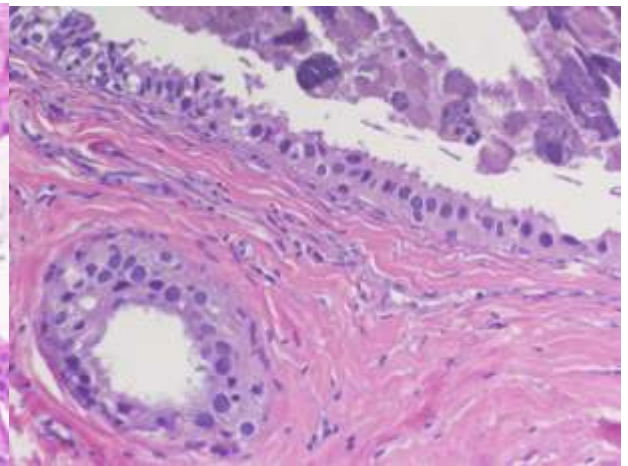
DD: Lesiones apocrinas con “atipia”

- “snouts” apicales
- Citoplasma amplio eosinófilo y granular.
- Ausencia de secrección luminal y calcificación
- RE negativos.

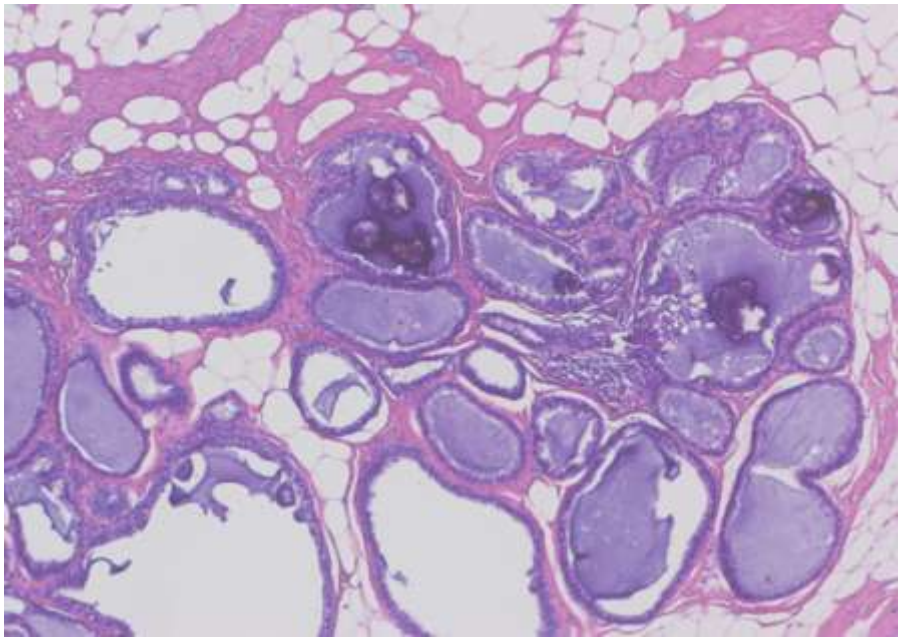


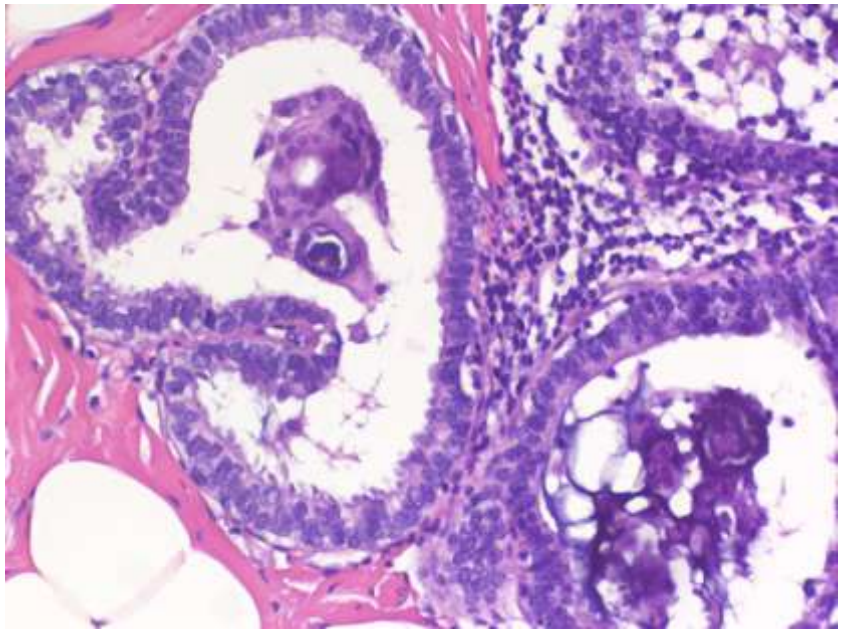


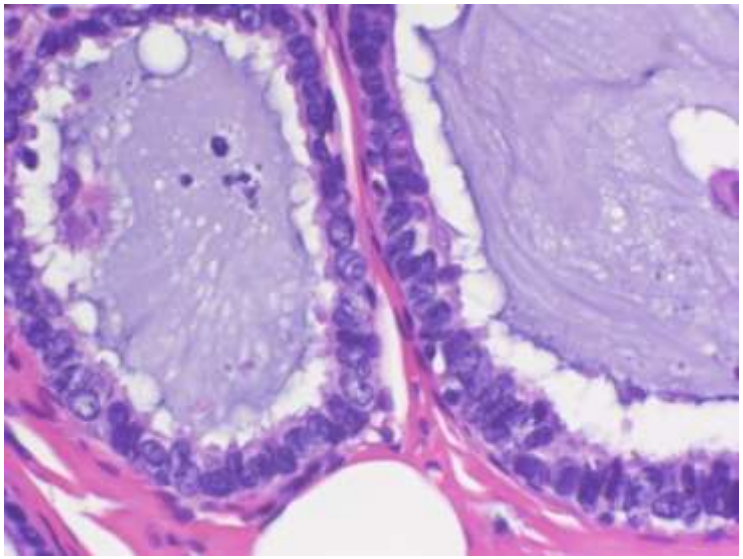


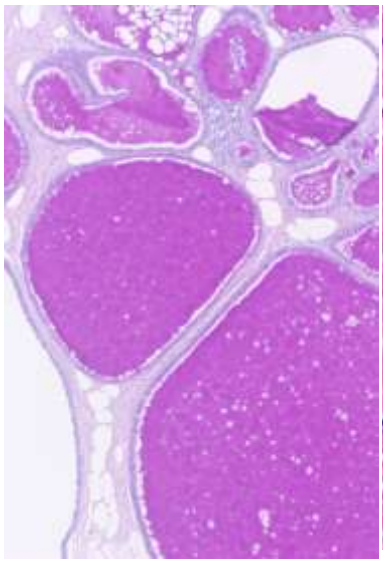


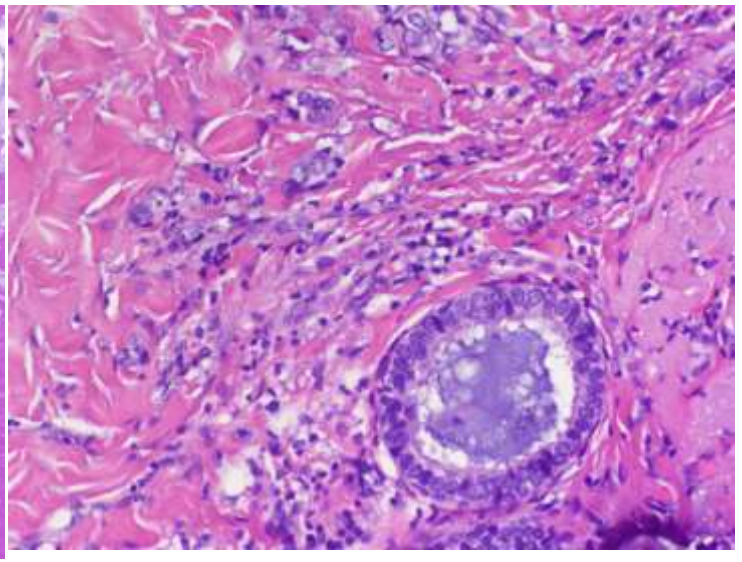
FEA con ¿metaplasia mucinosa?











Hum Pathol. 2007 Jan;38(1):35-41. Epub 2006 Nov 13. **Significance of flat epithelial atypia on mammotome core needle biopsy: Should it be excised?**

Kunju LP, Kleer CG.Department of Pathology, University of Michigan School of Medicine, Ann Arbor, MI 48331, USA.

The aim of this study was to determine the morphologic types, associations, and significance of flat epithelial atypia (FEA) with or without atypical ductal hyperplasia (ADH) in mammotome core needle biopsies. We evaluated the correlation of FEA in core biopsies with follow-up excision biopsies to predict the likelihood of upgrade to carcinoma. We also investigated the utility of Ki-67 in predicting which lesions were associated with carcinoma in the excisional biopsies. Core biopsies with a diagnosis of atypia were categorized as pure FEA, pure ADH, or both. The following parameters were recorded: indication for core biopsies, presence of microcalcifications, inflammation, and stromal changes. A total of **60 core biopsies** from 56 patients were studied. Pure ADH, pure FEA, and concomitant FEA and ADH were seen in 13%, 23%, and 64% of core biopsies, respectively. **The most common architectural pattern of FEA resembled blunt duct adenosis (52%), followed by cystically dilated ducts with secretions (38%) and apocrine features (10%). Chronic inflammation and stromal changes were noted in 29% and 36% of FEA,** respectively. Excisional biopsies in 48 of 56 patients demonstrated ductal carcinoma in situ and/or invasive carcinoma in 10 patients (21%), lobular carcinoma in situ or atypical lobular hyperplasia in 5 (11%), residual ADH in 11 (23%), and no atypia in 24 patients (50%). Three **(21%) of 14 pure FEA upgraded** to ductal carcinoma in situ and/or invasive carcinoma on excisional biopsy. The staining for Ki-67 in FEA/ADH was similar regardless of whether they were upgraded to carcinoma or not. In summary, we found a strong association between FEA and ADH, which may reflect a biologic progression**. Most FEAs have a low-power appearance of a well-circumscribed group of ducts. Chronic inflammation and stromal changes are present in a subset of cases. Flat epithelial atypia shows a risk of upgrade to carcinoma similar to that of ADH and, hence, should be recognized and warrants a follow-up excision**

FEA: Significado clínico y manejo

Eusebi V. (Sem Diagn Pathol 1989; 6:165-193)

- 21 casos CID clinging en 4000 BAG benignas con cambios fibroquísticos
- 2/21 murieron cáncer mama 12 y 5 años dp.
- **Riesgo absoluto 9.5%,** seguimiento 17 años
- No especifica si son CID clinging de bajo o alto grado.

Eusebi V. (Sem Diagn Pathol 1994; 11:223-235)

- 25 casos de CID clinging monomorfo en 9000 BAG benignas
- Un caso (4%) de recurrencia /persistencia de la lesión a los 19 años
- **Ningun caso evolucionó a c. invasivo**.

Bijker N. (J Clin Oncol 2001; 19:2263-2271)

- 59 casos CID clinging bajo grado
- Riesgo absoluto 11%.
- **Riesgo mayor de desarrollar carcinoma invasivo que la HDA**

FEA: Significado clínico y manejo

Lakshimi P. (Hum Pathol 2007; 38:35-41)

- 21% de FEA pura en BAG presentan CID o c. invasivo en biopsia excisional
- Riesgo de subdiagnóstico en BAG similar a la HDA
- **Manejo similar a la HDA**

Martel M. (Virchows Arch. 2007; 451:883-891)

- 63 casos FEA pura en 1751 BAG.
- 24 biopsias excisionales entre 0-10 años: 9 carcinomas invasivos (14%).
- FEA es un marcador de leve incremento del riesgo de desarrollo posterior de c. invasivo
- **Si en BAG FEA pura: - Biopsia excisional no obligatoria**
  - Control mamográfico estricto.

Breast Cancer Res Treat. 2010 Oct 14. **Pure flat epithelial atypia (DIN 1a) on core needle biopsy: study of 60 biopsies with follow-up surgical excision.**

Lavoué V, Roger CM, Poilblanc M, Proust N, Monghal-Verge C, Sagan C, Tas P, Mesbah H, Porée P, Gay C, Body G, Levêque J. Eugène Marquis Comprehensive Cancer Center, Rennes, France

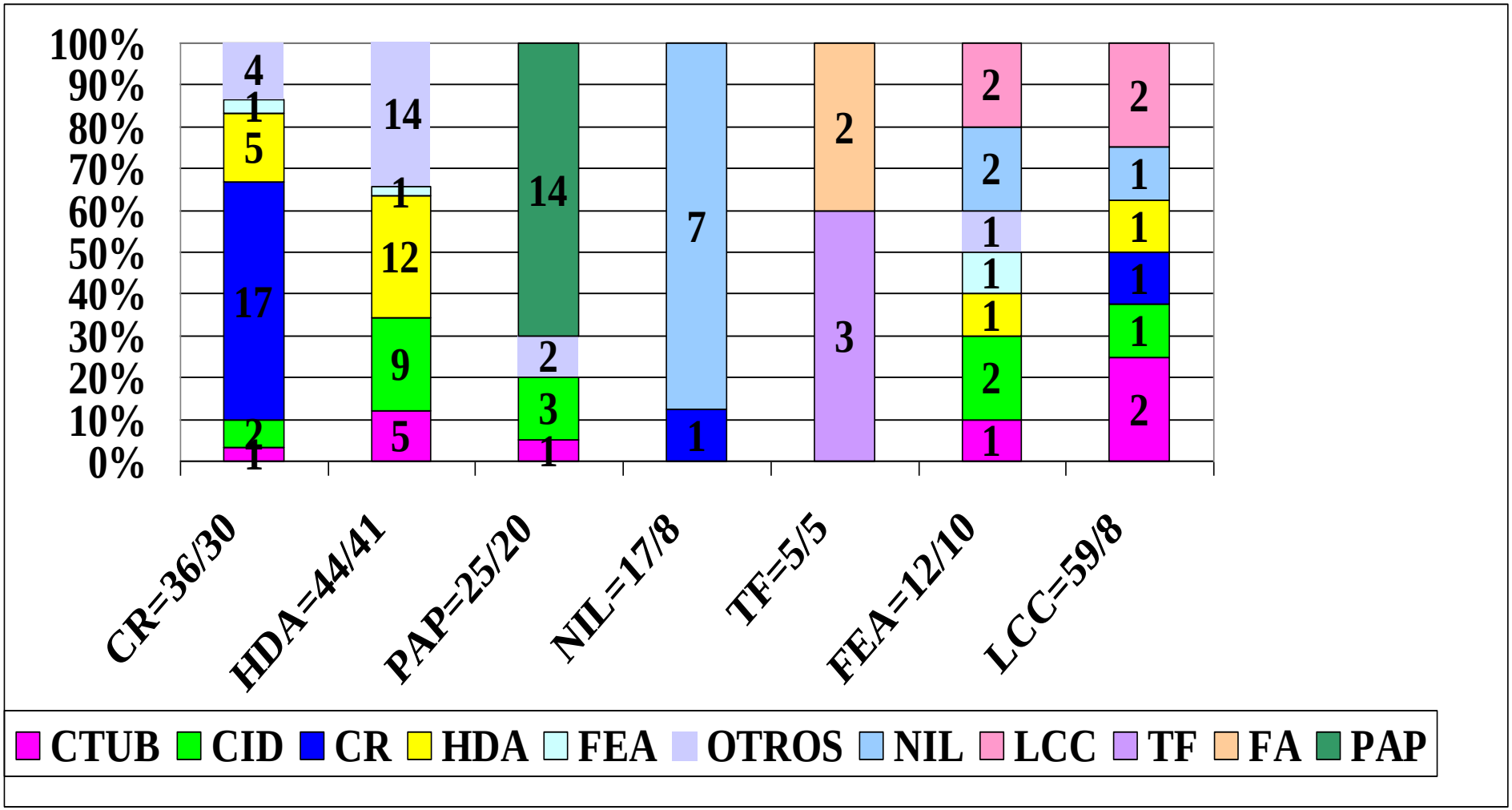
Flat epithelial atypia (FEA) is recognized as a precursor of breast cancer and its management (surgical excision or intensive follow-up) remains unclear after diagnosis on core needle biopsy (CNB). The aim of this study was to determine the underestimation rate of pure FEA on CNB and clinical, radiological, and pathological factors of underestimation. **4,062 CNBs** from 5 breast cancer centers, performed over a 5-year period, were evaluated. **A CNB diagnosis of pure FEA was made in 60 cases (1.5%)** (the presence of atypical ductal hyperplasia, lobular neoplasia, radial scars, phyllodes tumor, papillary lesions, ductal carcinoma in situ or invasive carcinoma at CNB were exclusion criteria), and subsequent surgical excision was systematically performed. The histological diagnosis was retrospectively reviewed using standardized criteria and the precise terminology of the World Health Organization by two pathologist physicians. **At surgical excision, 6 (10%) ductal carcinoma in situ and 2 (3%) invasive carcinoma were diagnosed. The total underestimation rate was 13%. FEA was associated with atypical ductal hyperplasia in 10 (17%) cases and with lobular neoplasia in 2 (3%) at final pathology.** Residual FEA was found in 14 (23%) cases. No clinical, radiological or pathological factors were significantly associated with underestimation. Our data highlight the importance of recognizing and diagnosing FEA in core needle biopsies. Thus, **the presence of FEA on CNB, even in isolation, warrants follow-up excision.**

Hum Pathol. 2010 Apr;41(4):522-7. Epub 2009 Dec 11.**Flat epithelial atypia is a common subtype of B3 breast lesions and is associated with noninvasive cancer but not with invasive cancer in final excision histology.**Noske A, Pahl S, Fallenberg E, Richter-Ehrenstein C, Buckendahl AC, Weichert W, Schneider A, Dietel M, Denkert C.Institute of Pathology, Universitätsmedizin Charité Berlin, 10117 Berlin, Germany.

The biological behavior and the optimal management of benign breast lesions with uncertain malignant potential, the so-called B3 lesions, found in breast needle core biopsies is still under debate. We addressed this study to compare histologic findings in B3 needle core biopsies with final excision specimens to determine associated rates of malignancy. Consecutive needle core biopsies were performed in a 3-year period (January 1, 2006-December 31, 2008). Biopsies were image-guided (31 by ultrasound, 85 stereotactic vacuum-assisted, 6 unknown) for evaluation of breast abnormalities. We reviewed **122 needle core biopsies with B3** lesions of 91 symptomatic patients and 31 screen-detected women and compared the B3 histologic subtypes with the final excision histology. A total **of 1845 needle core biopsies** were performed and **B3 lesions comprised 6.6%** of all B categories. **The most common histologic subtype in biopsies was flat epithelia atypia in 35.2%, followed by papillary lesions in 21% and atypical ductal hyperplasia in 20%.** Reports on excision specimens were available in 66% (81 patients). Final excision histology was benign in 73 (90.2%) and malignant in 8 (9.8%) patients (2 invasive cancer, 6 ductal carcinoma in situ). Of all B3 subtypes, atypical ductal hyperplasia and flat epithelial atypia were associated with malignancy, whereas only atypical ductal hyperplasia was accompanied by invasive cancer. Of all lesions, flat epithelial atypia was most frequently found in excision specimens (18%). In our study, **flat epithelial atypia and atypical ductal hyperplasia are associated with malignancy, whereas only atypical ductal hyperplasia was related to invasive cancer. We conclude that an excision biopsy after diagnosis of flat epithelial atypia is recommended depending on clinical and radiologic findings.**

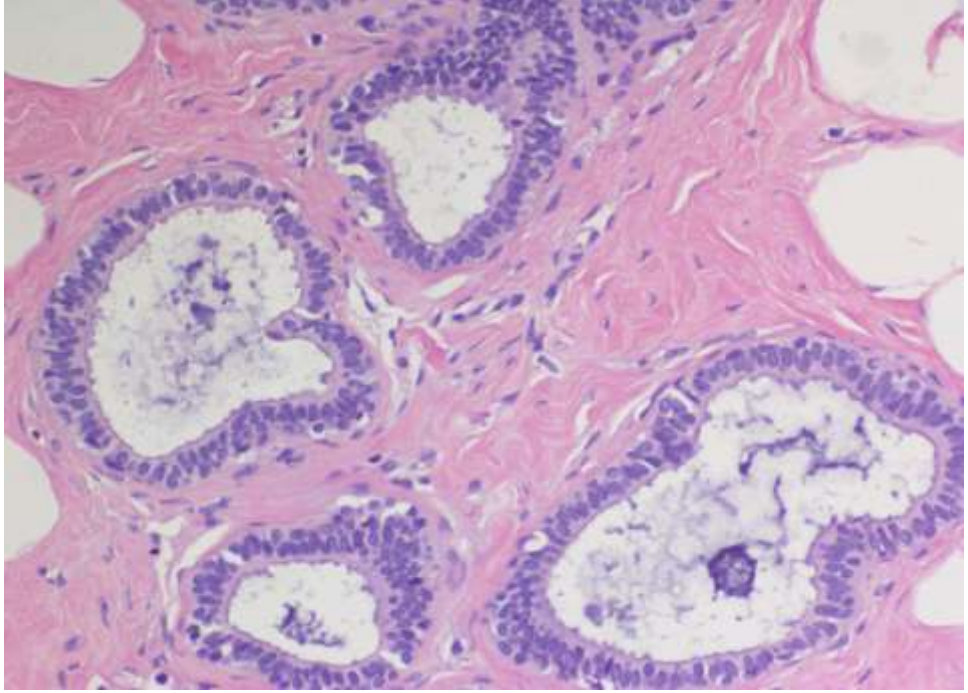
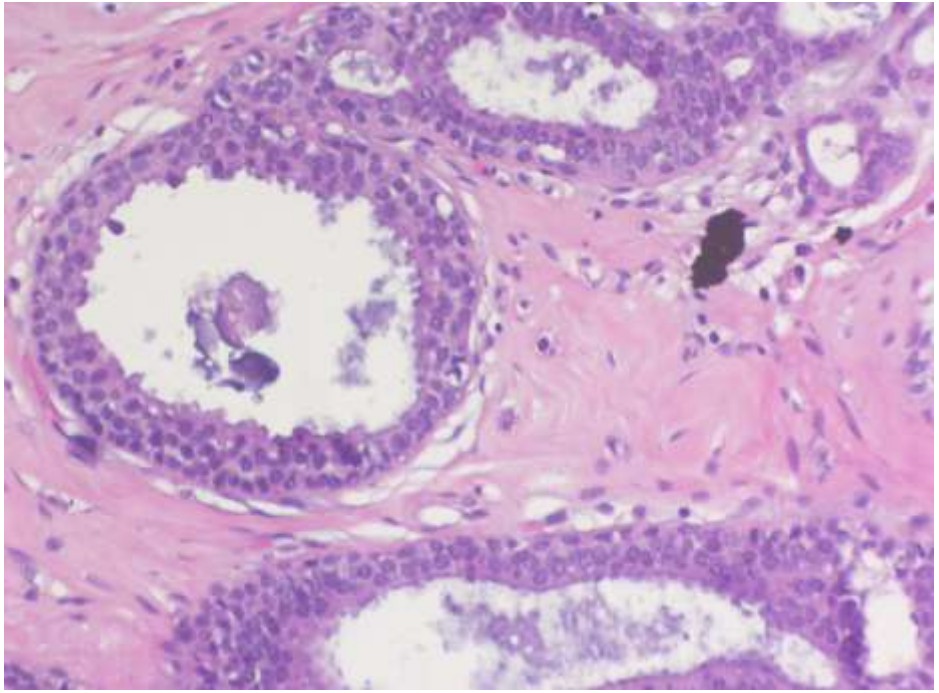
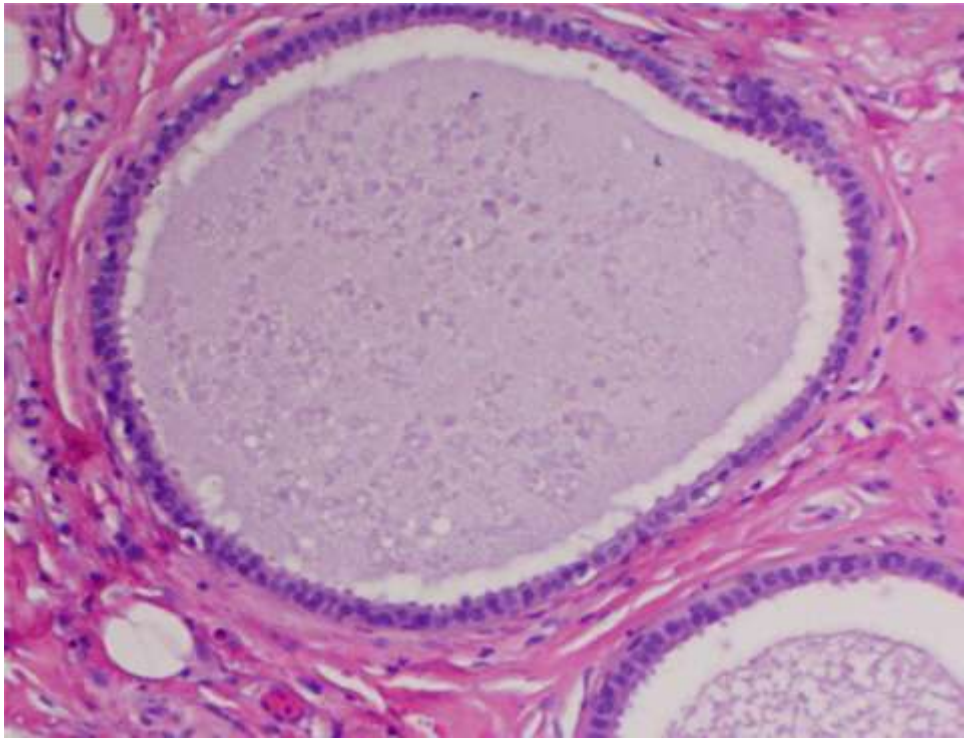
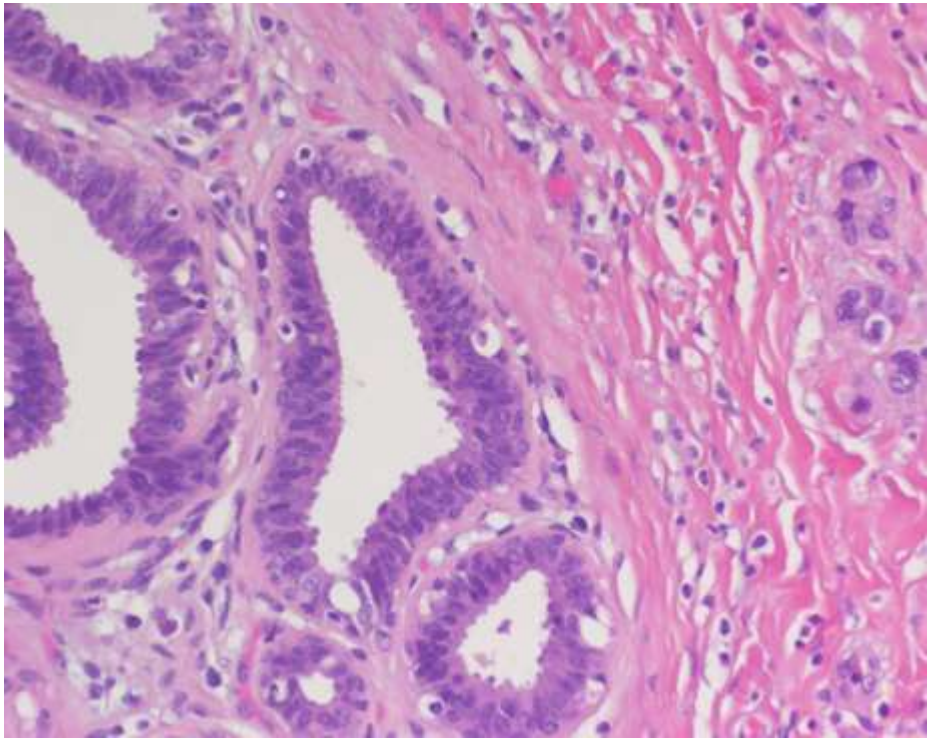
LESIONES B3
BAG/VAG/BIOPSIA QUIRURGICA

BAG/VAG=1591
B3=141(8.3%)
BQ=114 (81%)



Lesiones B3
Indice de infradiagnósticos

	CR	HDA	PAP	NIL	TF	FEA	LCC
Nº casos	36	44	25	17	5	12	59
BQ	30	41	20	8	5	10	8
Malignas	3	14	4	0	0	3	2
% infradiag.	30	32.5	20	0	0	30	25

FEA: Consideraciones prácticas

- Si en BAG diagnóstico de FEA:
  - Obtener más tejido: BAV o BAG-8G.
  - Si arcadas/micropapilas en epitelio: Diagnosticar HDA
- Si en BAG FEA pura:
  - Biopsia excisional no obligatoria
  - Control mamográfico estricto cada 6 meses
- **Si en BAG/biopsia quirúrgica: FEA: Examinar detenidamente para identificar c.tubulares o lobulillares muy pequeños.**

FEA: Consideraciones prácticas

- Si en biopsia quirúrgica focos de FEA: inclusión total de la muestra
- **FEA con atipia nuclear severa: diagnosticar CID alto grado** y manejarlo como tal. Márgenes positivos: ampliar.
- FEA frecuentemente multifocal/bilateral: los márgenes positivos no necesitan ampliación, similar al LIN.
- Criterios estandarizados de diagnóstico.
- Terminología uniforme