Actas Urológicas Españolas

www.elsevier.es/actasuro

Originals – Prostate cancer

Pseudohyperplastic carcinoma with xanthomatous changes: A neoplasm mimicking glandular hyperplasia of the prostate

J. Arista-Nasr, B. Martínez-Benítez, J.A. Fernández-Amador, L. Bornstein-Quevedo and J. Albores-Saavedra*

Department of Pathology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ), Mexico City, Mexico

ARTICLE INFORMATION

Article history:
Received on 12 May, 2009
Accepted on 16 September, 2009

Keywords:
Prostatic carcinoma
Xanthomatous
Foamy
Pseudohyperplastic
Prostatic biopsy

A B S T R A C T

Introduction and objectives: Varieties of prostatic adenocarcinoma whose architectural and cytological appearance mimicked benign lesions have been reported in recent decades. Such neoplasms include xanthomatous (foamy) carcinoma and pseudohyperplastic carcinoma. We recently studied five carcinomas showing a cytoarchitectural combination of both neoplasms which were mistaken for benign glandular proliferations.

Methods: Five cases (1.8%) of pseudohyperplastic carcinoma showing xanthomatous changes were selected from a total of 280 biopsies showing prostate carcinoma. Glandular prostatic hyperplasia was originally diagnosed in four such cases.

Results: Patient age ranged from 54 to 78 years (mean: 64 years). All patients had high prostate-specific antigen levels, and digital rectal examination showed abnormalities in four. Neoplasms showed minimal atypia and consisted of mid- to large-sized glands arranged in nests resembling hyperplastic nodules. Glands showed papillary projections, infoldings, and undulations. Most nuclei were basal, small and hyperchromatic, and nucleomegaly was observed only occasionally. Several useful criteria for the diagnosis of acinar carcinoma, such as perineural infiltration, mitosis, crystalloids, blue secretions, and prostatic intraepithelial neoplasia, were absent.

Conclusions: Prostatic carcinoma with a pseudohyperplastic pattern and xanthomatous changes mimics hyperplastic glands. Timely detection is critical to avoid treatment delay.

*Author for correspondence.
E-mail: brauliomb77@yahoo.com.mx, pipa5@hotmail.com (J. Arista-Nasr).

Carcicoma pseudohiperplásico con cambios xantomatosos: una neoplasia que semeja hiperplasia glandular de la próstata

Palabras clave:
Carcinoma prostático
Xantomatoso
Espumoso
Pseudohiperplásico
Biopsia prostática

RESUMEN

Introducción y objetivos: En las últimas décadas se han descrito variedades de adenocarcinoma prostático que por su arquitectura y su aspecto citológico semejan lesiones benignas. Estas neoplasias incluyen al carcinoma xantomatoso (espumoso) y al carcinoma pseudohiperplásico. Recientemente hemos estudiado cinco carcinomas que mostraron una combinación citoarquitectónica de ambas neoplasias y fueron confundidas con proliferaciones glandulares benignas.

Métodos: De un total de 280 biopsias con carcinoma prostático se seleccionaron cinco casos (1,8%) de carcinoma pseudohiperplásico que mostraron cambios xantomatosos. Cuatro de ellos fueron diagnosticados originalmente como hiperplasia glandular prostática.

Resultados: La edad de los pacientes varió de 54 a 78 años (promedio: 64 años). El antígeno prostático estuvo elevado en todos, y en el examen digital rectal se encontraron alteraciones en cuatro. Las neoplasias mostraron atipia mínima y estuvieron constituidas por glándulas de mediano y gran tamaño que se disponían en nidos semejantes a nódulos hiperplásicos. Las glándulas mostraron proyecciones papilares, plegamientos y ondulaciones. La mayoría de los núcleos fueron basales, pequeños e hipercromáticos, y sólo ocasionalmente se observó nucleomegalia. Varios criterios útiles en el diagnóstico de carcinoma acinar, incluyendo infiltración perineural, mitosis, cristaloides, secreciones azules y neoplasia intraepitelial prostática, estuvieron ausentes.

Conclusiones: Los carcinomas prostáticos con patrón pseudohiperplásico y cambios xantomatosos semejan glándulas hiperplásicas. Su reconocimiento oportuno es crucial para evitar retardo en el tratamiento.

Introduction

In recent decades, varieties of prostatic adenocarcinoma have been described whose cytological and architectural features mimic benign lesions. These neoplasms include foamy gland carcinoma of the prostate, also known as xanthomatous carcinoma[1-5], and pseudohyperplastic carcinoma[6-9]. Both neoplasms have been studied in specimens from radical prostatectomies, needle biopsies, and transurethral resections[1-9]. Foamy gland carcinoma is a cancer showing glands lined with cells with abundant foamy cytoplasm and small, hyperchromatic nuclei. Nucleomegaly and prominent nucleoli area rare and can be observed in isolated fields. Dense eosinophilic intraluminal secretions are common. In some cases, diagnosis requires immunohistochemistry to confirm the absence of basal cells. Most foamy gland carcinomas are moderately differentiated[2].

Under low magnification, pseudohyperplastic carcinoma displays a benign architectural pattern. It consists of medium and large glands arranged in nests resembling hyperplastic nodules. In most cases the glands have papillary infoldings, intraluminal undulations, or cystic dilations. The complex variety of this cancer shows multiple undulations and foldings, and glands crowded together. Most cases show nucleomegaly and/or prominent nucleoli that suggest malignancy[6].

We recently reviewed five needle biopsies showing a pseudohyperplastic pattern and cytological characteristics of foamy gland carcinoma. All biopsies showed minimal atypia, and four were originally interpreted as prostatic glandular hyperplasia. The aim of this study is to describe the clinicopathological characteristics of these neoplasms and to illustrate criteria that help recognize them as malignant.

Methods

From 2007 to 2008 we reviewed 280 biopsies with prostate carcinoma, five of which (1.8%) were carcinomas with a pseudohyperplastic pattern. The lining cells had a xanthomatous appearance, with small hyperchromatic nuclei. Sextant biopsies were taken from all five patients, and the number of fragments per biopsy ranged from six to ten. In each case, the following data were analyzed: age, digital rectal examination, prostate-specific antigen (PSA) level, additional biopsies, clinical course, and metastasis.

In the histological analysis the findings form the first biopsy were recorded, including number of fragments with carcinoma, size of the cancerous glands, growth pattern, glands with undulations, papillary projections and/or irregular borders, nucleomegaly, prominent nucleoli, mitoses, perineural invasion, basophilic or eosinophilic intraluminal secretions, crystalloids, prostatic intraepithelial neoplasia, and areas of conventional acinar carcinoma. When the nucleus occupied 10% of the cell surface or less, this was interpreted as a xanthomatous change[10]. The Gleason score was recorded only when areas of acinar carcinoma were

observed in the biopsy or the prostatectomy. Findings in the prostatectomy and in the additional biopsies were also recorded.

In all five cases immunohistochemical studies were done with high molecular weight keratins (34BE12 and keratin 5/6, Dako Corporation®) to establish the presence or absence of basal cells.

Results

Table 1 summarizes the clinical data, and table 2 the histological biopsy findings.

Case 1. A 54-year-old man. The digital rectal examination revealed prostate induration; PSA was 12.7 ng/mL. Two of the ten fragments obtained with the biopsy showed large neoplastic glands arranged irregularly (fig. 1), with papillary projections, luminal undulations, and cystic dilations. Most glands were lined with columnar cells with xanthomatous changes. The nuclei were small and hyperchromatic; there was no nucleomegaly or prominent nucleoli (figs. 1 and 2). The original diagnosis was glandular hyperplasia. When the biopsy was reviewed, carcinoma was suspected due to the irregular arrangement of glands and the xanthomatous changes in the lining cells. After confirming the absence of basal cells (fig. 3), it was concluded that this was a pseudohyperplastic carcinoma with xanthomatous changes. A radical prostatectomy was performed, which revealed foamy gland carcinoma in both lobes. The neoplastic glands were predominantly of medium and large size, had abundant intraluminal eosinophilic secretion, and were interspersed with smaller, apparently infiltrating neoplastic glands (fig. 4). Conventional acinar adenocarcinoma was observed in isolated fields, and the Gleason score was 7 (patterns 4 plus 3). The neoplasm involved approximately 40% of the prostate and was limited to the gland, with no pelvic lymph node metastases.

Case 2. A 62-year-old man with two high determinations of PSA (4.9 ng/mL and 5.2 ng/mL). The digital rectal examination did not reveal abnormalities. The neoplasm had large neoplastic glands with minimal nuclear atypia, a papillary pattern and multiple infoldings that closely resembled glandular hyperplasia. The lining cells were xanthomatous, and the nuclei were basal, small, and hyperchromatic (figs. 5 and 6). The immunohistochemical staining with high molecular weight keratins revealed an absence of basal cells (fig. 7). Radiological tests did not show metastasis.

Case 3. A 66-year-old man with prostate induration and PSA 4.6 and 6.2 ng/mL. The neoplasm was found in two of six fragments; it displayed irregularly arranged glands separated by a moderate amount of stroma (fig. 8). Most glands were of medium or large size, and had glandular foldings and intraluminal papillary projections. The lining cells had abundant clear cytoplasm and small, hyperchromatic basal nuclei (fig. 8). Small amounts of intraluminal eosinophilic secretions were found in isolated fields. The original diagnosis was glandular hyperplasia. One year after the first biopsy, PSA rose to 15.5 ng/mL, and a second biopsy was done; this showed areas of foamy gland carcinoma with pseudohyperplastic appearance in continuity with a high-grade foamy gland carcinoma (Gleason score 8, pattern 4 plus 4) (fig. 9).

Case 4. A 78-year old man with an indurated node in the right prostate lobe. PSA was 12 ng/mL. A sextant biopsy was taken. A pseudohyperplastic carcinoma with xanthomatous changes was found in one of the six slides. The neoplastic glands were arranged in irregular nodes, and were lined with columnar cells with abundant clear cytoplasm. The nuclei were small, basal, and hyperchromatic; nucleomegaly was observed only in isolated fields. The original diagnosis was nodular hyperplasia of the prostate. When analyzed retrospectively, the irregular growth pattern of the pseudohyperplastic glands and the foamy cytoplasm

Table 2 – Pseudohyperplastic carcinoma with xanthomatous pattern

Histological findings in prostate biopsy	
Medium and large glands	5
Glandular foldings and undulation	5
Intraluminal papillary projections	5
Xanthomatous cytoplasm	5
Columnar cells	5
Small, hyperchromatic basal nuclei	5
Eosinophilic secretions	2
Nucleomegaly	2
Prominent nucleoli	1
Basophilic secretions	no
Mitoses	no
Perineural invasion	no
Crystalloids	no
Prostatic intraepithelial neoplasia	no

Table 1 – Foamy gland carcinoma with pseudohyperplastic pattern

	Age	Digital rectal exam	PSA
Clinical findings			
Case 1	54 years	Prostate induration	12.7 ng/mL
Case 2	62 years	No abnormalities	4.9 and 5.2 ng/mL
Case 3	66 years	Prostate induration	4.6 and 6.2 ng/mL
Case 4	78 years	Node in the right lobe	12 ng/mL
Case 5	62 years	Bilateral induration	20.7 ng/mL

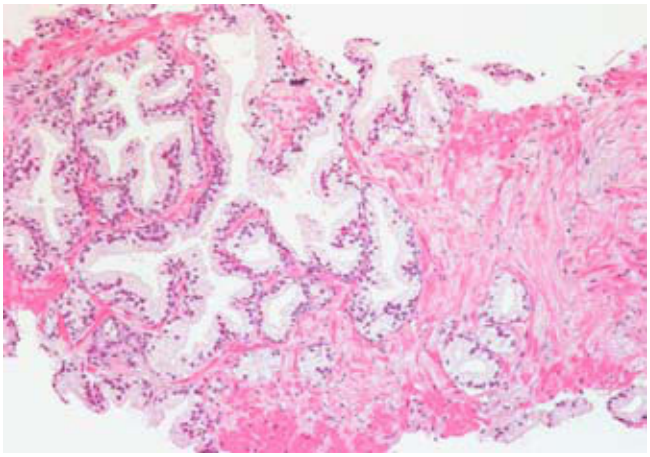

Figure 1 – (Case 1). Pseudohyperplastic carcinoma with xanthomatous pattern. The image suggests hyperplasia, but the neoplastic glands are arranged in poorly-defined nests, are irregularly distributed, and large.

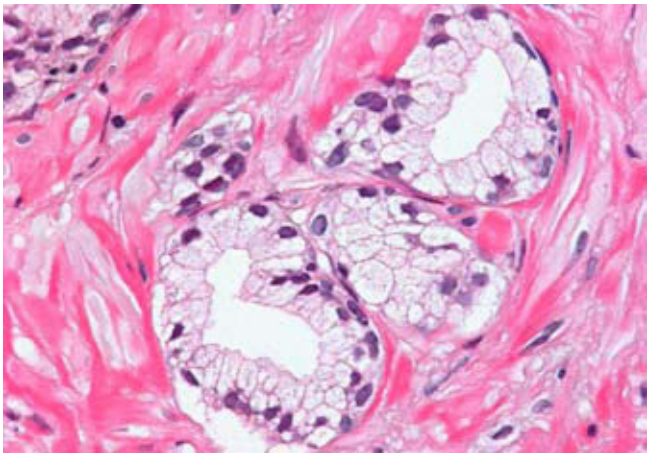

Figure 2 – (Case 1). Medium-sized glands in a pseudohyperplastic carcinoma with xanthomatous changes.

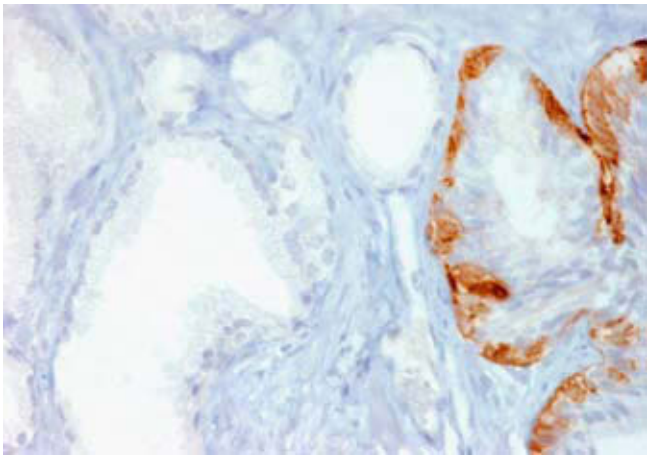

Figure 3 – (Case 1). High molecular weight keratin (keratin 5/6), positive in benign residual gland (right), and negative in a nest of neoplastic cells with a pseudohyperplastic pattern (left).

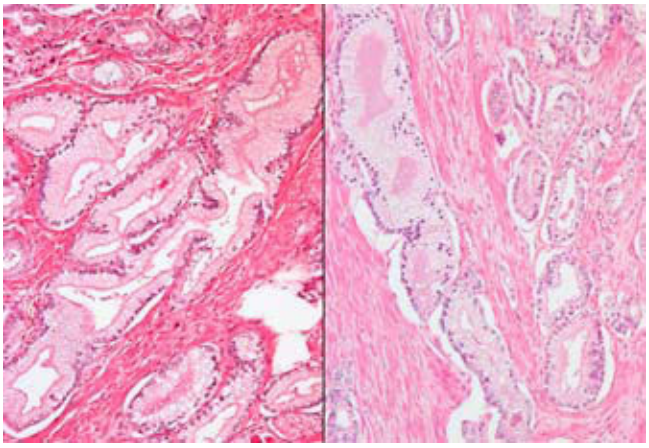

Figure 4 – (Case 1). Pseudohyperplastic carcinoma with xanthomatous pattern in a specimen from prostatectomy. The glands have a pseudohyperplastic aspect and xanthomatous cytoplasm (left). There is abundant intraluminal eosinophilic secretion in some fields (right). Near the foamy glands there are smaller, infiltrative-looking cells.

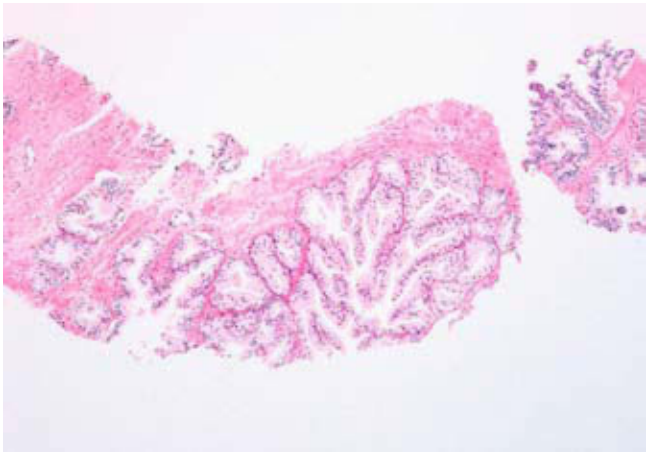

Figure 5 – (Case 2). Pseudohyperplastic carcinoma with xanthomatous changes and minimal atypia resembling a hyperplastic node.

suggested the diagnosis of pseudohyperplastic carcinoma with xanthomatous changes. After documenting the absence of basal cells, the lesion was reclassified as carcinoma, and hormone therapy was initiated. Fifteen months later, there was no evidence of extraprostatic disease, and the last PSA was 9.5 ng/mL.

Case 5. A 62-year-old man with PSA 20.7 ng/mL. The digital rectal examination revealed induration of both prostate lobes. Pseudohyperplastic carcinoma with xanthomatous changes was found in 3 of the 10 fragments. The neoplastic glands were large and had papillary projections and foldings (figs. 10 and 11). Nucleomegaly and prominent nucleoli were identified in isolated glands. In one fragment, the pseudohyperplastic carcinoma was admixed with acinar carcinoma consisting of small glands which were recognizably malignant due to their

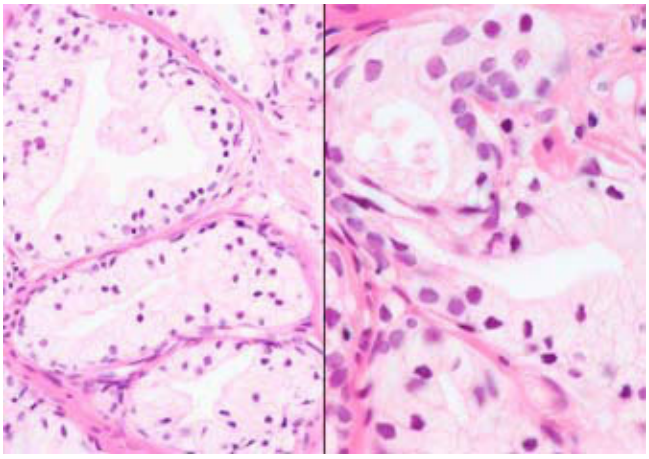

Figure 6 – (Case 2). Pseudohyperplastic carcinoma with xanthomatous changes. The cells have a foamy cytoplasm, and small hyperchromatic nuclei.

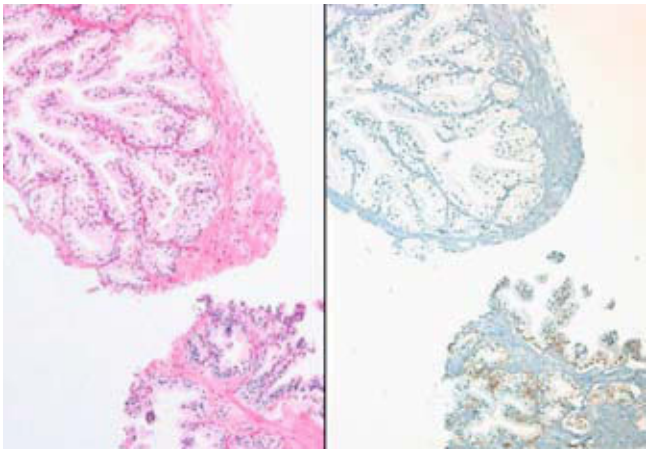

Figure 7 – (Case 2). Immunohistochemical staining with high molecular weight keratins. The pseudohyperplastic node is negative, in contrast to the benign residual tissue (right).

infiltrative appearance. The Gleason score in these areas was 8 (pattern 4 plus 4) (fig. 10). At the time of the review there was no evidence of metastasis, and a prostatectomy was planned.

None of the five biopsies showed mitoses, intraluminal basophilic secretions, neural invasion or prostatic intraepithelial neoplasia (table 2).

Immunohistochemistry

High molecular weight keratin testing (34BE12 and keratin 5/6, Dako Corporation) confirmed the absence of basal cells in the malignant glands, and was negative in neoplastic cells. In contrast, benign prostate tissue is strongly positive in the basal cells of the lining (figs. 3 and 7).

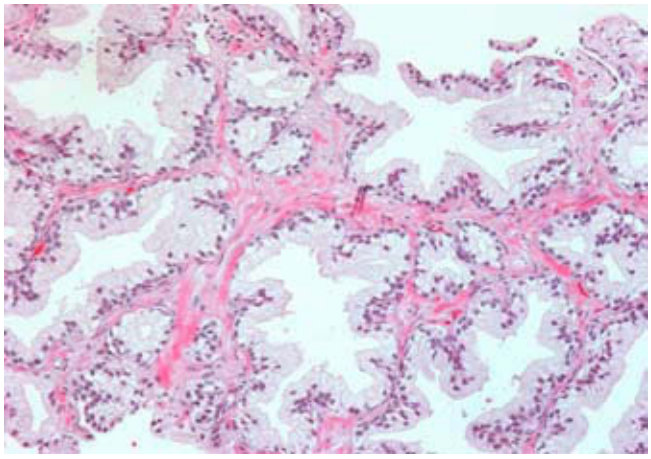

Figure 8 – (Case 3). First biopsy. Pseudohyperplastic carcinoma with xanthomatous changes. The neoplasm shows medium to large glands arranged in an irregular pattern. Most have multiple glandular foldings and intraluminal papillary projections. The cytoplasm is clear and abundant, and the nuclei are small and hyperchromatic.

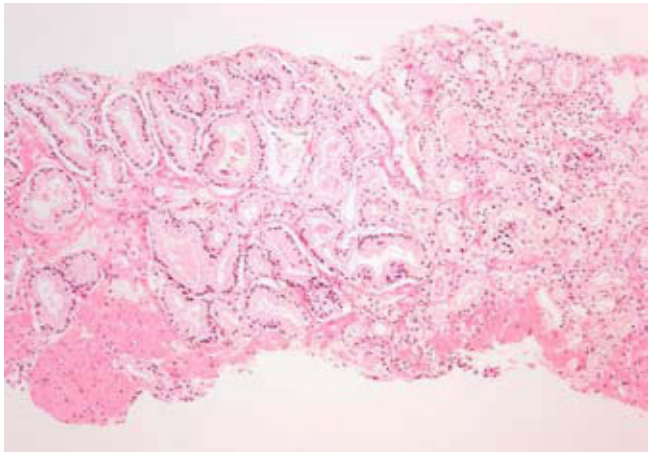

Figure 9 – (Case 3). Second biopsy On the left, pseudohyperplastic carcinoma with foamy changes, and medium and large glands. On the right, the glands are small and have an infiltrative aspect. There are small amounts of intraluminal eosinophilic secretions.

Discussion

The combination of histological patterns in human malignant neoplasms is a relatively common phenomenon, and has been documented in many organs. The association of conventional acinar carcinoma with several variants of carcinomas, such as atrophic, pseudohyperplastic, and foamy gland carcinoma, is common in the prostate[10].

The tumors described in this article resembled benign glandular proliferation because they presented the well-differentiated architectural pattern typical of

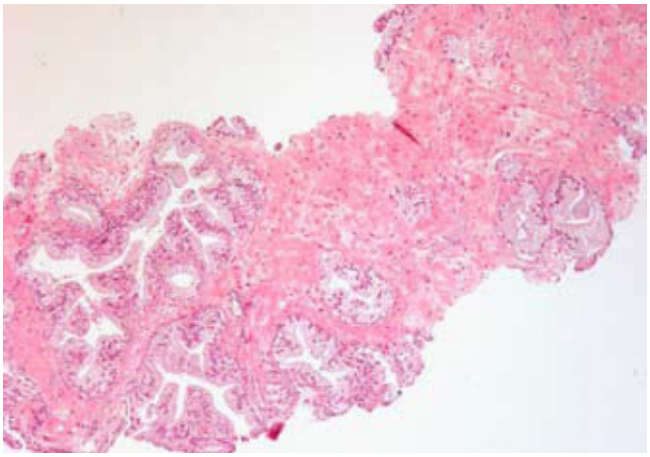

Figure 10 – (Case 5). On the left, the neoplasm shows glands in an branching pattern, with multiple foldings and papillary projections. On the right, smaller glands with infiltrative aspect are observed.

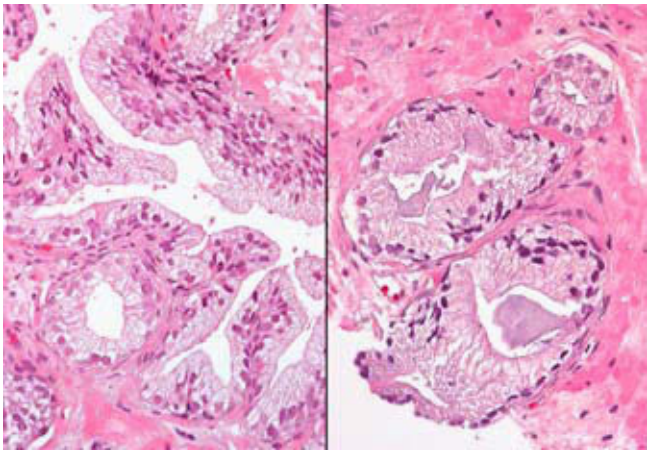

Figure 11 – (Case 5). Detail of the pseudohyperplastic glands. There are xanthomatous changes in the cytoplasm. The nuclei are small and hyperchromatic, and arranged uniformly at the base of the cells.

pseudohyperplastic carcinoma, and the minimal cell atypia characteristic of the foamy gland carcinoma. Four of the five cases were originally diagnosed with nodular hyperplasia of the prostate; the exception was case 5, which showed small glands in an infiltrative pattern.

The diagnosis of pseudohyperplastic carcinoma with xanthomatous changes should be suspected when there are irregularly-arranged medium or large neoplastic glands with foldings, undulations and papillary projections resembling hyperplastic nodes. If the lining cells have xanthomatous cytoplasm and small, hyperchromatic nuclei at the base, the diagnosis of pseudohyperplastic carcinoma with xanthomatous changes should be considered. When in doubt, the diagnosis should be confirmed with immunohistochemical staining, since xanthomatous cells are occasionally found in prostate hyperplasia[11]. Another difference that helps to distinguish between hyperplastic from pseudohyperplastic neoplastic glands is the presence of easily recognizable basal cells in most hyperplastic nodes.

Several useful criteria for diagnosis of prostate carcinoma, including perineural infiltration, mitoses, crystalloids, blue secretions, and prostatic intraepithelial neoplasia, were absent. Additionally, there were scarce intraluminal secretions, which were limited to isolated fields. The absence of several useful criteria for the diagnosis of malignancy in the usual type pseudohyperplastic carcinomas has been acknowledged[9].

The absence of nucleomegaly and the presence of prominent nucleoli in most cells in foamy gland carcinoma is well documented, and most of these neoplasms show small, hyperchromatic, basophilic nuclei[2,4,5]. In the five cases described here, the nuclei were small and hyperchromatic, and uniformly situated at the base of the neoplastic cells. Iczkowsky and Bostwick[12] have pointed out that nuclear hyperchromasia is often a staining artifact, and its presence may support the diagnosis of carcinoma in glandular proliferations suspected of malignancy.

The differential diagnosis of foamy gland carcinoma includes prostate adenosis, xanthogranulomatous prostatitis, Cowper glands, mucinous metaplasia, low-grade carcinomas[13], and clear cell cribriform hyperplasia[14]. Since the neoplastic glands in foamy gland carcinoma with a pseudohyperplastic pattern contain medium and large cells, the differential diagnosis includes nests of hyperplastic glands, low-grade carcinoma, clear cell cribriform hyperplasia, usual type pseudohyperplastic carcinoma, and prostatic intraepithelial neoplasia. The differences between hyperplastic glands and pseudohyperplastic carcinoma are mentioned above. Low-grade carcinoma may have glands lined with clear cells resembling those of foamy gland carcinoma[10]; however, cells often show nucleomegaly and prominent nucleoli, and have smaller amounts of clear cytoplasm. In clear cell cribriform hyperplasia, basal cells are identified in the periphery of the acini, which become more apparent with high molecular weight cytokeratin staining. Additionally, pseudohyperplastic carcinoma shows non-fused neoplastic glands, which provide a cribriform aspect[14]. The difference between pseudohyperplastic carcinoma with xanthomatous features and the usual pseudohyperplastic carcinoma resides in the absence of nucleomegaly and/or prominent nucleoli in the former; most cases of usual type pseudohyperplastic carcinoma show nucleomegaly and prominent nucleoli[2,6]. Prostatic intraepithelial neoplasia appears in medium and large ducts, lacks foldings, and the lining cells have variable amounts of nucleoli that contrast with the small, hyperchromatic nuclei present in pseudohyperplastic carcinoma with xanthomatous changes[15].

The prognosis of neoplasms with a combination of different histological findings described here is unknown. Metastasis was found in none of the five cases; however, the follow-up period was too short, never exceeding two years.

Conclusions

Pseudohyperplastic carcinoma with xanthomatous features is an uncommon neoplasm; however, when it is found in needle biopsies as the sole pattern, it can be easily mistaken for benign glandular proliferation. Both foamy gland carcinoma and pseudohyperplastic carcinoma are neoplasms described in the past few decades; their morphology may be more varied than recognized until now.

Conflict of interest

The authors state that they have no conflicts of interest.

REFERENCES

1. Schindler S, Usman NI, Yokoo H. Foamy gland carcinoma. Am J Surg Pathol. 1996;20:419-26.
   Schindler S, Usman NI, Yokoo H. Foamy gland carcinoma. Am J Surg Pathol. 1997;21:616-8.
2. Nelson RS, Epstein JI. Prostatic carcinoma with abundant xanthomatous cytoplasm. Am J Surg Pathol. 1996;20:419-26.
3. Berman DM, Yang J, Epstein JI. Foamy gland high-grade prostatic intraepithelial neoplasia. Am J Surg Pathol. 2000;24:140-4.
4. Llarena Ibarguren R, Lecumberri Castaños D, Padilla Nieva J, Crespo Atín V, Martín Bazaco J, Azurmendi Sastre V, et al. Foamy carcinoma of the prostate. Arch Esp Urol. 2003;56: 833-5.
5. Arista-Nasr J, Martínez-Benítez B, Camorlinga-Tagle N, Albores-Saavedra J. Foamy gland microcarcinoma in needle prostatic biopsy. Ann Diagn Pathol. 2008;12:349-55.
6. Humphrey PA, Kaleem Z, Swanson PE, Vollmer RT. Pseudohyperplastic prostatic adenocarcinoma. Am J Surg Pathol. 1998;22:1239-46.
7. Arista-Nasr J, Cortés E, Pichardo R. Low grade adenocarcinoma simulating benign glandular lesions in needle prostatic biopsy. Rev Invest Clin. 1997;49:37-40.
8. Arista-Nasr J, Martínez-Benítez B, Valdés S, Hernández M, Bornstein-Quevedo L. Pseudohyperplastic prostatic adenocarcinoma in transurethral resections of the prostate. Pathol Oncol Res. 2003;9:232-5.
9. Levi AW, Epstein JI. Pseudohyperplastic prostatic adenocarcinoma on needle biopsy and prostatectomy. Am J Surg Pathol. 2000;24:1039-46.
10. Epstein JI, Netto GJ. Diagnosis of limited adenocarcinoma of the prostate. En: Epstein JI, Netto GJ, editors. Biopsy Interpretation of the Prostate. Fourth edition. Philadelphia: Lippincott Williams; Wilkins, 2002; 72–104.
11. Bignardi P. Prostatic carcinoma of xanthomatous type and metaplasia of similar type in the prostate. Arch De Vecchi Anat Patol. 1961; 35:645-51.
12. Iczkowsky KA, Bostwick DG. Criteria for biopsy diagnosis of minimal volume prostatic adenocarcinoma: Analytic comparison with non diagnostic but suspicious atypical small acinar proliferation. Arch Pathol Lab Med. 2000;124:98-107.
13. Srigely JR. Benign mimickers of prostatic adenocarcinoma. Mod Pathol. 2004;17:328-48.
14. Ayala AG, Srigley JR, Ro JY, Abdul-Karim FW, Jhonson DE. Clear cell cribriform hyperplasia of prostate. Report of 10 cases. Am J Surg Pathol. 1986;10:665-71.
15. Bostwick DG. Progression of prostatic intraepithelial neoplasia to early invasive adenocarcinoma. Eur Urol. 1996;30:145-52 Review.