

ATYPICAL SMALL GLANDS IN PROSTATE NEEDLE BIOPSIES. DIAGNOSTIC VALUE OF CLINICOPATHOLOGICAL PARAMETERS

CARLOS ALVAREZ-ALVAREZ, E. ALEXSANDRO DA SILVA, DANIEL PESQUEIRA,
PILAR SAN MIGUEL-FRAILE, JOSÉ ANTONIO ORTIZ-REY, IOSU ANTÓN-BADIOLA,
ANA DE LA FUENTE-BUCETA

Departments of Pathology and Urology, POVISA Medical Center, Vigo, Pontevedra, Spain

ABSTRACT

Background: The purpose of this study was to report our experience on prostate needle biopsy specimens that contained foci of atypical suspected acini but not diagnosed for malignancy.

Material and Methods: We reviewed all the prostate needle biopsies performed at our institution between January 1988 and June 1999. Cases diagnosed as atypical with suspected malignancy and without previous histopathological diagnosis of prostate carcinoma were re-evaluated and several clinicopathological data were assessed. A comparison was made between eventually malignant and benign groups. For all cases the histological diagnostic suspicion was separated into 3 groups (probably benign; uncertain; probably malignant).

Results: 39 (2.89%) patients showed foci of atypical small acinar proliferation (ASAP). On review, 19 cases were found to have an adequate follow-up. Of these, 10 (52.63%) were later found to have adenocarcinoma, with a mean Gleason score of 6.28. Forty-two percent of cases with uncertain diagnosis and 63.6% from the probably malignant group were carcinomas. Proteinaceous eosinophilic secretions ($p = 0.006$) and acute inflammation ($p = 0.02$) were more frequent in patients with subsequent benign biopsies. Follow-up low PSA value was significantly associated with a benign outcome ($p = 0.04$).

Conclusions: The right clinical attitude after a diagnosis of ASAP must be careful patient follow-up considering the repetition of biopsy after few months.

Key words: prostate, atypia, needle biopsy, adenocarcinoma, hyperplasia, prostatic intraepithelial neoplasia (PIN)
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INTRODUCTION

The number of prostate needle biopsies has remarkably increased during the last few years. This increase is mainly explained by the development of screening programs for prostate cancer based on serum prostate-specific antigen. The use of thinner gauge needles to obtain biopsy specimens achieves smaller tissue cores than formerly, and makes it relatively common to see problematic lesions such as some acini containing atypical architectural or cytological features that represent a diagnostic challenge for the pathologist, because either the number of glands is small, or these are placed at the edge of the core and have artifacts that obscure the nuclei, or the degree of architectural atypia

is not concordant with the cytological one (1-6). For all cases that do not fulfil all of the diagnostic features of adenocarcinoma, the acronym ASAP (Atypical Small Acinar Proliferation) has been applied (2-7). This entity includes 1.5-10% of all prostate needle biopsies in the different series reported (1-9). The aim of this study was to report our experience on this issue at a general hospital, and to correlate the clinicopathological findings in these patients with their following evolution.

MATERIALS AND METHODS

We reviewed the prostate needle biopsies carried out at the POVISA Medical Center (Vigo, Spain) for all patients diagnosed as having "atypical

Table 1 – Clinicopathological data from patients with ASAP.

	n = 38 Patients	Intensity (0-3)†
Age	71.94 years (53-86)	
Initial PSA (n = 28)	12.43 ng/ml (2.3-42)	
Follow-up PSA (n = 10)	9.45 ng/ml (2.29-23.4)	
Abnormal DRE (n = 33)	25 (75.7%)	
Number of cores	3.78 (2-6)	
Number of foci	1.36 (1-4)	
Number of glands per foci	15.69 (3-37)	
Fibrosis	3 (7.89%)	
Atrophy	17 (44.73%)	
High grade PIN	7 (18.42%)	
Nucleomegaly	35 (92.1%)	1.52
Nucleolomegaly	25 (65.78%)	1.05
Proteinaceous eosinophilic secretions	27 (71.05%)	1.07
Intraluminal mucin	8 (21.05%)	0.28
Crystalloids	6 (15.78%)	0.23
Amphophilic cytoplasm	29 (76.31%)	1.13
Acute inflammation	11 (28.94%)	0.39
Chronic inflammation	25 (65.78%)	1.13

DRE: digital rectal examination, †: when available

glands with suspected malignancy” between January 1988 and June 1999, and without previous histopathological diagnosis of prostatic adenocarcinoma. In each of these cases, several clinical features (age, digital rectal examination -DRE- before the first biopsy with ASAP, and initial serum prostate specific antigen -PSA-) and histopathological features related to prostatic adenocarcinoma (7) (number of cores, number of atypical foci, number of acini per focus, high grade prostatic intraepithelial neoplasia -PIN-, atrophy of the parenchyma, fibrosis, amphophilic cytoplasm, nucleomegaly, nucleolomegaly, luminal eosinophilic secretions, intraluminal mucin, crystalloids, acute inflammation and chronic inflammation) were reviewed. The latter eight histological data were quantified as follows: 0 = none present; 1 = mild; 2 = moderate; 3 = severe. Nuclear and nucleolar size was evaluated by comparison with adjacent benign glands.

For all cases the suspected diagnosis was separated into 3 groups (probably benign; uncertain; probably malignant) before knowing the patients progress, in order to correlate this evaluation with the final diagnosis.

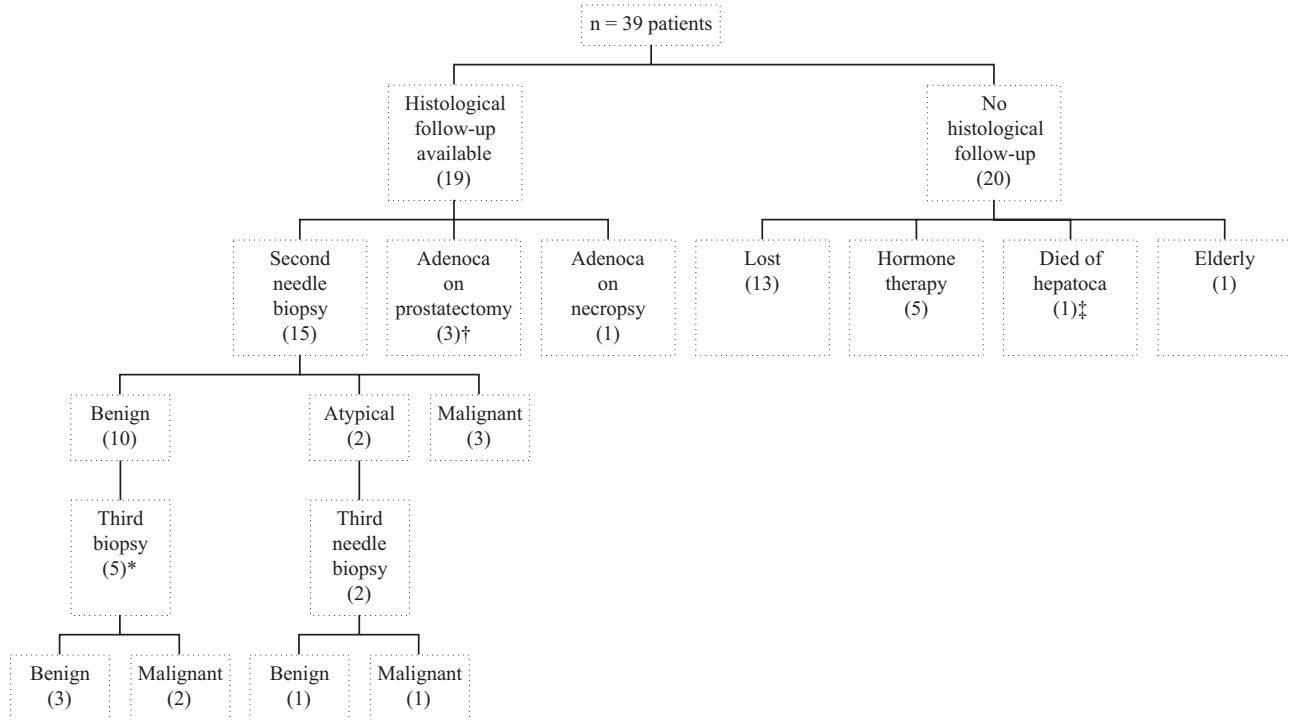
Subsequent prostatic specimens were reviewed when available, and the interval from the first biopsy until said review, serum PSA and Gleason score when an adenocarcinoma existed were recorded. A comparison was made between patients who finally were or were not malignant. Statistical analysis was performed using a 2-tailed Fisher exact test for bimodal variables and a nonparametric Mann-Whitney U test for continuous variables.

Immunohistochemistry was undertaken in cases where progress data and valid specimens were available using cytokeratin 34bE12 (DAKO; 1:50).

RESULTS

During the 10-year period that covers this review, 1,345 prostate needle biopsies were performed in our hospital, of which 48 (3.56%) were diagnosed as “atypical glands with suspected malignancy“ (Figures 1 to 3). After review, 6 (12.5%) were reclassified as malignant (one had an ASAP focus and a contralateral adenocarcinoma), 2 (4.16%) were artifactual and the specimen could

Table 2 – Progress data from patients with ASAP.



*: 3 transurethral resections and 2 needle biopsies; †: pathological stage pT3N0, pT3cN1 and pT3N1; ‡: necropsy not conceded

not be evaluated, and 1 (2.08%) was considered to be benign. The remaining 39 patients (2.89% of all prostate needle biopsies) had a mean age of 71.94 years (53-86). There were available histological specimens for 38 of the 39 patients, whose clinicopathological features are presented in Table-1.

From the 19 patients with available histological follow-up (Table-2), 10 (52.63%) were finally diagnosed as adenocarcinoma, with a mean Gleason sum of 6.28 (range: 4-9). Mean time between the first and second needle biopsy was 101.8 days (3-346), and between the second and third one were 200.8 days (10-474).

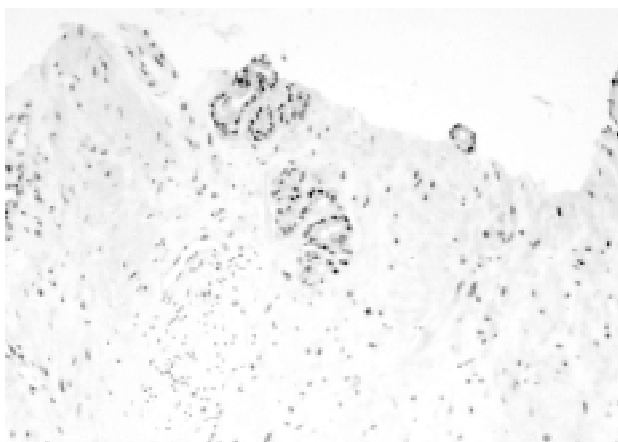


Figure 1 – Small focus of ASAP near the edge of a needle biopsy specimen (HE, X10).

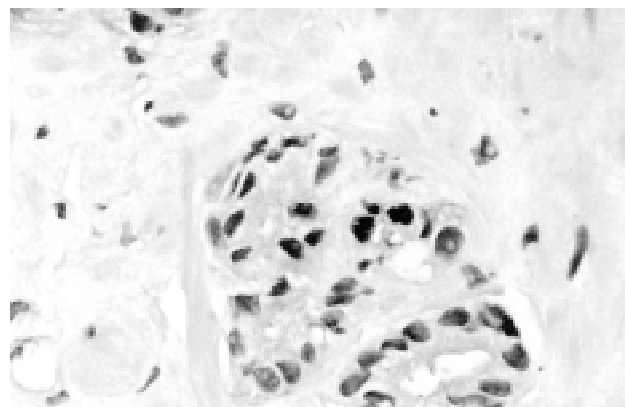


Figure 2 – Same specimen as Figure-1 showing uniform, small glands with increase in nuclear size and some nucleoli. The patient was finally diagnosed as adenocarcinoma (HE, X40).

Table 3 – Clinicopathological data from patients with ASAP (excluding ASAP + PIN), according to their final evolution.

	Benign (n = 8)	Malignant (n = 8)
Age	73 years	69.7 years
Initial PSA	‡9.6 ng/ml (3.1-21.8)	†11.29 ng/ml (3.79-25)
Follow-up PSA	‡7.81 ng/ml (2.29-17.3)	φ13.92 ng/ml (4.9-23.4)
Abnormal DRE	5 (62.5%)	*6 (85.71%)
Number of cores	4.5 (3-6)	*3.85 (3-5)
Number of foci	1.25 (1-2)	*1.28 (1-3)
Number of acini	14.5 (9-24)	*19.77 (10-37)
Nucleomegaly	8 (100%)	*7 (100%)
Nucleolomegaly	4 (50%)	*5 (71.42%)
Proteinaceous secretion	8 (100%)	*2 (28.57%)
Intraluminal mucin	2 (25%)	*1 (14.28%)
Crystalloids	1 (12.5%)	*1 (14.28%)
Amphophilic cytoplasm	6 (75%)	5 (71.42%)
Fibrosis	1 (12.5%)	*0
Atrophy	5 (62.5%)	*1 (14.28%)
Acute inflammation	4 (50%)	*0
Chronic inflammation	6 (75%)	*4 (57.14%)

PSA: prostate specific antigen; DRE: digital rectal examination
‡: n = 6; †: n = 5; φ: n = 4; *: n = 7

A comparison was made between patients who finally were and were not malignant (Table-3). Lower follow-up PSA value (p = 0.04), proteinaceous secretion (p = 0.006) and acute inflammation (p = 0.02) were significantly more frequent in the benign group. No statistically significant differences were noted for the other variants.

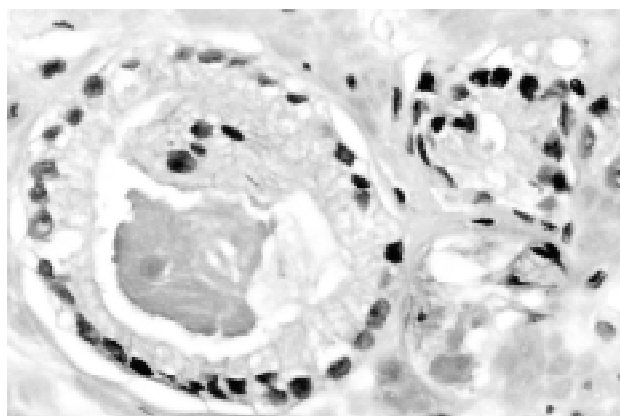


Figure 3 – High magnification microphotograph with glands showing a greater variation in size and intraluminal eosinophilic secretions. The patient was finally diagnosed as non-malignant (HE, X40).

All cases were divided for review into 3 groups (probably malignant; uncertain; probably benign). After excluding the cases of ASAP + PIN, 7 cases were considered uncertain, 1 probably benign and 8 probably malignant. 3 cases from the first group (42.85%) and 5 from the third (62.5%) were adenocarcinomas. The patient considered as probably benign was finally diagnosed as not malignant.

Immunohistochemistry with 34βE12 cytokeratin was performed in the 19 cases with progress data available. 15 cases were negative, 10 being malignant (66.66%) and 5 (33.33%) non-malignant. 4 cases were positive for basal cells, all being non-malignant.

DISCUSSION

The term ASAP is an useful designation to classify lesions made up by a small number of acini that do not fulfil all the histological criteria of adenocarcinoma but that are worrisome because of their atypia, or for being located at the periphery of the core with crush artifact so that it is impossible to

evaluate nuclear characteristics (1-4,6). Nevertheless, histological or cytological findings are useless to reliably differentiate these lesions from a focal adenocarcinoma, and this decision must rely on the pathologists' criteria and experience. In fact, some authors believe that over 50% of ASAP are tangentially biopsied adenocarcinomas (1). None of our foci disappeared on step levels, another possible cause of ASAP diagnosis (2).

The diagnosis of atypical acinar proliferation, with suspected malignancy must be interpreted as the uncertain tumorous nature of the lesion. Histological data such as the existence of a florid inflammatory reaction or atrophic glands in the vicinity would make us think of a benign lesion, although malignancy should not be excluded. It is advisable to take a careful stand in order to avoid false malignant diagnosis. In our laboratory, a minimum of 9 sections of every core were studied, a seriation that we consider necessary to drastically reduce the chances of an incorrect diagnosis.

After review we excluded 9 from the 48 initial cases diagnosed as ASAP (6 considered to be adenocarcinomas, 2 artifactual and 1 benign). The reevaluation of some biopsies by the same observers who initially diagnosed them may be due to the improved definition of some concepts in prostatic pathology over the past years (3).

The degree of nuclear and nucleolar size increase was moderate and mild, respectively. 65.78% patients presented chronic and 28.94% acute inflammation in the parenchyma not related with foci of ASAP. Proteinaceous intraluminal secretions and acute inflammation were more frequent in patients who finally had a benign biopsy than in those who evolved to carcinoma (statistically significant differences). No significant differences were noted for the other histological variables.

In our series, 51.28% (20/39 cases) of patients with ASAP did not undergo a second biopsy, an average similar to other reports (1-4,6,10), so it would be reasonable to assume that we are not taking into account some patients with a high likelihood of having a tumor. It is noteworthy that 5 patients with an elevated serum PSA and abnormal DRE (3 elderly, 1 refused re-biopsy and 1 with bad health) were treated

with hormonal therapy and 3 were submitted to prostatectomy after diagnosis of ASAP without subsequent biopsies.

Ten patients (52.63%) were found to have adenocarcinoma, although only 3 were diagnosed on the second needle biopsy and 3 needed a third one. The average time interval between ASAP diagnosis and the second needle biopsy was 101.8 days, a short enough period to consider it unlikely that the tumor was not present at the time of the first biopsy. After excluding the 3 patients with ASAP foci and coexistent high-grade PIN from the group, 50% (8 cases) of patients finally underwent adenocarcinoma. In the largest series, 34-60% of patients with ASAP showed tumor (1-6,11-13), and 3-9 % were still atypical (1,2,11) on subsequent biopsies. The right clinical attitude after a diagnosis of ASAP must be patient follow-up with repetition of biopsy after some months (1,2,4,8,11,14). This could detect 90% of tumors after the second biopsy and 99% after the third one (1). It is important to emphasize that a benign biopsy after ASAP does not exclude tumor: in our series, 2 patients with this evolution showed carcinoma on the third biopsy. We found that the follow-up PSA value was lower in men with subsequently benign biopsies than in those who were malignant (7.81 vs. 13.92 ng/ml, $p = 0.04$), so its measurement may be useful for the follow-up of these patients.

Immunohistochemistry using cytokeratin 34 β E12 may assist in placing ASAP into benign or malignant categories (15), above all when a positive stain exists, because it nearly definitely facilitates a diagnosis of non-malignancy. Its negativity does not exclude this same diagnosis, because the histology of the atypical foci may be not so clear as to be able to base oneself on this technique for a diagnosis of malignancy (2,5,10).

The differential diagnosis for ASAP must be posed with morphologically similar entities, such as atypical adenomatous hyperplasia (AAH), basal cell hyperplasia (typical and atypical), sclerosing adenosis, atrophy, postatrophic hyperplasia or hyperplasia of mesonephric remnants (16). The diagnosis of AAH must be reserved to proliferation of small acini, most often in the transition zone, placed at the edge of areas with nodular hyperplasia, and

can rarely be performed on a needle biopsy (4,5). Moderately differentiated prostate adenocarcinomas, such as some ASAP foci, show atypical glands crowded without intermingled stroma that usually have a wide variation in size and shape, so the Gleason score would be 3 or more. In fact, the mean Gleason sum of adenocarcinomas after ASAP seen in our series was 6.28; similar to some others previously reported (1-3). In a prospective study of 156 patients with minimal cancer or ASAP (6), Iczkowski et al. found 10 significantly different histological features that could help to differentiate the two groups.

Cases were separated into 3 groups (probably malignant, uncertain, probably benign), according to suspected histological malignancy, and before knowing data on patients' progress. After excluding the cases of ASAP + PIN for the aforementioned, 42.8% of cases with an uncertain diagnosis and 63.6% from the probably malignant group were adenocarcinomas. These data seem to support a certain predictive value of this stratification of the level of suspected histological malignancy (11), although the limited number of cases that we present may influence this affirmation.

ASAP should be kept in mind to avoid false diagnosis of adenocarcinoma, and to induce urologists to repeat the biopsy in cases with atypical acini not related to inflammation, atrophy or former biopsy areas. The interobserver level of consensus in ASAP is barely sufficient (1,3), although the description of new series with cases of this hereto little-known entity will probably help us to achieve a greater diagnostic concordance.

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Correspondence address:

Dr. Carlos Alvarez-Alvarez
 Servicio de Anatomía Patológica
 POVISA Medical Centre, C/ Salamanca 5
 36211, Vigo, Pontevedra, Spain
 Fax: ++ (34) (986) 421-439
 E-mail: netpat@arrakis.es

EDITORIAL COMMENT

More prostate biopsies are being performed than ever before, often in men with minimal or marginal indications. The early dividend of screening and biopsy includes downward migration of stage, grade, and cancer volume. Later dividends will likely in-

clude a decline in recurrence and death rates. The increase in number of biopsies has also generated great interest in the two known histopathologic risk factors for prostate cancer: atypical small acinar proliferation (ASAP, or "suspicious") and high grade prostatic intraepithelial neoplasia.

The current study expands our understanding of the diagnosis of ASAP ("suspicious"), an uncomfortable and unsettling finding for the pathologist, urologist, and, ultimately, the patient. Yet, prostate biopsy is prone to sampling variation, and in a small but significant number of cases (2.9% in this study), the findings fall short of the diagnosis of malignancy. What should the pathologist report? It is imprudent to render an unequivocal diagnosis of cancer without absolute confidence in the biopsy findings, yet the alternative diagnosis of "benign" might be a serious underdiagnosis. The authors note that additional biopsies in patients with ASAP reveal cancer in about half of cases, indicating that this is an important (and reproducible) risk factor that warrants clinical attention. It is critical that the pathologist not overuses this diagnostic category, but we have not seen this in our experience. The urologist and patient is best served by reports that provide as definitive a diagnosis as possible; in occasional cases, the pathologist is "absolutely positively uncertain", and this suspicion in prostate biopsies is best summed up as ASAP.

Dr. D. G. Bostwick

*Bostwick Laboratories Richmond
 University of Virginia, Charlottesville, VA, USA*