Atypical Small Acinar Proliferation

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Introduction

Atypical small acinar proliferation (ASAP) has been reported in approximately 5–6% of all of the prostate biopsies and is a clinically controversial diagnosis. Surveys have shown that many clinicians might not fully appreciate its definition finding it equivalent to high-grade prostatic intraepithelial neoplasia (HGPIN). The purpose of this chapter is to clarify the definition of ASAP, its histological findings, and clinical consequences. We propose a new follow-up approach following the diagnosis of ASAP, by increasing the number of repeat biopsies with consecutive negative results from two to three.

Definition and Incidence

Epstein and Kahane et al. [1, 2] described prostate biopsies that were "atypical but not diagnostic" and "small focus of atypical glands suspicious for, but not diagnostic of cancer." However, the acronym ASAP (atypical small acinar proliferation) was coined by Bostwick et al. that same year [3]. Since then ASAP has been the subject of numerous comments and critiques [4–6].

Isolated ASAP has been reported in approximately 5–6%* of prostate biopsy accessions (range 0.4–31%) in 30 studies (Table 19.1) [2, 3, 7–39]. (*The studies with 100% reported frequency have not been considered for average determination.)

For urologists, ASAP is a controversial diagnosis [40]. In a survey sent to 42 members of the Society of Urological Oncology, 98% would rebiopsy a patient with ASAP as a diagnosis, 52% would treat ASAP and high-grade prostatic intraepithelial neoplasia (HGPIN) the same, 29% considered ASAP to be worse than HGPIN, 12% considered HGPIN to be worse than ASAP, and 7% were unsure which was worse [41]. This survey also found that the clinicians might not fully appreciate the definition of ASAP even given the definition in a comment accompanying the diagnosis. On another survey directed to urologists, 37% of the 110 respondents considered ASAP as being equivalent to HGPIN [42].

An important fundamental difference between HGPIN and ASAP is that HGPIN is considered a dysplastic process confined to architecturally benign glands with basal cells and as such is considered to be a precursor of adenocarcinoma. ASAP, on the other hand, is a different pathological entity, representing a wide variety of histological findings that are suspicious for, but not diagnostic of, adenocarcinoma (qualitatively, quantitatively, or both). When reporting ASAP, the pathologist must convey to the urologist that the

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Table 19.1 Literature review. The frequency of isolated ASAP, ASAP associated with HGPIN, time to repeat biopsy, and frequency of prostatic adenocarcinoma on repeat biopsy is shown

References	Year	Setting	Frequency of diagnosis of isolated ASAP per total	%	ASAP associated with HGPIN	%	Frequency of repeat biopsy in isolated ASAP	%	Time to repeat biopsy (months)	Frequency of diagnosis of cancer on subsequent biopsies (%)	%
Bostwick et al. [3]	1995	Community	3/200	1.5	2/200	1	N/A	N/A	N/A	N/A	N/A
		Academic	1/200	0.5	2/200	1	N/A	N/A	N/A	N/A	N/A
Kahane et al. [2]	1995	Laboratory	15/4,047	0.4	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Roehrborn et al. [7]	1996	Academic	38/123	31	N/A	N/A	38/38	100	6	8/38	21
Cheville et al. [8]	1997	Community	48/1,009	4.8	N/A	N/A	25/54	46	N/A	15/25	60
Iczkowski et al. [9]	1997	Community	33/33	100	14/33	42	33/33	100	1–27 Median:3	15/33	45
Wills et al. [10]	1997	Academic	18/439	4.1	2/439	0.5	N/A	N/A	N/A	N/A	N/A
Allen et al. [11]	1998	Academic	124/124	100	N/A	N/A	124/124	100	N/A	56/124	45.2
Iczkowski et al. [12]	1998	Community	295/295	100	N/A	N/A	295/295	100	0.1–43.2 Mean: 5.7	125/295	42
Renshaw et al. [13]	1998	Academic	167/2,219	7.5	N/A	N/A	59/167	35	9–19	22/64	34
Reyes and Humphrey [14]	1998	Academic	128/795	16.1	10/795	1.3	N/A	N/A	N/A	N/A	N/A
Weinstein et al. [15]	1998	Community	96/1,192	8	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Community	170/2,792	6.1	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Community	62/1,306	4.7	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Chan and Epstein [16]	1999	Consults	200/200	100	N/A	N/A	92/144	64	0.5–36	45/92	49
Hoedemaeker et al. [17]	1999	Screening	43/1,824	2.4	N/A	N/A	39/43	91	6	15/39	38.5
Novis et al. [18]	1999	Multiinstitutional	1,121/15,753	7.1	N/A	N/A	N/A	N/A	N/A	N/A	N/A
O'dowd et al. [19]	2000	Laboratory	3,269/132,426	2.5	440/132,426	0.3	1,321/3,269	40.4	3	529/1,321	40
Borboroglu et al. [20]	2001	Academic	53/1,391	3.8	8/1,391	0.6	48/53	91	12	23/48	48
Ouyang et al. [21]	2001	Academic	21/331	6.3	N/A	N/A	17/21	81	2–12	9/17	53
Park et al. [22]	2001	Academic	45/45	100	N/A	N/A	45/45	100	Mean: 24	23/45	51
Iczkowski et al. [23]	2002	Laboratory	184/7,081	2.6	N/A	N/A	129/227	57	12	51/129	40
Mian et al. [24]	2002	Academic	33/939	3.5	N/A	N/A	10/33	30	N/A	7/10	70
Brausi et al. [25]	2004	Academic	71/1,327	5.3	N/A	N/A	23/45	51.1	6	6/23	26

Fadare et al. [26]	2004	Academic	36/1,964	1.8	N/A	N/A	24/36	67	2–24 Mean: 8	9/24	38
Gupta et al. [27]	2004	Community	18/515	3.5	13/515	2.5	N/A	N/A	N/A	N/A	N/A
		Community	17/933	1.8	9/933	1	N/A	N/A	N/A	N/A	N/A
Kobayashi et al. [28]	2004	Academic	6/104	5.8	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Naya et al. [29]	2004	Academic	12/1,086	1.1	10/1,086	1	12/12	100	3	7/12	58.3
Postma et al. [30]	2004	Screening	108/4,117	2.6	N/A	N/A	96/108	89	N/A	35/96	36.5
		Screening	50/1,840	2.7	N/A	N/A	47/50	94	N/A	8/47	17
Leite et al. [31]	2005	Laboratory	26/1,420	1.8	40/1,420	2.8	16/26	61.5	4.26	7/16	43.8
Moore et al. [32]	2005	Academic	72/1,188	6	N/A	N/A	53/72	73.6	2.5	19/53	36
Schlesinger et al. [33]	2005	Community	78/336	23	54/336	16	78/78	100	Mean: 3.8	29/78	37
Mallén et al. [34]	2006	Academic	69/3,600	1.9	N/A	N/A	64/69	92.75	1–13 Median: 2	27/64	42
Rodríguez-Patrón Rodríguez et al. [35]	2006	Academic	127/6,000	2.1	N/A	N/A	50/127	39.3	0.7–83 Mean: 13–17	20/50	40
Mearini et al. [36]	2008	Academic	76/1,274	5.9	6/1,274	0.4	65/76	85.5	5	25/65	38.4
Ploussard et al. [37]	2009	Community	23/2,006	1.2	N/A	N/A	17/23	74	5.9	7/17	41.1
Ryu et al. [38]	2010	Community	244/3,130	7.8	N/A	N/A	170/244	70	3–6	57/170	33.5
Kopp et al. [39]	2011	Academic	199/2,628	7.6	N/A	N/A	139/199	67	<4, >12.8	41/139	29

lesion is not merely *atypical* but is actually *suspicious* for adenocarcinoma. Published reports suggest that ASAP has a significantly higher likelihood of prostate cancer on a subsequent biopsy (40.2% mean) as compared with HGPIN (31.5% mean) [32, 40]. ASAP is a diagnostic category [12, 43], whereas HGPIN is a preneoplastic lesion [44]. ASAP is defined as small acini suspicious for, but not diagnostic of, malignancy. This diagnostic category arose to encompass small lesions where there was an absolute "uncertainty" regarding the definitive diagnosis of prostatic adenocarcinoma [43]. Since the diagnosis of isolated ASAP confers a substantial risk of subsequent prostatic adenocarcinoma, its identification warrants careful follow-up with repeat biopsy. Therefore, rendering a diagnosis of ASAP should indicate to the clinician that the biopsy specimen in question exhibits inconclusive histological features that are neither clearly malignant nor clearly benign [43, 45].

The mean age of patients with ASAP is in the seventh decade (60s) and does not differ significantly from patients with prostatic adenocarcinoma [46].

Difficulties in Diagnosing Small Lesions

Often, on biopsy material, the abnormal focus of interest is very small, composed of just a few acini. Deeper levels, or ancillary studies, such as immunohistochemical stains sometimes can help; however, the focus may disappear on deeper levels. The clinical consequences of a definitive diagnosis of prostatic adenocarcinoma are not trivial – radical prostatectomy or definitive radiation therapy – procedures with potentially severe morbidity for the patient. Erectile dysfunction in a middle-aged man and its resulting effects on his lifestyle is not to be ignored, especially if the radical prostatectomy specimen turns out negative for adenocarcinoma [47–50]. According to Bostwick and colleagues, there are three highly important questions needed to be answered prior to diagnosing ASAP or cancer in such small lesions [43]:

1. Would you be absolutely confident of this biopsy diagnosis if it were followed by a radical prostatectomy with negative findings?
2. Would another colleague pathologist agree with the diagnosis of cancer?
3. Can you confidently support the diagnosis of adenocarcinoma based solely on this biopsy result?

If the answer to any of the above questions is "no," Bostwick et al. recommend the use of the more conservative diagnosis of ASAP [43].

Stratification of ASAP in subcategories or levels of suspicion for malignancy (*favor benign*, *suspicious,* and *highly suspicious*) has been attempted; however, it has been demonstrated that it was not predictive of cancer in specimens from repeat biopsies despite multiple attempts [9, 12, 43, 51]. In clinical practice some expert pathologists occasionally subclassify an atypical diagnosis as "highly suspicious," but only if carcinoma is strongly favored. Similarly "mildly atypical" is used if there is low suspicion for adenocarcinoma [40].

Diagnosis: Lack of Distinct Criteria

A diagnosis of ASAP is not characterized by distinct morphological criteria, but rather reflects the lack of diagnostic criteria for a definitive diagnosis of adenocarcinoma [40, 43]. Urologists must understand the uncertainty the pathologist faces when confronted with such lesions. In the following discussion (and summarized in Tables 19.2 and 19.3), the "how" and "why" of this diagnostic category are discussed.

Table 19.2 Reasons for diagnosing ASAP [9, 33, 43]

Size of focus
Very small (see Table 19.3 for specifics)
Lesion present at the core edge (incomplete sampling)
Loss of focus on deeper levels
Histology
Distorted histological detail
Crush artifact
Prominent inflammation (reactive atypia)
Processing artifact (thick sections, overstaining)
Lack of convincing malignant features
Clustered growth pattern (mimicking adenosis)
Conflicting immunohistochemical findings
Focally positive for basal cell markers
Negative AMACR stain
Presence of adjacent HGPIN
Tangential cutting (budding PIN)

Table 19.3 Histological features of ASAP compared to adenocarcinoma in prostate core needle biopsies [8, 9]

	ASAP	Prostatic adenocarcinoma
Architectural		
Mean size of focus (mm)	0.4 +/− 0.3	0.8 +/− 0.5
Mean number of involved acini	11 +/− 10	17 +/− 14
Infiltrative growth	Sometimes	Always
Cytological		
Nuclear enlargement	Mild	Moderate
Nuclear hyperchromasia	More common	Less common
Prominent nucleoli	Sometimes	Always
Luminal secretions		
Blue-gray luminal mucin	Less likely	More likely
Eosinophilic proteinaceous secretions	Equally present	Equally present
Crystalloids	Equally present	Equally present
Associated pathological features		
Atrophy	More common	Less common
Inflammation	Equally present	Equally present
HGPIN	Less common	More common
Immunohistochemical features		
Racemase	Sometimes negative	Usually positive [40, 59–61]
P63	Sometimes positive	Usually negative [57, 65, 66, 74]
34betaE12	Sometimes positive	Usually negative [57, 65, 66]

Firstly one of the most important factors in consideration of the diagnosis of ASAP is the size of the focus of interest [9]. A small focus has been defined as a focus representing less than 5% of the core [3], or less than 0.4 mm, comprising less than two dozen acini [46], or being less than the size of the head of a pin [43]. In all of these instances, there is major concern for overdiagnosis of cancer based on insufficient evidence [43] (Fig. 19.1). The same applies if the focus of concern is present at the edge of the tissue core (fractured core) or disappears on deeper levels suggesting incomplete sampling [43]. Moreover, the specimen may be composed of acini of small size, that is, smaller than normal ducts and acini, but it may also include glands with a diameter similar to that of normal ducts and acini [52].

The presence of infiltrative growth, a common feature of adenocarcinoma, is not reliable as a sole criterion for malignancy in that it has been reported in up to 75% of ASAP [8, 46].

Mild nuclear enlargement (relative to the adjacent benign epithelial cells) with more prominent nuclear hyperchromasia is characteristic of ASAP as compared to more pronounced nuclear enlargement and less hyperchromasia seen with malignancy [43]. Hyperchromasia however has to be interpreted carefully taking into account the laboratory's technical staining protocols.

The presence of mitotic figures in suspicious foci usually points to a diagnosis of adenocarcinoma; however, in small foci mitotic figures are rarely encountered (in either adenocarcinoma or its mimics) [43].

Blue-gray luminal mucin (Fig. 19.2) may be encountered in both ASAP and adenocarcinoma, and the presence of eosinophilic secretions and crystalloids is also nonspecific, found in atypical adenomatous hyperplasia and occasionally even normal glands (Fig. 19.3) (although all are encountered with a greater relative frequency in adenocarcinoma) [8, 9, 53].

Associated inflammation or mechanical distortion (crush artifact) following the biopsy procedure might also cause distorted glands with an atypical look posing further difficulty in interpretation (Fig. 19.2) [40]. The individual submission and processing of prostate biopsies in 6–12 containers decrease the rate of atypical diagnosis by preventing core entanglement and fragmentation. It is also more difficult to embed

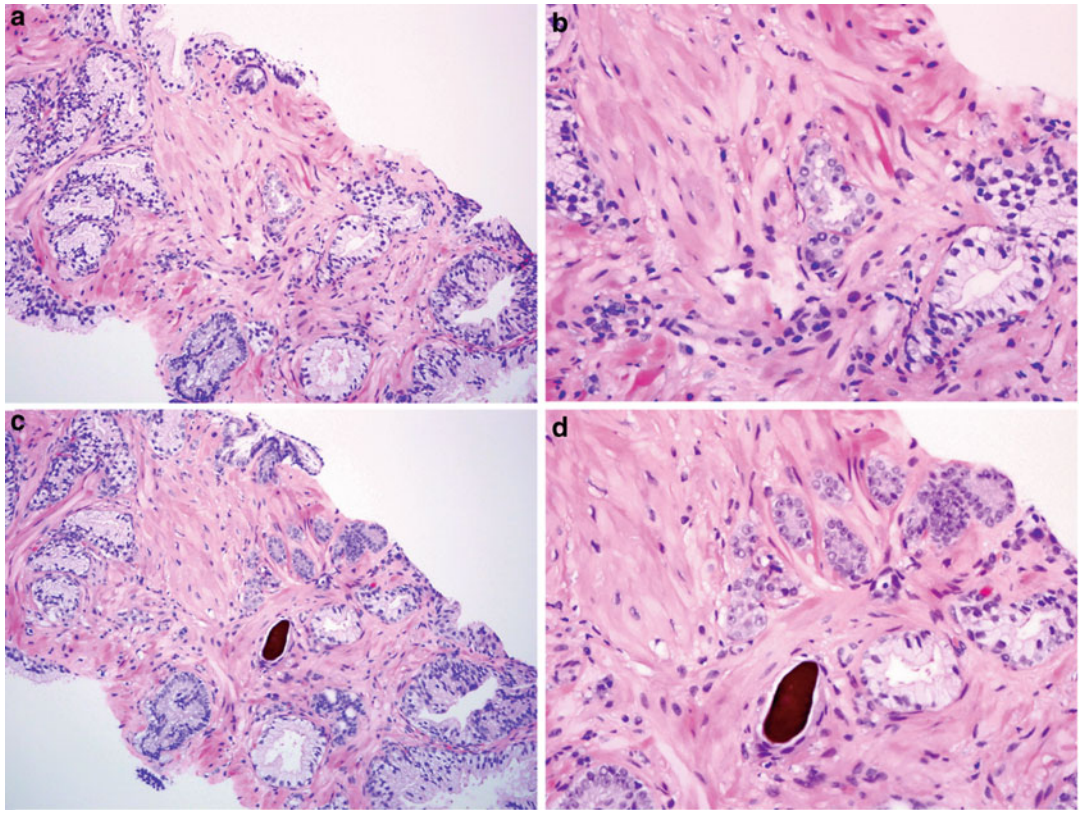

Fig. 19.1 A small focus composed of two acini shows nuclear atypia with prominent nucleoli (**a** – HE, 200×; **b** – HE, 400×). Deeper levels unveil a total of 12 acini showing the same nuclear atypical features (**c** – HE, 200×; **d** – HE, 400×). The focus is too small for a definitive diagnosis of adenocarcinoma, however is highly suspicious due to its morphology. A diagnosis of ASAP is warranted

multiple cores in a single plane following processing [27]. Epstein recommends that no more than two cores should be submitted per container to optimize sectioning and visualization [40].

Often ASAP coexists with HGPIN (see Table 19.1) [3, 9, 10, 14, 19, 20, 27, 29, 31, 33, 36]. The small foci of atypical small proliferating glands may be immediately adjacent to a focus of HGPIN (Fig. 19.4) [40]. In this instance, the concern is that the focus of ASAP actually represents budding or tangentially sectioned glands from the adjacent HGPIN gland rather than a true and independent cancer focus [8]. HGPIN with adjacent atypical (suspicious) glands shows a higher risk of cancer on subsequent biopsies compared to HGPIN alone [54, 55].

An adequate number of histological levels should be considered before a final diagnosis reflecting uncertainty is rendered. Because atypical foci sometimes may still be missed on one or two levels, Renshaw et al. recommend that a minimum of three levels should be prepared from each block for an adequate visualization of the focus [56] with additional deeper levels if warranted [14].

Ancillary studies are highly recommended and encouraged to help in differentiating these challenging situations. Appropriate controls must always be used [52]. P63, a nuclear protein, and high molecular weight cytokeratin (HMWCK) detected by antibody clone 34betaE12 are prostatic basal cell-specific immunohistochemical markers not expressed by the secretory cells [57, 58]. Alpha-methyl-CoA racemase (AMACR, P504S) is a mitochondrial and peroxisomal enzyme involved in the β (beta)-oxidation

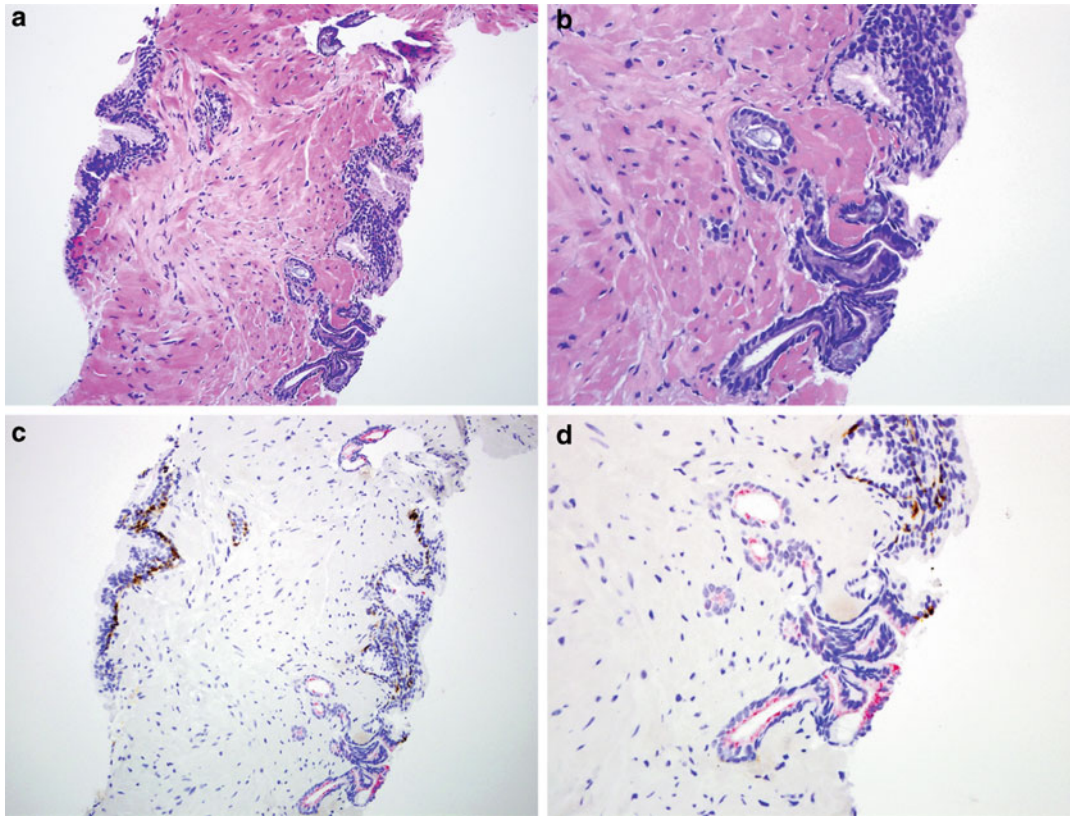

Fig. 19.2 A small distorted suspicious focus is present at the *right lower edge* of a core needle biopsy (**a** – HE, 200×). The acini show intraluminal mucin and nuclear hyperchromasia, but assessing the basal cell layer is difficult due to the distorted nature of the tissue (**b** – HE, 400×). PIN4 immunohistochemical cocktail does not identify basal cells, and the acinar cells faintly express racemase (**c** – PIN4, 200×, **d** – PIN4, 400×). An additional suspicious focus is highlighted (*right upper corner*), a focus that could have been otherwise missed on HE (**c**)

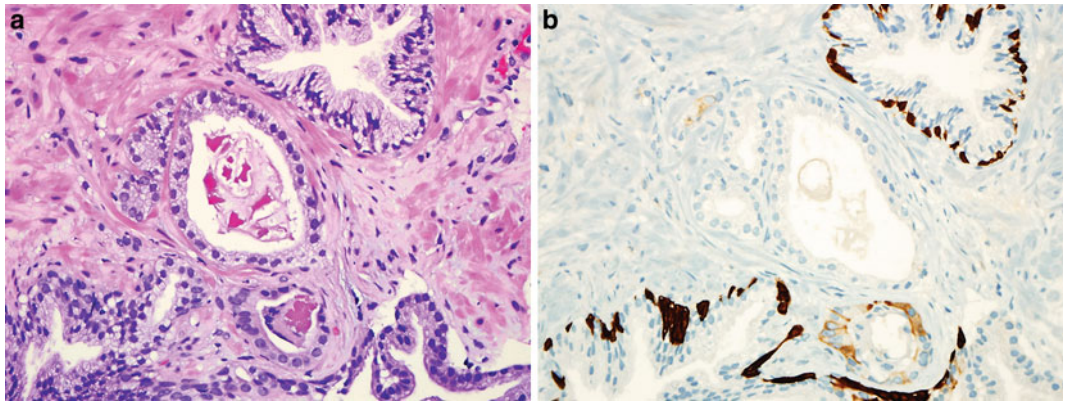

Fig. 19.3 A few small acini show prominent nucleoli and intraluminal eosinophilic secretions (**a** – HE, 400×). No basal cells are identified, but the secretory cells are not expressing racemase (**b** – PIN4, 400×). This focus is suspicious for adenocarcinoma; however, it is too small and the immunohistochemical features are atypical. A confident definite diagnosis of adenocarcinoma cannot be made.

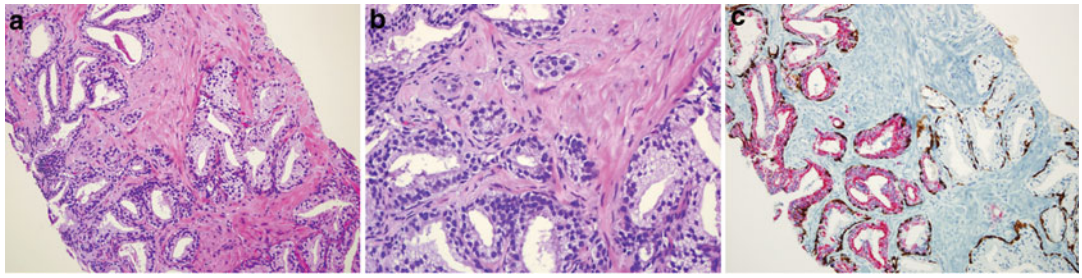

Fig. 19.4 A focus of HGPIN is identified (*left*) (**a** – HE, 200×). A higher magnification illustrates adjacent small acini with prominent nucleoli (**b** – HE, 400×). PIN4 illustrates the presence of basal cells and strong racemase staining in the focus of HGPIN compared to the negative staining of the normal glands on the *right* (**c** – PIN4, 200×). These small atypical acini present adjacent to a focus of HGPIN could be tangential sections of the dysplastic focus also known as budding PIN. However, the atypical focus is small and a confident diagnosis cannot be made. A repeat biopsy should be performed to confirm or rule out adenocarcinoma.

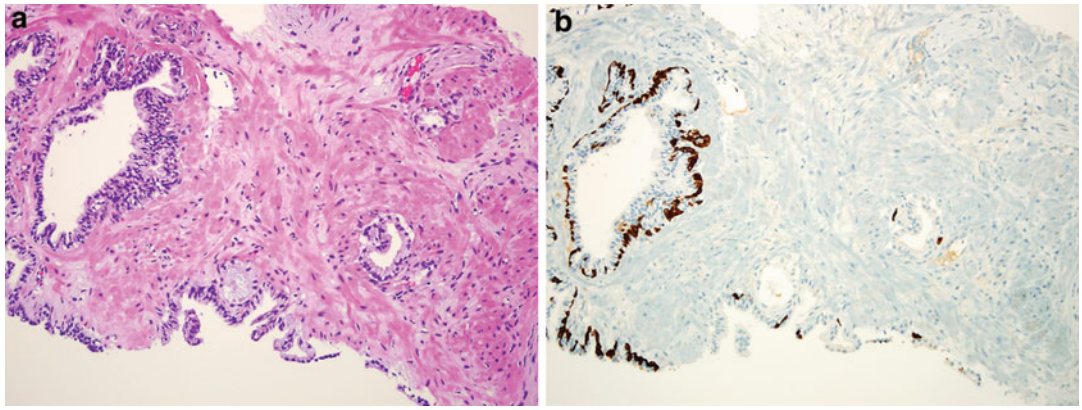

Fig. 19.5 A few scattered acini are worrisome for malignancy (*left upper* and *lower* edge) (**a** – HE, 200×). There are only a few basal cells present, and the acinar cells do not express racemase (**b** – PIN4, 200×). A diagnosis of ASAP is appropriate in this case.

branched chain fatty acids and bile acid intermediates. It is usually upregulated in malignancy and HGPIN [59]. However, numerous false-positive and false-negative results have been reported, and interpretation must be performed with caution [40].

Multiple studies have reported AMACR expression in HGPIN, atypical adenomatous hyperplasia (AAH), partial atrophy, and occasionally benign secretory cells [60, 61]. Absence of staining has been reported in approximately 18% of prostatic adenocarcinomas [62–64] and also in ASAP [61]. Due to this fact, AMACR should not be used alone for a diagnosis of adenocarcinoma [40]. Invasive adenocarcinoma invariably lacks basal cells and therefore will be negative for p63 and HMWCK [57]. However, lack of immunoreactivity should be interpreted in the context of suspicious morphology, as various mimickers of carcinoma can have an absent or partially absent basal cell layer (AAH, partial atrophy, basal cell hyperplasia) [65]. Also very rarely, small foci of adenocarcinoma can retain a few basal cells [66].

Epstein and Herawi recommend the use of basal cell immunohistochemical stains to verify suspicious foci as cancer and not to establish a diagnosis of cancer. For example, if a focus is morphologically favored benign but without confidence and the basal cell markers are negative, they diagnose the focus as suspicious (similar examples are illustrated in Figs. 19.3 and 19.5).

If benign morphology is favored with confidence and the basal markers are negative, they diagnose the focus as benign. They also recommend using a positive AMACR stain (with negative basal cell markers) to convert an atypical diagnosis to cancer in cases that are highly suspicious morphologically [40].

Maximum information should be obtained from the available tissue [33]. Careful hematoxylin-eosin interpretation, with additional deeper levels if necessary, followed by immunohistochemical and molecular studies should be integrated. The clinical parameters (PSA, age, digital rectal examination findings) should not unduly influence the morphological diagnosis of adenocarcinoma.

Last but not least, it is extremely important to note that there is interobserver reproducibility and interpretative variability depending on the experience and skill of the pathologist. Studies have shown that it is more common for an atypical case to be finalized as carcinoma as opposed to benign upon expert review [9, 12, 13, 23, 40, 67]. Cases finalized as atypical or suspicious in the community setting have a not insignificant likelihood of being changed to adenocarcinoma upon expert review. Therefore, patients and urologists should consider having such cases for expert consultation in such situations before subjecting the patient to a repeat biopsy [67]. A prudent diagnostic strategy may include review of such challenging cases by multiple general or expert pathologists to develop a consensus opinion [40].

Finally, Epstein has recommended the use of descriptive terminology (rather than a diagnostic category of ASAP), for example, "prostate tissue with small focus of atypical glands" with a comment explaining "While these findings are atypical and suspicious for adenocarcinoma, there is insufficient cytological and/or architectural atypia to establish a definitive diagnosis" [40]. In a similar view, we use "few small glands suspicious for adenocarcinoma" at our institution. Our feeling is that "suspicious" conveys a higher risk category to the urologist than "atypical."

What Is Next? Clinical Follow-Up

Repeat biopsy is warranted when faced with a diagnosis of ASAP and was performed in an average of 6–7% (Table 19.1) of the cases with a diagnosis of ASAP in 20 reviewed studies [8, 13, 16, 17, 19–21, 23–26, 30–32, 34–39].

Multiple studies have reported the presence of adenocarcinoma on subsequent follow-up biopsies initially diagnosed with ASAP ranging from 17% to 60% (see Table 19.1) with an average of 41% [7–9, 11–13, 16, 17, 19–26, 29–39].

Brausi et al. reported malignancy in 100% (25/25) radical prostatectomy specimens performed immediately following a diagnosis of ASAP without a confirmatory biopsy [25]. However, due to the aforementioned clinical implications, this radical surgical procedure is not recommended without a confirmatory repeat biopsy showing definite adenocarcinoma.

The presence of ASAP associated with HGPIN in biopsy specimens has a significant predictive value for concurrent or subsequent cancer in repeat biopsy specimens [43]. On the other hand in about 40% of cases, ASAP represents under sampled cancer that might not be detected even in multiple subsequent biopsy specimens [43].

What should the needle biopsy sampling protocol be after the diagnosis of isolated ASAP? On subsequent biopsies it is recommended to sample the entire prostate and not just the site initially diagnosed as ASAP, as multiple studies demonstrated the presence of cancer contralateral to or in a different sextant site from the initial ASAP diagnosis site in 26–39% of cases [11, 12, 20]. Based on these studies, the following recommendations emerged:

1. Increased sampling of the initial atypical site (three cores)
2. Increased sampling of the adjacent ipsilateral and contralateral sites (two cores each site)
3. Routine sampling of all sextant sites (one core)

In order for these recommendations to be carried out appropriately, it is imperative for urologists to submit biopsy specimens in a manner that the location of each core is clearly delineated [40].

The current guidelines [68] recommend extended pattern rebiopsy (12 cores) within 6 months with increased sampling of the ASAP site and adjacent areas. If no cancer is found, close follow-up with serum PSA and digital rectal examination (DRE) is recommended. According to these guidelines after two negative extended transrectal ultrasound (TRUS)-guided biopsies, cancer is not commonly found on an additional repeat biopsy.

Multiple studies analyzed the rate of cancer diagnosis following multiple repeat biopsies after a diagnosis of ASAP. Iczkowski et al. identified 99% of cancers on the second and third repeat biopsies following a diagnosis of ASAP [12]. However, in the same study, a case of cancer was diagnosed following a primary diagnosis of ASAP followed by two consecutive negative biopsies. Ryu et al. reported the cancer detection rates of the first, second, third, and fourth repeat biopsies as 24.1% (41/170), 34.1% (14/41), 18.2% (2/11), and 0% (0/2), respectively [38]. Rodríguez-Patrón Rodríguez et al. found cancer following a diagnosis of ASAP on the first, second, and third repeat biopsies of 34% (17/50), 33.3% (2/6), and 33.3% (1/3), respectively, with mean biopsy intervals approximately ranging from 13 to 17 months [35]. It appears that most of the cancers are diagnosed on the first repeat biopsy. Also Moore et al. reported cancer following ASAP in 36% (19/53) and 16% (3/19) of the first and second repeat biopsies [32].

We agree with the current guidelines, and we believe that repeat biopsy should be performed in the setting of a diagnosis of ASAP. The question is how many successive biopsies with a negative result should be performed and when should we stop? One study reported cancer following two consecutive negative biopsies and multiple studies have reported cancer on the third biopsy [12, 35, 38]; however, according to Bostwick [43], some cancers are never detected. We propose raising the number of follow-up biopsies to a total of at least three and pausing after three negative results. Additional clinical follow-up (PSA, DRE) should be continued, and a repeat biopsy protocol should be reinstated if there are strong clinical indications (rising PSA, DRE positivity).

It has been reported that there is no correlation of encountering cancer on repeat biopsy with serum PSA following an atypical diagnosis [9, 12, 16, 22, 26, 30, 32], with DRE [9, 12, 30, 32], and with transrectal ultrasound [20, 30]. Finding, however, recently PSA density (PSAD), PSA velocity (PSAV), and a decreased total prostate volume (TPV) were reported as predictive for prostate cancer in patients with an initial diagnosis of ASAP of the prostate [36, 38, 51].

Usually adenocarcinoma diagnosed following a diagnosis of ASAP is of favorable grade (likely Gleason 6), confined to the prostate, with negative margins, with a few reported exceptions [8, 13, 25].

Differential Diagnosis

Various small foci of benign pathological entities can mimic adenocarcinoma on needle biopsy and, therefore, may be occasionally diagnosed as ASAP (Table 19.4). There is a broad spectrum of entities ranging from benign glandular lesions such as atypical adenomatous hyperplasia [53, 69], atrophy, postatrophic hyperplasia [70], and sclerosing adenosis [71, 72] to treatment effect

Table 19.4 The differential diagnosis of ASAP

Adenocarcinoma
Atypical adenomatous hyperplasia [53, 69]
Sclerosing adenosis (typical and atypical) [71, 72]
Atrophy-postatrophic hyperplasia [70]
Basal cell hyperplasia [75, 76]
HGPIN
Mesonephric hyperplasia [77–79]
Nephrogenic adenoma [80, 81]
Radiation atypia [70, 73]
Androgen deprivation [70, 73]
Inflammation associated atypia
Verumontanum hyperplasia [70, 82]
Clear-cell cribriform hyperplasia [70, 76]
Xanthoma [70]
Normal anatomic structures [70, 73]
Seminal vesicles/ejaculatory ducts
Cowper's glands
Ganglia

and even normal benign prostate histology [70, 73]. Further studies such as immunohistochemistry may serve to appropriately classify these lesions as entities apart from ASAP. This has led some to suggest that ASAP is merely a "wastebasket" term for atypical proliferations that cannot be classified with certainty. For a detailed coverage of these entities, please refer to the references provided in Table 19.4 and to the corresponding chapters in this book.

Conclusions

The diagnosis of ASAP should indicate to the clinicians that the biopsy findings are "uncertain," neither clearly malignant nor clearly benign, and that follow-up biopsy is warranted [43]. It is crucial for urologists to understand the difference between HGPIN and ASAP when present on pathology reports as these two entities have different morphology and ASAP is associated with a much higher risk of cancer on repeat biopsy [40]. Extended pattern repeat biopsy is recommended every 6 months until three consecutive negative results, then clinical follow-up with serum PSA and DRE is warranted.

Editorial Commentary

ASAP seems to confuse urologists more than almost any issue in prostate cancer diagnostics. Unfortunately, the most common response that I observe – by far – is to ignore it. This is illogical, as the author describes that this pathological finding is often actually prostate cancer that has simply been under sampled.

I teach our residents that ASAP is a way for pathologists to tell urologists, "I think this is cancer, but there just isn't enough evidence on the slide to prove it." It is our job to provide that additional evidence. Regardless of your preferred biopsy technique – we use 20 core transrectal office-based saturation biopsies – it is imperative to give the pathologist more tissue. Alternatively, it is not uncommon that a subspecialty pathologist will make the call for a cancer diagnosis on the original biopsy tissue, so a second pathological opinion should be considered if there is any doubt on the part of the pathologist or if the initial pathologist is not highly experienced with prostate biopsy interpretation.

Another issue that I see which causes problems for many people is the relatively widespread concept that repeat biopsy for ASAP should be performed within 6 months. I find that many urologists interpret this to imply that they should wait 6 months. It is not clear why this interpretation is so prevalent, but I hypothesize that it is because patients historically are not keen to proceed right back to another biopsy immediately, so the urologists probably believe they are doing the patient a favor by not recommending immediate repeat biopsy. Nevertheless, with modern periprostatic block, this is rarely a concern to the large numbers of patients that I see for second opinions for this diagnosis. Quite the opposite, many of them are unhappy that they have been told they have to wait 6 months, and they are relieved when informed that there is no reason to delay the biopsy. They usually don't want to worry another day once they know that this reading implies a high likelihood that they have unrecognized cancer, and they usually want to proceed to repeat biopsy (dare I say?), ASAP.

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