Asian Journal of Urology 9 (2022) 12–17

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Review

Atypical small acinar proliferation and its significance in pathological reports in modern urological times

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Received 1 February 2020; received in revised form 11 May 2020; accepted 8 September 2020
Available online 30 April 2021

KEYWORDS
Prostate cancer;
Repeat biopsy;
Significant cancer;
Grade;
Atypical small cell proliferation;
Lesion suspicious for cancer

Abstract Atypical small acinar proliferation is a histopathological diagnosis of unspecified importance in prostate needle-biopsy reports, suggestive but not definitive for cancer. The terminology corresponds to some uncertainty in the biopsy report, as the finding might represent an underlying non-cancerous pathology mimicking cancer or an under-sampled prostate cancer site. Therefore, traditional practice favors an immediate repeat biopsy. However, in modern urological times, the need of urgent repeat biopsy is being challenged by some authors as in the majority of cases, the grade of cancer found in subsequent biopsy is reported to be low or the disease to be non-significant. On the other hand, high risk disease cannot be excluded, whereas no clinical or pathological factors can predict the final outcome. In this review, we discuss the significance of the diagnosis of atypical small acinar proliferation in the biopsy report, commenting on its importance in modern urological practice.

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Peer review under responsibility of Tongji University.

https://doi.org/10.1016/j.ajur.2021.04.008

1. Introduction

Atypical small acinar proliferation (ASAP) is a descriptive terminology used in the pathology report of a needle prostate biopsy. An alternative terminology is "lesion suspicious for cancer" (LSC) which is considered to be more accurate [1]. ASAP has been highlighted in several studies as an independent predictive factor of prostate cancer (PCa) in future biopsies [2—4], whereas the risk of malignancy seems to be constant and not related with biopsy intervals [5]. ASAP is not a precancerous lesion; it should be regarded as an ambiguous report that might encompass either benign lesions mimicking malignant glandular proliferation or under-sampled PCa [6]. Also, men who are diagnosed with adenocarcinoma after ASAP diagnosis have no differences in prostate-specific antigen (PSA), Gleason score (GS) or stage in comparison to men with diagnosis of PCa and not preceded by an ASAP diagnosis [7]. As the underlying background is uncertain, the strategy traditionally includes repeat biopsy because of the high probability of malignancy diagnosis in repeat sampling [8,9]. However, in the modern era of deferred treatment for PCa and active surveillance (AS), some authors and researchers are challenging the immediate biopsy in patients with ASAP as most of them found with PCa harbor a non-high-risk disease [10,11]. Towards this direction, a close monitoring approach is preferred involving PSA readings and multiparametric magnetic resonance imaging (mpMRI) for the follow-up of patients initially diagnosed with ASAP [12]. Indeed, mpMRI of the prostate has a high negative predictive value for the detection of PCa, which makes this an effective imaging modality for targeting biopsies and for following up patients on AS for PCa [13]. All the above have actively questioned the clinical impact of ASAP in modern urological practice. However, the report still raises the dilemma of further management and repeat biopsy might be needed [14]. In this review, we present the significance of ASAP in the histopathological report of patients being investigated for PCa.

2. Pathological significance of ASAP

ASAP might be found in 5% of specimens of initial prostate biopsy [15]. It reflects increased suspicion for cancer, but findings are insufficient to establish a diagnosis. Qualitatively, the lesions exhibit some degree of atypia which is suggestive but not definitive for cancer and the average diameter of the atypical glands and the number of acini are less than seen in cancer [8]. Specific factors which could attribute to the diagnosis of ASAP include small number of acini in the focus of concern, small focus size, atypical morphology in acini or conflicting immunohistochemical findings such as ambiguous p63 staining and other architectural or cytologic changes which might be found in non-cancerous entities [16]. Technical limitations and subsequent crush artifacts (result of mechanical tissue compression and distortion by an outside force) related to the needle-biopsy can lead to the diagnosis of questionable atypia [17]. Prostatic epithelium might also resemble atypical findings in a small amount of prostate biopsies [18]. Several histopathological parameters such as concurrent inflammation or atrophy, size and number of the acini and nuclear characteristics used in combination might favor cancer in case of ASAP [19,20]. Better sample preparation (*e.g.*, limited number of cores in tissue cassette) and the performance of a cocktail of immunochemistry markers such as p63 might increase significantly the pathologist's level of confidence, reducing the incidence of ASAP diagnosis and thus, the need for repeat biopsy [21]. As ASAP could represent both an under-sampled cancer and reactive atypia of benign origin, clinical correlation is strongly advised. For example, no cancer was reported in repeat biopsies in men found with concurrent prostatitis and ASAP in initial biopsy [22].

3. Clinical features and biopsy parameters which could implicate cancer

In general, clinical characteristics such as PSA, digital rectal examination (DRE) of the prostate or age of the patient have been reported inaccurate to predict the outcome of repeat biopsy, although older age and pathological DRE are independent risk factors of cancer [23,24]. However, as both ASAP itself and cancer are accompanied by increases in PSA and pathological DRE of the prostate, the differentiation in the clinical context is impossible [25]. The number of positive cores with ASAP in the initial biopsy is not relevant and one single core of ASAP is considered more than enough to trigger a repeat biopsy in the near future [26]. Moreover, a core biopsy length less than 10 mm and a limited number of cores (less than eight cores) in the initial biopsy might implicate under-sampled, and thus missed cancer in patients with ASAP [27]. However, atypia on prostate biopsy is linked to a high likelihood of underlying malignancy regardless of the number of cores taken on initial biopsy (>20 cores *vs.* standard 12 cores or less) [28]. Regarding the role of prostatic volume, lower prostate volume has been associated with increased possibility of PCa diagnosis on subsequent biopsy [29]. Scattoni et al. [30] also observed that in patients with isolated ASAP the detection rate was lower in the presence of an enlarged prostate volume more than 50 mL if only a transrectal ultrasound (TRUS)-guided 12-core protocol biopsy was followed, whereas prostate volume less than 30 mL was predictive of cancer, as reported by Leone et al. [27] reflecting the quality of sampling and cores taken from these patients. The topography of sampling is important as PCa might be presented in areas not sampled in the initial biopsy, such as the anterior gland and the apical prostate [31]. Leone et al. [27] using an end-fire transrectal TRUS-guided approach in the initial biopsy observed that clinically significant cancer was mostly located in anatomical sites and difficult to be reached, such as the apex, the anterior gland, and the midline. Regarding the association of ASAP and high-grade prostatic intraepithelial neoplasia (HGPIN), the presence of the former one has been reported as a stronger predictive factor of cancer in immediate repeat biopsy compared to HGPIN [32]. The observation is reasonable as ASAP might represent a missed cancer whereas HGPIN is considered a precursor of PCa. Regarding the co-existence of ASAP and HGPIN and the subsequent cancer, Merrimen et al. [33] reported that the detection

rate might reach up to 71%. Conversely, Aganovic et al. [34] reported that the specificity for PCa in repeat biopsies for both lesions together is reported up to 91%. In another study, the cancer detection rate for ASAP alone and for ASAP and HGPIN combined did not differ significantly, reported to be 37% and 33%, respectively [35]. In a recent retrospective study of 411 patients undergoing a repeat biopsy, the combination of multifocal HGPIN (MF-HGPIN) plus ASAP in initial report showed the highest probability of cancer in repeat biopsy (adjusted probability 0.50, 95% confidence interval 0.35—0.65). Moreover, the detection rate of cancer of GS 7 or greater was 41.1% in patients with MF-HGPIN plus ASAP which was almost twofold compared to those with ASAP only (22.5%) or MF-HGPIN only (20%) [36].

4. The probability of significant PCa

Regarding the association with cancer grade in subsequent biopsies, the majority of cancers are reported to be of low grade and low volume in up to 77% of detected cases [37]. Some studies have reported the distribution of GS in patients with repeat biopsy and previous ASAP. In a landmark study, Warlick et al. [38] reported that the incidence of significant PCa disease (defined as GS 7 or more) in patients with initial ASAP diagnosis who had repeat biopsy at any time was 17.3%; interestingly, higher PSA density was associated with GS 7 disease or above, both at 1 year and anytime following a diagnosis of ASAP. In another study, Dorin et al. [39] observed that a GS equal or less than 6 was found in 81% of patients in repeat biopsies; 15% had GS 7; and 4% had GS 8. Also, by applying modified Epstein criteria (clinically organ confined disease, GS equal or less than 6, up to two positive cores, 50% of core involved with tumor, PSA$<$10 ng/mL), the authors observed that up to 51% of patient may harbor so called significant disease, whereas 38% of patients who finally underwent radical prostatectomy had GS 7 or more in their final pathological specimen. Importantly, 14% of tumors had extracapsular extension [39]. Following 264 patients who underwent repeat 12-core transrectal biopsy due to initial diagnosis of ASAP, Leone et al. [10] reported a cancer incidence of 32% in repeat biopsy; 69 (78%) patients were found with GS 6, whereas 21 (22%) patients harbored "high-risk" disease on repeat biopsy defined as GS equal or above 7. The authors concluded that the number of patients needed to repeat biopsy to detect one additional case of significant cancer (defined as GS equal or more than 7) was 13 and therefore, not all patients warrant repeat biopsy at 6 months; however, no clinicopathologic variables were significantly associated with high-grade disease [10]. Furthermore, in another retrospective review of 49 patients with ASAP who underwent repeat biopsy, 15 (31%) were diagnosed with cancer, 10 (20%) with ASAP again, and 24 (49%) had benign lesions [15]. In the cancer group, 12 patients (80%) had GS 6 disease, whereas GS equal or more than 7 was found in three patients only (6% of all patients with a repeat biopsy). Thus, authors concluded that patients with ASAP may not require repeat biopsy within 6 months in the appropriate clinical context [15]. Another study examining the racial contribution in patients with ASAP showed that at repeat biopsy 25 out of 42 patients met the Epstein criteria for significant disease whereas any amount of GS pattern 4 was present in 10 patients; in this study, both African American and Caucasian American men shared the same risk of PCa in repeat biopsy [40]. Last but not least, in a large retrospective review performed by Wiener et al. [41], clinically insignificant PCa at repeat biopsy (defined as GS$<$7, PSA$<$10 ng/mL, $<$50% core volume, and $<$3 involved cores) was more common for patients with ASAP at initial diagnosis comparing to HGPIN or benign tissue in the specimen (26.1% *vs.* 13.5% *vs.* 11.6%) but the difference was not significant.

5. The re-biopsy strategy post ASAP-diagnosis

If a decision for a repeat biopsy has been made, the performance of a three-dimensional magnetic resonance imaging (MRI-3D) transrectal ultrasound fusion biopsy instead of a standard 12-core transrectal biopsy has been reported to decrease significantly the risk of missing a significant disease (defined as GS equal or more of 3+4) in patients with previously diagnosis of ASAP [42]. Cool et al. [42] concluded that if only Prostate Imaging-Reporting and Data System (PIRADS) $\geq$3 lesions were targeted, then no significant PCa would have been missed, while 60% of patients would have avoided biopsy. Similarly, another study reported that when MRI-fusion guided transrectal biopsy detects isolated ASAP on initial biopsy, early repeat biopsy is unlikely to detect clinically significant PCa; in this context, targeted biopsies should be preferable than random ones [43]. Regarding the approach for repeat biopsy, transperineal biopsy seems to be advantageous as it can offer extensive sampling especially in sites that cannot be reached by transrectal biopsy. Martorana et al. [44] reported that saturation biopsy through a single transperineal access can increase the detection rate of PCa up to 63% in patients previously diagnosed with ASAP, even in repeated transrectal biopsies. In another study, Merrick et al. [31] reported that improving by the sampling process using transperineal template-guide biopsies, the detection rates of high risk (GS above or equal to 7) cancers was increased up to 35.6%; a predilection for anterior apex cancer was identified whereas no patient underwent mp-MRI prior to repeat biopsy. Nakai et al. [45] drew similar conclusions endorsing the effectiveness of transperineal biopsy in the detection of significant PCa in men with ASAP in the initial TRUS-biopsy, reporting a detection rate of PCa of 83% (10/12) patients. Additionally, using a median number of cores as high as 37 and a median rate of biopsy core per prostate volume of 1.00 (cores/mL), the authors reported that significant disease, defined as GS 7 or above at repeat biopsy, was found in eight out of 10 patients diagnosed with PCa; five of these patients had GS 4+3; two patients overall had GS 6 whereas no GS 8 or higher was found [45]. Regarding the topography of the repeat biopsy, sampling the whole gland seems mandatory as it has been reported that in 39% of cases, the cancer will be found in a different site from the initial ASAP diagnosis site [46]. Similarly, Borboroglu et al. [47] noted that repeat biopsy directed only to the site

of atypia on initial biopsy would have missed 53% of cancer cases, whereas Aglamis et al. [48] observed that cancer was detected in 67% of ipsilateral adjacent biopsy sites, and in 54% of contralateral biopsies.

6. Discussion

ASAP is an equivocal histopathological description which inevitably, raises the suspicion of an underlying, undersampled adenocarcinoma. Despite current guidelines, the discovery of ASAP at initial biopsy seems to be a debate among urologists as a significant proportion of patients are not offered an immediate repeat biopsy as advisable [36]. Indeed, some studies bring current indication into question as the incidence of significant underlying disease is reported to be low, whereas careful monitoring in selected patients might replace unnecessary biopsies and avoid subsequent complications [10,12]. It must be taken into consideration that the distribution of high grade or significant disease cannot be predicted accurately as there are no clinicopathological findings which could assist reliably [12]. Older patient age and abnormal digital rectal examination have been reported as independent predictors of cancer though [24]. On the contrary, some authors observed that younger patients with initial ASAP diagnosis seem to be at increased risk to have significant prostate cancer in repeat biopsy reflecting higher D'Amico risk stratification [49]. Delaying the repeat biopsy may be an option only in those patients in whom the benefit of further PCa diagnostics is regarded as low, or in patients in whom the benefit of any treatment for localized disease would be debatable, *e.g.*, patients with limited life expectancy or significant comorbidities [50]. If a repeat biopsy has been decided, increasing the number of cores and targeting previously undersampled areas are mandatory; a transperineal approach seems preferable due to the ability to sample anterior gland lesions more efficiently and thus to achieve high rates of significant PCa disease detection [27,31]. On the other hand, little is known regarding the clinical relevance of ASAP in the modern era of the increasing use of MRI. It has already been shown that the sensitivity of mpMRI for significant disease is excellent, and the modality has already secured its routine role in the evaluation of patients with suspicion of PCa [51]. Furthermore, the risk of overdiagnosis is reduced and detection of clinically significant disease can be notably improved [52]. Whether the performance of MRI alone could substitute the traditional strategy of repeat biopsies to clarify an initial ASAP diagnosis remains uncertain. MRI seems efficient to differentiate reliably between normal and pathological prostate tissue but not among PCa, HGPIN and ASAP [53]. However, as already mentioned, MRI-TRUS fusion biopsy has an excellent negative predictive value for the detection of significant disease in patients with previously diagnosed ASAP [42]. From the above, it seems that the negative predictive value of MRI probably can be trusted when evaluating a patient with the initial diagnosis of ASAP. Regarding the hot topic of patients diagnosed with PCa and being on AS, the prognostic role of ASAP is uncertain. Pietzak et al. [11] observed that concomitant ASAP did not affect the final pathology of the low-risk patients who had met the criteria of AS undergoing radical prostatectomy in the past, whereas the equivocality did not have any impact on the 5-year biochemical recurrence. Nevertheless, in another study, the initial diagnosis of ASAP in patients retrospectively regarded as AS candidates was a risk factor for unfavorable final disease in the prostatectomy specimen whereas a single core of GS 3+4 or GS 3+3 PCa was not [54]. That confirms that in selected group of patients candidate for AS, the significance of ASAP needs to be clarified. Once again, further studies should enlighten if the currents protocols will change the clinical impact of histopathological observations such as ASAP in the clinical context of patients being on AS or other kind of deferred treatment.

7. Conclusion

In summary, ASAP remains a dilemma for both the pathologist, who is not able to provide a definite diagnosis, and the urologist who should rely on patient's characteristics, biopsy report and current guidelines for further management. Beyond the scope of the latter ones, no definitive clinical selection criteria for repeat biopsy in patients previously diagnosed with ASAP exist. Any patient regarded as candidate for all radical treatments with persistently raised PSA and suspicious prostate will benefit from repeat biopsy as the probability of significant disease is existent. Regarding the clinical relevance of ASAP diagnosis together with mpMRI, data are still being emerged. Although the exact nature of an ASAP lesion cannot be clarified through pre-biopsy mpMRI, the modality carries high negative predictive value for significant PCa, and appears to date that it can be used convincingly in patients with previous ASAP. Additionally, the performance of MRI-fusion transrectal biopsy seems to be a reliable approach for repeat biopsy as the possibility of missing significant PCa is low. A transperineal template approach can increase the cancer detection rate significantly, as it can sample areas previously omitted or not reached, whereas it must be kept in mind that the PCa might well be found in different areas than those reporting ASAP in the initial biopsy. Finally, future research should clarify the role of ASAP diagnosis in patients being under an AS protocol for PCa.

Author contributions

Study design: Georgios Tsampoukas, Victor Manolas, Athanasios Papatsoris.
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Conflicts of interest

The authors declare no conflict of interest.

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