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Original Article

Atypical diagnosis in prostate needle biopsies from a developing country (Philippines): The essential role of a urological pathologist

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ABSTRACT

Purpose: Borderline prostatic lesions, with insufficient histomorphologic features, to be definitely diagnosed as prostatic adenocarcinoma (PCa) are often signed out as "atypical glands suspicious for carcinoma" or atypical small acinar proliferation (ASAP). These findings that eventually warrant either immunohistochemical (IHC) studies or a repeat biopsy, prove to be more burdensome to patients in developing countries (such as the Philippines), where health care is not as progressive nor is it an utmost priority. At the same time, in countries like the Philippines, there is a shortage of urological pathologists.
Methods: In this study, we compared the transrectal ultrasound-guided prostate (TRUS) biopsies signed out by general surgical pathologists in St. Luke's Medical Center Quezon City from 2008–2010, and the TRUS Biopsies primarily signed out by a urologic pathologist in both St. Luke's Medical Center Quezon City and Global City from July 2013 to July 2014, and from September 2013 to July 2014, respectively.
Results: From 2008 to 2010, 30.6% (129 of 421) of the cases were signed out as atypical. Of these, 79 underwent IHC staining, 21 (26.6%) of which were eventually signed out as PCa. Compared to those signed out in 2013 to 2014 by our genitourinary pathologist, only 16.6% (39 of 235) of the cases were signed out as atypical. Of these, 16 underwent IHC staining, with 15 (93%) of them being definitively diagnosed as PCa. Among the 21 cases wherein a repeat biopsy was recommended, only three followed and two of these had findings of PCa on repeat biopsy. Looking at our 16.6% rate of atypicals and subtracting those that were eventually established as PCa after IHCs, our atypicals would be down to 10% (24/235) in 2013–2014 compared to 25.7% (108/421) in 2008–2010.
Conclusions: These results highlight the critical role a specialist has in the field of urological pathology, especially in developing countries. It is in the diagnosis of PCa in needle biopsies that a urological pathologist impacts the use of an atypical diagnosis, by ensuring its judicious use. This ultimately benefits the patients, by lessening unwarranted expenses through the decreased dependence on IHC staining and if necessary, a repeat biopsy.

1. Introduction

Terms such as "atypical glands suspicious for carcinoma" and "atypical small acinar prolilferation (ASAP)" are two of the more common terms that have been used to describe those borderline prostatic lesions that do not show any pathognomonic feature of prostatic adenocarcinoma (PCa), but at the same time, reveal some histomorphologic characteristics suggestive of PCa too worrisome to be diagnosed as benign. The presence of an atypical finding commonly necessitates either the use of immunohistochemical (IHC) stains or a repeat biopsy, both of which require additional finances. To patients in developing countries such as the Philippines, however, these additional finances are a heavier burden, as compared to patients in already developed countries.

In the current study, we aim to determine the impact of a trained urological pathologist on our current rate of atypical diagnoses, now that he has been primarily evaluating our transrectal ultrasound-guided prostate biopsy (TRUS) specimens for a 1 year period.

2. Materials and methods

We searched through the databases of St. Luke's Medical Center-Quezon City (SLMC-QC), and St. Luke's Medical Center-Global City

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(SLMC-GC), Philippines. All TRUSs from 2008 to 2010, which were diagnosed by general surgical pathologists, were collected. These cases from 2008 to 2010 were chosen because of a previous study performed by the senior author (JSS) on the rate of "atypicals" in their institution.[1] These cases were then compared to those, which were diagnosed by the senior author (a trained urological pathologist) at both SLMC-QC (from July 2013 to July 2014), and SLMC-GC (from September 2013 to July 2014).

On both time frames, two pathologists have to agree on a diagnosis of PCa or atypical in order for the final diagnosis to be released. Based on the final diagnosis, cases were categorized into three groups: Atypical glands present, Adenocarcinoma, and Benign. The Atypical group was further subdivided to those that required IHC staining and those that warranted a repeat biopsy. A repeat biopsy was not an option during the 2008–2010 period. The general pathologists who diagnosed an atypical finding were not aware that such a suggestion could be a possible alternative or could be the better recourse for the patient. IHC staining in our institution, when requested by the pathologist, would require the permission of the patient in order for it to proceed. This would necessitate calling up the patient to make sure that they are able and willing to pay for the said IHC stains. Only upon the documented consent of the patient does the IHC staining proceed.

The groups that underwent IHC staining and repeat biopsy were recategorized to the three main groups of Atypical glands present, Malignant, and Benign to get the final percentages of each group.

From 2008 to 2010, IHC staining was performed using three separate antibodies for P504s/alpha-methylacyl-CoA racemase (AMACR), p63 and high-molecular weight cytokeratin (HMWCK).

With the exposure of the senior author to the more recent PIN4 cocktail stain—which incorporates the three previously mentioned stains (AMACR, p63 and HMWCK)—the use of separate slides for separate stains was now replaced. These ensured that the atypical focus for IHC staining was still present in the tissue. Therefore, those cases from 2013 to 2014 that required IHC staining made use of the more recent PIN4 cocktail stain.

3. Results

A total of 421 TRUS biopsies were identified from January 2008 to December 2010, while a total of 235 TRUS biopsies were evaluated by our urological pathologist at SLMC-QC and SLMC-GC from July 2013 to July 2014, and from September 2013 to July 2014, respectively (Table 1).

We were able to identify 41/137 (29.9%) atypical diagnoses in 2008, 46/150 (30.7%) in 2009 and 42/134 (31.3%) in 2010. In this 3-year period, a total of 129/421 (30.6%) atypical diagnoses were rendered in TRUS biopsies (see Table 2).

From these atypical cases from 2008 to 2010, 79 (61.2%) underwent IHC staining and among them, 21 (26.6%) were ultimately diagnosed as prostatic adenocarcinoma.

The senior author evaluated a total of 235 TRUS cases in 2013 and 2014. An atypical finding was rendered in 39/235 (16.6%) of these TRUS cases. Among these cases from 2013 to 2014, 21/39 (53.8%) cases were advised to undergo staining. Of these, however, only 16 (76.2%) pursued IHC. From the cases that did undergo IHC staining, 15/16 (93.8%) cases were diagnosed as carcinoma, while the one remaining case remained atypical with a patchy basal cell staining pattern.

Unlike during the first time frame (2008–2010), a patient with an atypical diagnosis also had the option of having a repeat biopsy instead of undergoing stains. Repeat biopsy was suggested in 18/39 (46.2%) cases. Among them, only three of 18 (16.7%) underwent a repeat biopsy. Prostatic adenocarcinoma was identified in 66.7% subsequent TRUS biopsies.

Table 2
Data analysis.

	Atypical cases		Total	*P*
	+	−		
GSP	129	292	421	0.0003
GUP	39	196	235	
	Atypical cases			
	w/IHC	w/o IHC		
GSP	79	50	129	0.013
GUP	16	23	39	
	Cases diagnosed after IHC			
	+ PCa	− PCa		
GSP	21	58	79	<0.001
GUP	15	1	16	
	Total after IHC			
	+ Atypical	− Atypical		
GSP	108	313	421	<0.001
GUP	24	211	235	

Data are presented as *n*.
GUP, genitourinary pathologist; GSP, general surgical pathologist; IHC, immunohistochemical staining; PCa, prostatic adenocarcinoma.

4. Discussion

Prostate cancer remains one of the most common malignancies diagnosed among men.[2] A pathologist plays a critical role, not only in the diagnosis, but also in whatever therapeutic modality a prostate cancer patient will undergo.[3] However, the diagnosis of PCa can often be challenging, especially with the limited amount of tissue that is submitted for a definite diagnosis. This is where the use of an "atypical diagnosis" has tremendously aided pathologists. With the use of an atypical diagnosis, a pathologist need not commit to a benign or malignant diagnosis if he feels that the features he is identifying are not satisfactory for either a benign or malignant lesion.

An atypical diagnosis in TRUS biopsies, based on the literature, is rendered in about 0.7–23.4% of cases, with an average of approximately 5%.[3] An atypical diagnosis is usually given when the histomorphologic atypical features are not adequate to definitively

Table 1
Data comparison between time frames.

	Total TRUS	Total ATYP	ATYP which underwent IHC	Cases diagnosed as PCa after IHC	Total ATYP after IHC	Cases with suggestion of repeat biopsy	Cases which underwent repeat biopsy	Cases diagnosed as PCa after repeat biopsy (*n*)
2008–2010	421	129 (30.6)	79	21 (26.6)	108 (25.7)	0	0	0
2013–2014	235	39 (16.6)	16	15 (93)	24 (10)	18	3	2

Data are presented as *n* or *n* (%).
ATYP, atypical cases; IHC, immunohistochemical staining; PCa, prostatic adenocarcinoma; TRUS, transrectal ultrasound-guided prostate biopsy.

differentiate an atypical focus from carcinoma, high grade prostatic intraepithelial neoplasia (HGPIN) or various benign mimickers of cancer. As previously mentioned, multiple terms have been used to diagnose atypical glands. To those pathologists who do not encounter enough TRUS specimens, the use of an atypical diagnosis may be overused, even among those cases that are sometimes overtly diagnosable as adenosis, atrophy (simple, partial, and postatrophic), basal cell hyperplasia, and HGPIN—the more common benign mimickers of PCa.[4–9]

Based on our data from 2008 to 2010, our number of atypical diagnosis, 30.6%, is beyond that of the range (0.7–23.4%) reported in the literature.[10] Most (79 cases) of these atypicals underwent IHC staining. We compared these data with those TRUS biopsies, which were diagnosed by the senior author, a urological pathologist. Our data showed that there was a significant drop in the number of cases signed out with an atypical diagnosis. From a rate of 30.6% in 2008–2010 to 16.6% in 2013–2014—almost half of those reported in 2008–2010. Another important piece of data, which we were able to show, was the percentage of PCa after IHC staining. In 2008–2010, only 26.6% of those that underwent IHC were finally diagnosed with PCa, while in 2013–2014, 93% were established as PCa. We want to emphasize that our goal in this study was not to minimize the value of an atypical diagnosis, because as has been shown by Epstein and Herawi,[10] the diagnosis of "atypical" carried an average of 40.2% (median, 38.5%, range, 17–70%) increased risk of PCa on subsequent biopsy. What we do aim for is to emphasize the critical role of a pathologist in the diagnosis of PCa, more specifically the number of atypical cases that are diagnosed. Based on our data, a specialist in the field of genitourinary pathology has a great impact in minimizing the number of atypicals and reserving this atypical diagnosis to those cases which are truly worthy of being labeled as such, especially those which are really suspicious for prostatic adenocarcinoma or other prostatic malignancies.

A specialist's presence is felt more in countries like the Philippines, wherein most of the population lacks funds for the most basic of necessities, even more, proper health care. Therefore the use of IHC, though an indispensable tool in PCa diagnosis,[11,12] is usually beyond the financial capabilities of the common Filipino patient. That is why the percentage of cancer diagnoses, after IHC in 2008–2010, of 26.6% is a low number to justify the number of atypicals as well as the request for IHCs. Thus the access, which our patients have to our urological pathologist, has truly benefited them by decreasing the dependence on IHCs as well as lessening those unwarranted atypical diagnoses. Furthermore, our final number of atypical diagnoses would be lower if we take into consideration the fact that we would have to ask for the permission of a patient to proceed to IHC, unlike in developed countries, such as the USA where patients have health insurance, which would automatically cover the expenses for these stains. Looking at our 16.6% rate of atypicals and subtracting those which were eventually established as PCa after IHC, our atypicals would be down to 10% (24/235) versus 25.7% (108/421) in 2008–2010. From a financial standpoint of a patient, they would benefit from a more definite diagnosis instead of an unwarranted atypical finding because they would not need further IHC staining or repeat biopsy, which will eat up their finances that they may eventually have to utilize for their treatment.

5. Conclusion

In this day and age where most of the advances in medicine have been happening mostly at the molecular level, we hope that this study will show that there is still a tremendous need for trained specialists in various fields to practice in developing countries. We feel that the diagnosis of PCa is just a small part of pathology, and medicine for that matter, that needs the transfer of knowledge from more developed countries.

The senior author (JSS) has been active in trying to educate his fellow surgical pathologists in the hope of minimizing the unwarranted use of an "atypical diagnosis". He has also been trying to convey to local urologists the tremendous impact that a needless "atypical diagnosis" has on a patient.

The authors' goal in publishing this study is to be able to remind our fellow pathologists about our tremendous role in the evaluation of TRUS biopsies. We hope that through this study, our fellow local surgical pathologists would aim to further educate themselves to minimize their unwarranted "atypical diagnosis" rates. Another study can also be done wherein, based on this present study, we can analyze what are the most common reasons for unwarranted atypical diagnosis among general pathologists.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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