ORIGINAL ARTICLE

Diagnostic usefulness of the cytological study of the transport buffer in transrectal prostate core biopsies

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KEYWORDS
Cytology; Histology; Core biopsy; Prostate adenocarcinoma; Sensitivity; Specificity

Abstract
Background: To evaluate the diagnostic usefulness of the cytological study of the transport buffer in the diagnosis of prostate adenocarcinoma in transrectal core biopsies.

Methods: A total of 256 consecutively biopsied patients have been included in the analysis, 100 of them diagnosed of prostate adenocarcinoma. The procedure included the cytological analysis of the transport buffer and conventional histology. Cytological evaluation was performed in a blind way by the same pathologist.

Results: Overall sensitivity, specificity, and positive and negative predictive values to detect malignancy in the cytological slides were 54%, 98%, 94% and 76%, respectively. When restricting the analysis to cases with Gleason score higher than 8, sensitivity and negative predictive value increased to 85% and 97%, respectively. Similarly, when the analysis focused exclusively to cases with more than 5 mm of cancer in the biopsy, sensitivity and positive predictive value increased to 66% and 96%, respectively.

Conclusions: This study shows that whilst specificity was maintained in 98%, sensitivity, and positive and negative predictive values significantly improved in high grade and high volume adenocarcinomas. Our findings confirm that the cytological study of the transport buffer may complement the histology in the diagnosis of prostate adenocarcinoma.

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Utilidad diagnóstica del estudio citológico del tampón de transporte en biopsias por punción prostática transrectal

Resumen

Antecedentes: Evaluar la utilidad diagnóstica del estudio citológico del tampón de transporte en el diagnóstico de adenocarcinoma de próstata en biopsias por punción transrectal.

Métodos: Un total de 256 pacientes biopsiados consecutivamente se han incluido en el análisis, de ellos diagnosticados de adenocarcinoma de próstata. El procedimiento incluyó el análisis citológico del tampón de transporte y la histología convencional. Se realizó evaluación citológica de una manera ciega por el mismo patólogo.

Resultados: La sensibilidad, especificidad y valores predictivos positivos y negativos globales para la detección de malignidad en los portaobjetos citológicos fueron 54, 98, 94 y 76%, respectivamente. Cuando se restringió el análisis a los casos con una puntuación de Gleason superior a 8 la sensibilidad y el valor predictivo negativo aumentaron a 85 y 97%, respectivamente. Del mismo modo, cuando el análisis se centró exclusivamente en los casos con más de 5 mm de cáncer en la biopsia la sensibilidad y el valor predictivo positivo aumentaron a 66 y 96%, respectivamente.

Conclusiones: Este estudio muestra que mientras que la especificidad se mantuvo en el 98% la sensibilidad y los valores predictivos positivos y negativos mejoraron significativamente en los adenocarcinomas de alto grado y de alto volumen. Nuestros hallazgos confirman que el estudio citológico del tampón de transporte puede complementar la histología en el diagnóstico de adenocarcinoma de próstata.

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Introduction

Prostate adenocarcinoma (PAC) is the most common malignancy among the male population in western countries and its diagnosis and management remain a problem of major concern for urologists and health authorities. This has led in the last two decades to the implementation of strategies for the early detection of this malignancy which lead to the discovery of an increasing number of low-grade, low-volume cases which are potentially curable.

Although fine-needle aspiration cytology (FNAC) was the initial diagnostic approach, and it is still used at some institutions, transrectal needle biopsy (NB) has gained general acceptance all over the world and is the method of choice for PAC detection in patients with a suspicious digital examination and/or high PSA levels (cut, 4.0 ng/ml).

This study aims at defining the diagnostic efficacy of the cytological analysis of the transport buffer of prostate needle biopsies in a consecutive series of non-selected patients with clinical suspicion of PAC. This diagnostic approach has not been used before in the case of this prostate disease, but it has shown satisfactory results in previous studies carried out on various systems and organs, such as the musculoskeletal system, the kidney, the spleen, the lymph nodes and the thyroid gland, among others.

Patients and methods

The NBs of 256 patients with a clinical suspicion of PAC were submitted from the urologist’s office to the pathology laboratory at our institution immersed in a cell-washing solution and in a transport buffer (ThinPrep® Cytolyt® Solution, Hologic Inc., Marlborough, MA, USA). Cases were not clinically selected and were consecutively included in the series in a prospective manner from December 2012 to April 2013. The series was closed when PAC reached 100 cases. Age, serum PSA at the time of biopsy, rectal digital examination, number of punctures, prior biopsy, prostate volume, and transrectal ultrasound findings were the data collected in each case. This study complies with the principles of the Declaration of Helsinki.

The right prostate punctures of the right and left sides were presented together in two different flasks and were routinely processed within the first 3 h after surgery. Two cytological examples were obtained from each sample using successive cyto-centrifugations, one of which was Papanicolaou-stained and the other one remained unstained for possible techniques. At the same time, NBs were fixed with formalin and then embedded in paraffin according to routine laboratory methods. Four consecutive stages of histological sections stained with hematoxylin and eosin in all cases were analyzed. Immunohistochemistry for cytokeratin 34βE12 (Dako, prediluted) and α-methylacyl-CoA racemase (AMACR)/p63 cocktail (BioCare Medical, prediluted) was performed in selected cases, either on unstained cytological slides or in histological cuts as needed in an automated immunostainer (EnVision FLEX, Dako Autostainer Plus).

The cytological and histological specimens were blindly analyzed by the same pathologist (JIL) in all cases. Only two diagnostic categories were considered in the cytological samples: malignant vs. non-malignant. Table 1 summarizes the cytological differential diagnosis of cells found in the cytological specimens. Suspicious cases were assigned to the non-malignant category. The diagnosis of PAC included the Gleason score (GS) involved and the amount of tumor known as total millimeters of cancer (TM).
Table 1 Spectrum of cells found in cytological samples and their features.

<table>
<thead>
<tr>
<th>Malignant cells</th>
<th>Cell groups of several non-cohesive layers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal/hyperplastic cells</td>
<td>Plates of the cohesive monolayer cells</td>
</tr>
<tr>
<td>Basal cells</td>
<td>Cohesive multilayer cell groups</td>
</tr>
<tr>
<td>Transitional cells</td>
<td>Cell plates of several cohesive layers</td>
</tr>
<tr>
<td>Seminal vesicle cells</td>
<td>Nuclear anaplasia</td>
</tr>
<tr>
<td>Colonic mucosa cells</td>
<td>Cohesive cell groups of several layers</td>
</tr>
</tbody>
</table>

The results were grouped at the end of the study and were statistically analyzed using SPSS 19.0 software.

Results

NBs were collected from 256 patients, 100 of whom (39%) were diagnosed with PAC. The patients' average age was 69.7 years (50–87) for those patients with PAC and 65.2 years (52–86) for those without PAC. It was bilateral in 56 cases. The distribution of GS was as follows: 31 cases were GI 3 + 3, 26 GI 3 + 4, 15 GI 4 + 3 and 28 GI 4 + 4 or more. The average TM was 20 mm (range: 1–91).

Cytologically speaking, normal/hyperplastic glands are monolayer plates of multifaceted monotonous cells with well-defined edges and a geographical shape located in a clean background. PAC cells can be arranged in groups with several layers or forming small tubules in a dirty background with a number of individual cells which increases with GS. Cell groups show little cohesion, with a trend toward cell detachment. A varying number of other cells can be observed, that is, transitional cells, basal cells, colonic mucosa cells, seminal vesicle cells, as well as inflammatory cells. Particular attention should be paid to the groups of basal cells, since they can imitate malignant tumors (Table 1; Fig. 1).

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for cancer detection in the cytological analysis were 54.98%, 94 and 76%, respectively. However, these figures varied significantly when cases were grouped into 2 groups taking into account the Gleason score cut-off of 8 and the TM cut-off of 5 mm (Table 2). Therefore, sensitivity more than doubled in the GS ≥ 8 group (85%, n = 28) when compared to GS < 8 (41%, n = 72) (χ² = 0.000) and NPV increased from 77% (GS ≤ 8) to 97% (GS ≥ 8) (χ², p = 0.019). Similarly, sensitivity in the TM > 5 mm was more than double (66%, n = 69) when compared to TM ≤ 5 mm (29%, n = 31) (χ², p = 0.0004) and PPV increased from 75% (TM ≤ 5 mm) to 93% (TM > 5 mm) (χ², p = 0.01).

Discussion

PAC is the most common malignancy among the male population in Spain. Epidemiological data on prostate cancer have shown in recent decades that the effect of serum PSA determination in common practice translates into a sharp increase in the diagnosis of this neoplasm and in the discovery of a large number of potentially curable cases, the numbers of which increased from 20–30% in the pre-PSA era to 70–80% at present. The arrival of population checks resulted in a decrease in mortality rates, but did not achieve acceptance all around the world due to the risk of overtreatment in those cases with clinically insignificant disease. Along with serum PSA determination, FNAC was introduced in Sweden in order to obtain material for definitive diagnosis. Since FNAC was an easy, cheap, and reliable method for PAC diagnosis, its application was rapidly extended to all western countries and brought pathologists closer to patients and placed them at the center of the diagnostic process of this malignancy. Nevertheless, NB was rapidly developed and gained acceptance all over the world since the technique provided “tissue” for histological analysis at a similar cost and with similar clinical complications when compared to FNAC.

The NB procedure started with six punctures. However, several studies soon demonstrated the necessity for more punctures in order to increase the probability of PAC detection. This strategy increases the probability of discovering low-grade and low-volume PAC which can eventually lead to overtreatment in some cases. Current guidelines recommend obtaining between 12 and 18 punctures with extended NB. Although NB is the generalized approach for pathological diagnosis, cytology should not be discarded for diagnosis. In fact, the benefits of the combined use of cytological and histological approaches in thyroid disease have been highlighted and it has been successfully carried out in several organs, but never in the prostate gland. Besides, the study of liquid transportation from needle biopsies of musculoskeletal masses, and...
renal tumors, spleen nodes, lymphadenopathies and the thyroid gland has provided very useful information for complementing histological diagnoses in a significant number of cases.

This combined cyto-histological approach offers the rapidity of cytology on the one hand and the accuracy of histology on the other. We consider that centrifuging the transport buffer of prostate punctures is an innovative and easy tool for early diagnosis. The specificity of this technique has shown very good numbers in our hands. Obviously, sensitivity is affected by the small amount of PAC in some punctures and by the different capacity of cancer cells for their release in the buffer. Sensitivity for PAC detection improved significantly in the high GS group and, to a lesser extent, in the TM > 5 mm group, which confirms that the higher the GS and the TM, the higher the possibility of cancer detection with this technique. The figures in these subsets of patients make this technique helpful in routine practice in a significant number of cases.

To our knowledge, there are no previous studies on this approach in prostate disease. The spectrum of cells which can be found in the cytological sample is wide, and its differential diagnosis has sometimes been difficult in our experience. In fact, three cases of false positives within this series showed prominent hyperplasia of basal cells on the histological slide. We observed in these three cases groups of several layers of hyperchromatic cells with a high nucleus/cytoplasm proportion in the cytological slides which make the diagnosis for malignancy feasible. Immunocytocchemistry with basal cytokeratins and/or AMACR of the cytological sample may be helpful in resolving the diagnostic dilemma in some of these cases.

**Conclusions**

In conclusion, the cytological analysis of the transport buffer can complement the histological study of prostate punctures and be helpful in the early diagnosis of PAC. This cytological material may have an additional forensic importance in the event of technical, logistical, or file incidents which result in the loss of needle biopsy material. Pathologists should consider the wide range of cells which may be found in the cytological sample and be aware of their pseudo-malignant characteristics. The use of some transport buffers of prostate punctures seems critical for ensuring the optimum preservation of the cell.

**Conflict of interest**

The authors declare that they have no conflict of interest.
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References