DOI: 10.7860/JCDR/2024/73534.20334

Short Communication

Pathology Section

Unusual Signet Ring Cell Change in Prostate Specimens Obtained after Transurethral Resection: An Immunohistochemical Study

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Keywords: Adenocarcinoma, Cytoplasmic vacuole, Nodular hyperplasia

INTRODUCTION

The term 'signet ring cell' is used to describe the histological appearance of a tumour cell characterised by a compressed peripheral nucleus in the shape of a crescent and a large cytoplasmic vacuole [1]. Traditionally, such cells have been considered a hallmark of high-grade signet ring cell adenocarcinoma [2]. In prostatic tissue, these cells signify either primary or secondary adenocarcinoma. Similar-looking cells were observed in specimens exhibiting only nodular hyperplasia. While searching the literature, very few articles were found that report such non neoplastic signet ring cell changes in Transurethral Resection of the Prostate (TURP) specimens [3-5]. These non malignant cells have been identified as either lymphocytes or stromal cells [4,5]. Alguacil-Garcia regarded this as an artefactual, degenerative change induced by the TURP procedure [4].

Hence, this study was undertaken to determine the frequency of signet ring cell changes in TURP specimens and to evaluate the nature of these cells using appropriate histochemical stains and immunostains.

MATERIALS AND METHODS

A descriptive and retrospective cross-sectional study was conducted in the Department of Pathology at the Pondicherry Institute of Medical Sciences, Puducherry, India, from October 2014 to February 2015, after obtaining approval from the Institute Ethics Committee (IEC) (RC/14/72). All 34 consecutive cases of TURP, with a minimum of two paraffin blocks to a maximum of ten paraffin blocks, were retrieved from the period of January 2012 to September 2014. Each case had a minimum of 20 prostatic fragments and a maximum of 70 prostatic fragments. Histopathology slides of these cases were reviewed during the period from October 2014 to January 2015 by four pathologists. Immunohistochemistry was performed during the period of February 2015.

Inclusion criteria: TURP cases with a minimum of 20 prostatic fragments were included in the study.

Exclusion criteria: Any case with fewer than 20 prostatic fragments was excluded from the study.

Study Procedure

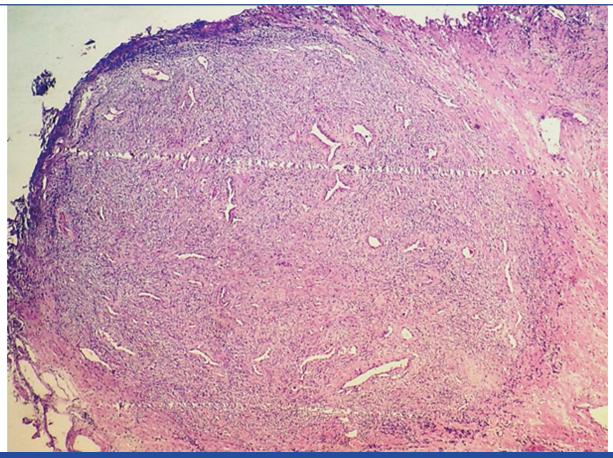
In all 34 cases, age, clinical details, and other relevant data were recorded from case files. Histopathology slides were blinded and reviewed by four pathologists to specifically detect signet ring cells. The findings of all four members were taken into account. There was no interobserver variation among them; therefore, the Kappa value was not calculated in this study. In the cases where such cells were observed, they were stained using two histochemical stains: Periodic Acid-Schiff with diastase predigestion (PAS-D) and Alcian Blue. Immunohistochemical (IHC) studies were also performed on the above cases. IHC was conducted on formalin-fixed tissue using antibodies directed against Leukocyte Common Antigen, Dako, Santa Clara, USA (LCA; DAKO) and a cytokeratin cocktail (Pan CK; Clone AE1/AE3, DAKO). Sections were taken on positively charged slides and incubated for two hours at 58°C. Antigen retrieval was performed using Tris Ethylenediamine Tetraacetic Acid buffer (Tris EDTA) at pH 9.0 by the pressure cooker method. The secondary antibody, 'Anti-mouse/rabbit polydetector horseradish peroxidase technique with 3,3'-Diaminobenzidine Tetrahydrochloride (DAB),' was used as the chromogen. Histochemical stains and immunostains were performed manually using appropriate controls. Special stains for acid mucin, such as PAS-D and Alcian Blue, were carried out to rule out the possibility of secondary signet ring cell adenocarcinoma arising from other organs. When vacuolated signet ring cells showed intense membranous and cytoplasmic immunoreactivity for Pan CK (clone AE1/AE3), they were considered to be of epithelial origin. Intense membranous immunoreactivity for LCA was considered positive for lymphocytic origin.

STATISTICAL ANALYSIS

The demographic data, clinical details, and histopathological findings of the 34 cases were entered into Microsoft Excel (Microsoft Corp., USA), and percentages were calculated.

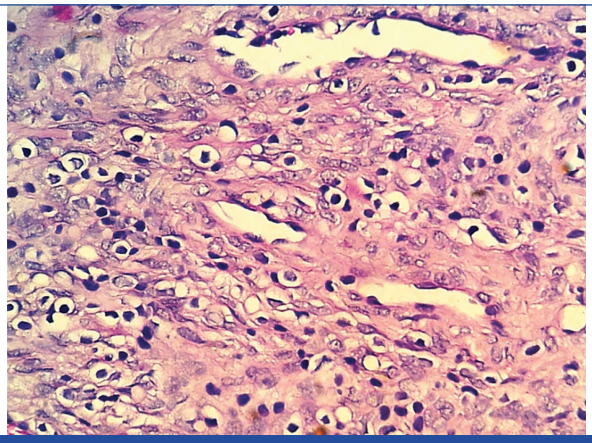
RESULTS

Out of the 34 TURP specimens studied, 32 (94.1%) were classified as nodular hyperplasia and two (5.9%) as prostatic adenocarcinoma. Vacuolated cells with clear or pale blue cytoplasm and a peripheral hyperchromatic nucleus, raising suspicion of signet ring cell carcinoma, were detected in three cases (8.8%). After an in-depth examination of each slide in every case, all four pathologists reached a consensus regarding the signet ring cell changes in these three cases. Two of the cases were found in nodular hyperplasia (two out of 32 nodular hyperplasia cases, 6.25%), while one was noted in a prostatic adenocarcinoma case. In both nodular hyperplasia cases, vacuolated cells were observed in aggregates within early stromal nodules [Table/Fig-1], mixed with other chronic inflammatory



[Table/Fig-1]: Stromal nodule of the prostate (H&E, 100x magnification).

cells [Table/Fig-2]. One case of prostatic adenocarcinoma with a Gleason score of 4+4=8 showed a few signet ring cells adjacent to the tumour [Table/Fig-3].

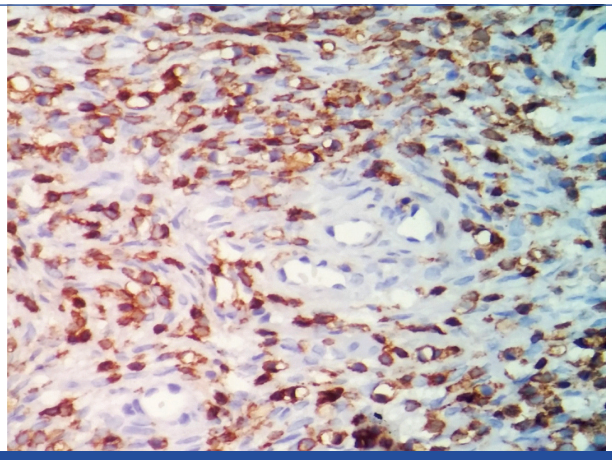


[Table/Fig-2]: Aggregates of lymphocytes and signet ring cells in the stromal nodule (H&E, 400x magnification).

Case No.	Histological diagnosis	PAS-D	Alcian blue	LCA	Pan- CK
1	Nodular hyperplasia	Negative	Negative	Positive	Negative
2	Nodular hyperplasia	Negative	Negative	Positive	Negative
3	Prostatic adenocarcinoma	Negative	Negative	Negative	Positive

[Table/Fig-3]: Histochemical staining and Immunohistochemical (IHC) staining in three cases having signet ring cells.

In all three cases, these cells were negative for PAS-D and Alcian Blue. In immunostains, these cells were positive for LCA in the two cases of nodular hyperplasia, suggesting their lymphoid nature [Table/Fig-4]. However, in the case of prostatic adenocarcinoma, these cells were positive for Pan CK and negative for LCA, indicating a carcinomatous nature.



[Table/Fig-4]: Positive immunoreactions for Leukocyte Common Antigen (LCA, 400x magnification).

DISCUSSION

Signet ring cells, characterised by hyperchromatic, peripherally pushed nuclei and vacuolated cytoplasm, have traditionally been considered a hallmark of signet ring cell adenocarcinoma. The vacuole may have a pale basophilic appearance, as it represents cytoplasmic mucin [1,2]. Prostatic tissue exhibiting signet ring cells raises two possibilities: primary prostatic adenocarcinoma and, rarely, metastatic spread from signet ring cell carcinoma of the colon, rectum, stomach, etc., [6,7]. In primary prostatic adenocarcinoma, the occurrence of signet ring cell changes is estimated to be around 2.5% in adenocarcinoma of the prostate [8]. Additionally, there is a rare variant known as signet ring type prostatic adenocarcinoma [6,8]. The cells may or may not exhibit cytoplasmic mucin, as indicated by staining with PAS and Alcian Blue [6]. These cells are cytokeratin positive and LCA negative. One case from the present study involved prostatic adenocarcinoma with a Gleason score of 4+4=8, which had a few signet ring cells present within the tumour proper. The PSA levels were elevated, and perineural invasion was evident. The cells demonstrated positive cytokeratin staining, while the other stains and the LCA IHC marker were negative, indicating a carcinomatous nature. Metastatic spread from signet ring cell carcinoma originating from other primary sites is another rare possibility. In such cases, appropriate clinical and surgical findings would be expected. The signet ring cells are anticipated to show cytoplasmic PAS/Alcian Blue positive mucin [7].

The present study was initiated after observing an unusual presence of signet ring cells in a case of nodular hyperplasia with normal PSA levels. Consequently, 34 consecutive archived specimens of TURP were reviewed by four pathologists, leading to the identification of three cases that exhibited signet ring cells. One was adenocarcinoma, as mentioned earlier. However, two cases with signet ring cells against a background of nodular hyperplasia was observed. These unusual cells were observed in early stromal nodules, intermingled with chronic inflammatory cells, primarily lymphocytes. The cells showed negative staining with PAS-D and Alcian Blue. Based on a literature search, LCA and cytokeratin immunostaining was performed, which revealed positive staining with LCA, suggesting their lymphoid nature. This finding was also noted by Alguacil-Garcia A [4]. Similarly, Coyne JD and Ahmed K observed exaggerated and florid signet ring cell changes in bladder biopsy cases, noted in both stromal and lymphoid cells [9].

In fact, lymphoid cells are known to exhibit such rare morphological changes. A rare variant of non Hodgkin's lymphoma, referred to as signet ring lymphoma, is recognised, which can be of B-cell or T-cell origin [10]. The nature of the cytoplasmic vacuole or inclusion-like material in lymphoma cells is still under debate, as it may represent IgG or IgM forming Russell-body-like globules.

Thus, in the present study, the frequency of artefactual signet ring cell changes found in TURP specimens of nodular hyperplasia was 6.25% (two out of 32 nodular hyperplasia cases).

What could explain such morphological changes in prostatic lymphoid cells? A literature search revealed very few articles mentioning such changes. The authors considered various possibilities, such as procedure-related trauma, cautery thermal artefact, fixation artefact, etc., [3,4,11]. Alguacil-Garcia A mentions that such changes were not noted in any of the seven open prostatectomy specimens author studied. Therefore, author favoured the degenerative nature of the changes related to the TURP procedure. Tprkov K, on "Benign Mimics of Prostatic Adenocarcinoma," refers to this change in lymphocytes as a result of thermal artefact [12]. Present study also favoured the possibility of thermal effects; however, further studies should be conducted to confirm this.

Another query raised was regarding the location of the cells-why are they seen in early stromal nodules? Wang HL and Humphrey PA also found them only in early stromal nodules. They hypothesised that the cells might be myofibroblasts, as they showed vimentin positivity and weak desmin positivity. However, LCA staining was not performed in their study [3]. These LCA-positive signet ring cells can be mistaken for signet ring carcinoma during routine reporting, as they possess hyperchromatic nuclei, possibly due to their lymphoid nature. However, primary signet ring cell prostatic adenocarcinoma is extremely rare, with only 20 cases reported from the year 2000 to 2020 after an extensive literature search [13].

Limitation(s)

In present study, only 34 consecutive cases received over a period of 32 months were analysed. A more extensive study with a larger sample size and a broader panel of IHC stains would help in estimating the prevalence and nature of the signet ring cells.

CONCLUSION(S)

In TURP specimens, signet ring cell changes should be approached with caution. Therefore, histochemical and IHC markers must be employed to determine whether they represent carcinomatous cells or lymphoid cells. Awareness of this distinction may help in avoiding erroneous labelling of signet ring cells as carcinoma. A greater number of studies with larger sample sizes are needed to ascertain the prevalence of this change.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Jun 14, 2024
- Manual Googling: Aug 12, 2024
- iThenticate Software: Oct 07, 2024 (10%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Jun 13, 2024**
Date of Peer Review: **Aug 10, 2024**
Date of Acceptance: **Oct 08, 2024**
Date of Publishing: **Nov 01, 2024**