

Basal Cell Hyperplasia Observed at Biopsy Specimens after HIFU Therapy: Implication of Stemness for Organ Regeneration

Teiichiro Aoyagi*, Go Nagao, Isao Kuroda

Ibaraki Medical Center, Department of Urology, Tokyo Medical University, Ibaraki, Japan
Email: *aoyagite@tokyo-med.ac.jp

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Abstract

Prostatic basal cell is thought to play a pivotal role in hyperplastic change or carcinogenesis of prostate by their proliferation and stem cell transformation. We investigated stem cell transformation of basal cell hyperplasia observed at biopsy specimens after High Intensity Focused Ultrasound (HIFU) therapy for early stage prostate cancer. **Patients and Methods:** Basal cell hyperplasia was observed at biopsy specimens in two patients after HIFU therapy. Of these patients, one showed cancer recurrence. Specimens were studied with usual HE, and immunohistochemical studies for prostate specific antigen (PSA), stem cell markers such as CD44, CD117 (c-kit), CD133 and Vimentin. **Results:** Both basal cell hyperplasia cases indicated PSA (-), CD44 (++) , CD117 (-), Vimentin (-) and one specimen showed CD133 (++) . Basal cell hyperplasia was presumed to appear during the regeneration process of normal prostate tissue after HIFU therapy, when basal cell proliferated and transformed to acinal cells through epithelial to mesenchymal transition.

Keywords

Prostate, Basal Cell Hyperplasia, HIFU, Epitelial to Mesenchymal Transition

1. Introduction

The prostate consists of three cell types. Basal cells are relatively undifferentiated, androgen-independent cells. Secretory luminal, and glandular cells are differentiated mature cells presenting androgen receptor and prostate specific antigen (PSA). The neuroendocrine cells are androgen-independent cells without presenting PSA [1]. Some basal cells are supposed to act as androgen-independent progenitor stem cells, and play an important role for initiating prostatic hyper-

plasia and/or cancer formation [2]. Stemness refers to the properties that cells have a potential to self-renewal, multi-lineage differentiation and proliferation [3]. Stem cells have two types, embryonic type from early division of fertilized egg, and somatic type from developed tissues and organs. Each organ has somatic type stem cells preparing for repair of tissue injury, usually residing in specialized microenvironment or niches. Basal cell hyperplasia (BCH) is observed in association with a repairing process of tissue damage such as inflammation or injury [4]. Basal cell hyperplasia also has a relation to prostate carcinogenesis [5]. Histopathological findings after high-intensity focused ultrasound (HIFU) therapy mainly composed of coagulation necrosis and granulomatous inflammation. Biermann *et al.* reported that basal cell hyperplasia was observed in 68% of benign prostate after treated by HIFU [6]. Here we report two BCH in biopsy specimens observed after HIFU therapy for early stage prostate cancer, and discuss the meaning of them by immunohistochemical studies.

2. Cases Presentation

Case 1. Sixty five year-old man presenting Gleason 4 + 3 adenocarcinoma on 4 out of 12 biopsy site, initial PSA was 5.87 ng/ml. He had HIFU with short-term Degarelix therapy, that is, adding LH-RH antagonist (Degarelix) twice between HIFU therapy [7], as T1cN0M0 early stage prostate cancer. Nadir PSA was 0.024 ng/ml at 9 months after the therapy, however it suddenly rose 1.653 ng/ml at 12 months. Re-biopsy indicated no cancer relapse from six biopsy specimens, and also showed BCH on one specimen. The patient's PSA gradually decreased spontaneously without any therapy, keeping as low as 0.371 ng/ml after three years.

Case 2. Sixty eight year-old man presenting Gleason 3 + 4 adenocarcinoma on 2 out of 10 biopsy site, initial PSA was 6.09 ng/ml. He underwent HIFU therapy as T1cN0M0 early stage prostate cancer. Nadir PSA after the therapy was 3.45 ng/ml, and re-biopsy after 1 year from HIFU at PSA 6.03 ng/ml, indicated Gleason 4 + 3 adenocarcinoma on 2 out of 6 biopsy site. BCH was observed one of the re-biopsy specimen. The patient underwent second HIFU adding short-term Degarelix this time [7]. After the second HIFU therapy, he showed no relapse with PSA 0.365 ng/ml at 5 years.

3. Immunohistochemical Staining and Results

Cancer and BCH histological specimens of both cases were examined the stemness comparing the normal tissue. Hematoxylin and Eosin (HE), PSA, prostatic stem cell marker [8] such as CD44 (Gene Tex Hsinchu, Taiwan), CD117 (c-kit) (abcam Cambridge, England), Vimentin (Santa cruz Dallas, USA), CD133 (ENOGENE NY, USA) were immunohistochemically stained following previously reported method [7]. Both patients accepted on the study and report by signature and the study was approved the hospital's IRB committee (Institutional Review Board of Tokyo Medical University, Ibaraki Medical Center, approved

2013.6). The stained results were indicated in **Table 1**. Normal gland and cancer tissues showed positive PSA and negative for all stem cell markers (**Figure 1**). Both BCH showed PSA negative (**Figure 2(b), Figure 3(b)**), CD 133 positive in case 1 (**Figure 2(c), Figure 3(c)**), CD117 negative, Vimentin negative, and CD44 strongly positive (**Figure 2(d), Figure 3(d)**). Vimentin was stained only in interstitial cells for normal tissue.

4. Discussion

Only a few reports have observed on the histological findings after HIFU therapy. Especially histological reports after a long period from HIFU are very few [8] [9]. BCH was reported to be seen among the usual findings after HIFU therapy such as vast coagulation necrosis, fibrosis and inflammation [6]. Stem cells are reported to be engaged by bi-directional action according to microenvironment [10]. Vast and strong tissue damage induced by HIFU might activate stem cells residing in environmental niche. Although the exact mechanism of forming

Table 1. Histological findings of biopsy specimens.

case	specimen	H & E	PSA	CD44	CD133	c-kit	vimentin
1, 2	Pre-HIFU	cancer	+	—	—	—	—
		normal	+	—	—	—	Int. cell
1	Post-HIFU	BCH	—	++	++	—	—
2	Post-HIFU	BCH	—	++	—	—	—

Post HIFU specimens were obtained after 1 year of HIFU therapy respectively.

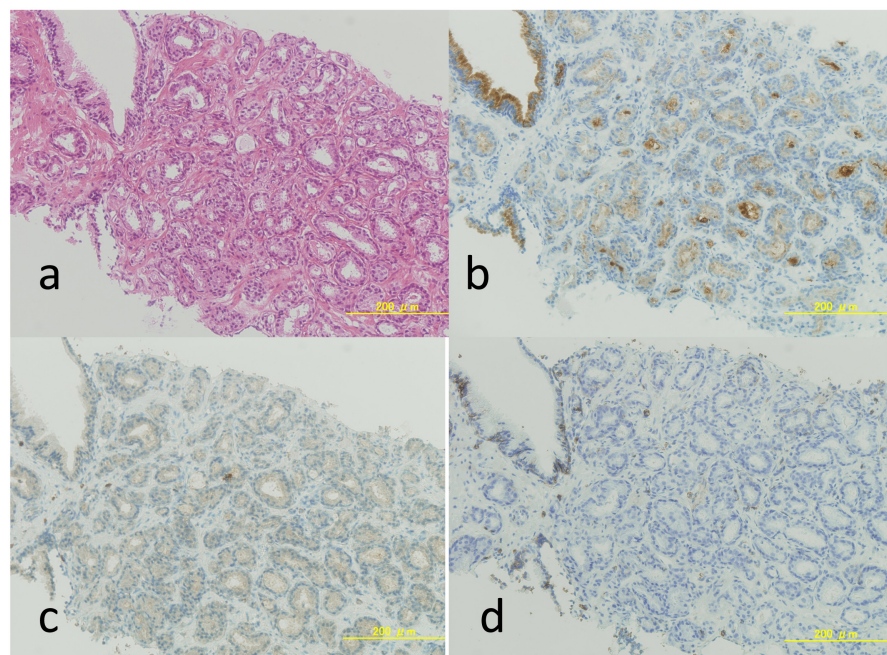


Figure 1. Pre-HIFU biopsy findings of case 1. (a) H & E Gleason 4 + 3 adenocarcinoma, reduced from 40×, (b) PSA weakly positive 40×, (c) CD133 negative 40×, (d) CD44 negative 40×.

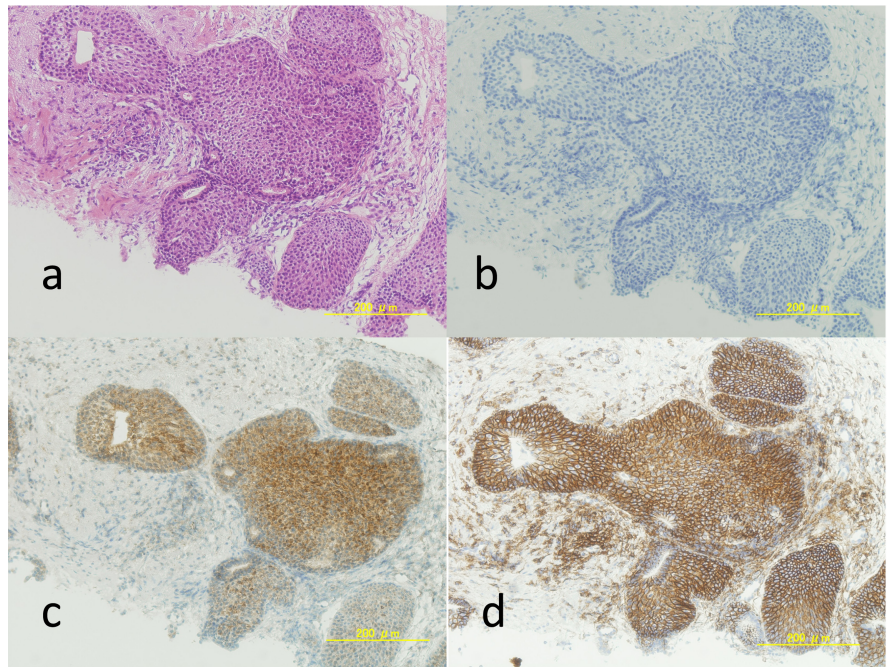


Figure 2. One year, post-HIFU biopsy findings of case 1, (a) H & E Basal cell hyperplasia, reduced from 10×, (b) PSA negative 10×, (c) CD133 positive 10×, (d) CD44 positive 10×.

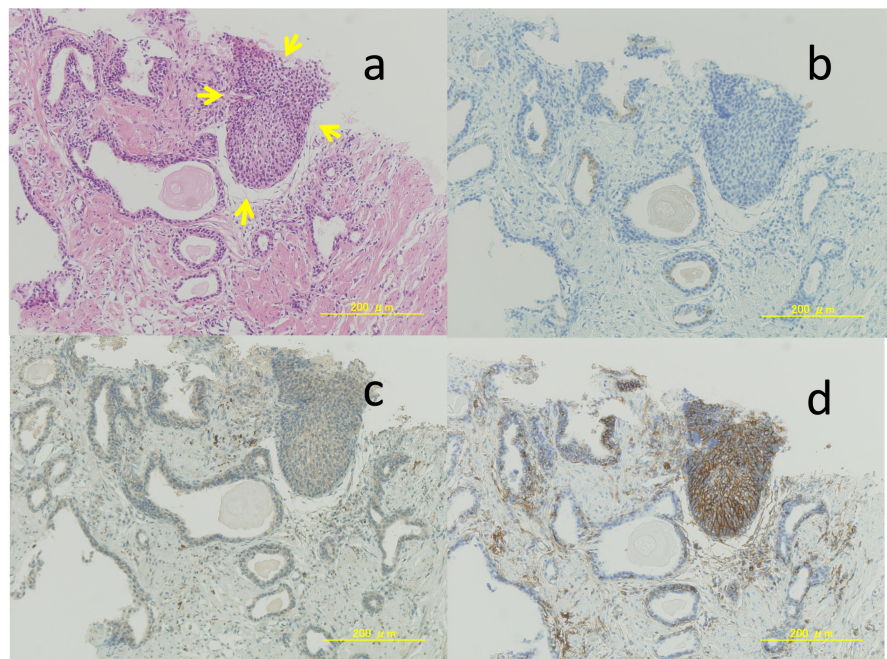


Figure 3. One year, post-HIFU biopsy findings of case 2, (a) H & E basal cell hyperplasia (arrows) 40×, (b) PSA negative 40×, (c) CD133 negative (positive in only small numbers of interstitial cells) 40×, (d) CD44 positive 40×.

BCH was unclear, the proliferation of basal cell differentiated stem cells may trigger the initiation of cancer or hyperplastic formation [11] [12] [13]. The apoptosis of luminal cells is also reported as a trigger of proliferation induced by inflammation or change of hormonal environment [14]. The stemness property

of these basal cells is thought to be very important for tissue regeneration [15].

After HIFU therapy, all prostatic tissues including cancer become necrosis, and consequently change to fibrotic tissue. Small amount of survived basal cells are assumed to be a stem cell for tissue regeneration. It is probable that BCH is grown from one of these proliferated basal cells showing stemness. Usually basal cells produce CD44, and CD44 are reported to play an important role for cells indicating stemness [16]. Various kinds of cells turned to positive for CD44 by epithelial to mesenchymal transition. Prostate cancer cells are reported that expression of CD44 and/or CD133 contributed to acquisition of hormone refractoriness and metastasis [17] [18] [19]. Wei *et al.* reported that expression of CD133 might indicate some proliferation activity in prostatic cells [20]. Interestingly, in our case, one showed strongly positive for CD133, and the others did not. Case 1 BCH might be a new proliferating hyperplasia. BCH is presumed the consequence of stem cell transformation of basal cell, and BCH represents the possibility of development of benign prostatic hyperplasia and/or cancer in the somewhere of background [11] [16].

5. Conclusion

Stem cell transformation of BCH was observed at biopsy specimens after HIFU therapy for two early stage prostate cancer patients. BCH is presumed to represent regeneration of prostatic tissue, and also this “stemness of basal cell” might induce benign hyperplastic change and/or malignant transformation in the future.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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