福岡大医紀（*Med. Bull. Fukuoka Univ.*）：42(2)，223–227，2015

Crystalloids of Prostatic Adenocarcinoma on Prostatectomy

Mikio MIZOGUCHI, Hiroyuki HAYASHI, Kazuki NABESHIMA,
Hiroshi IWASAKI, Morishige TAKESHITA

Department of Pathology, Faculty of Medicine, Fukuoka University

Abstract

Reaching a diagnostic decision based on a prostate biopsy specimen is often a daunting challenge. Some of the factors contributing to the difficulty in diagnosing a prostatic adenocarcinoma with a lower Gleason grade arises from rare structural atypia, low nuclear atypia, and limited atypical fcoi in the specimen. Crystalloids, the red substance seen inside the glandular cavity of prostate cancers, serves as a useful diagnostic clue for prostatic carcinoma in biopsy specimens. It is rectangular or acicular shaped and can be easily identified in hematoxylin and eosin (H&E)-stained specimens. In the present study, we examined 113 cases with total extirpation of prostatic adenocarcinoma. The purpose of the study was twofold: (1) to assess the frequencies of prostatic crystalloids and (2) to identify whether crystalloid deposition occurs in glands other than the carcinomatous glands. Crystalloids in the glands of adenocarcinoma were detected in 78 (69.0%) out of 113 cases. We observed crystalloid structure without prostatic adenocarcinoma in 4 out of 113 cases with high-grade PIN (3.5%) and 3 out of 113 cases in benign glands (2.7%). Glands not affected by prostatic cancer with crystalloids were all located adjacent to the prostatic carcinoma. Even when small atypical foci are detected, glands with crystalloids are highly likely to be confirmed as being affected by prostatic carcinoma. Furthermore, prostatic carcinoma should be suspected in surrounding regions when crystalloids are observed in high grade PIN or benign glands.

Key words: Prostatic adenocarcinoma, Crystalloids, P63, 34βE12, P504s

Introduction

It is often difficult to discriminate between malignant and benign prostate biopsies, making diagnosis challenging. Small atypical foci often confused with prostatic carcinoma include adenosis, partial atrophy, postatrophic hyperplasia, benign crowded glands, cribrifom hyperplasia, and basal cell hyperplasia [1]. In well differentiated prostatic adenocarcinoma, structural atypia is rare, and nuclear atypia tends to be low. Basal cells are absent in prostatic adenocarcinoma. However, even benign glands cannot often recognize basal cells by H&E staining.

In contrast, crystalloids are far easier to identify. This intraluminal substance of prostatic adenocarcinoma is bright red with H&E staining, meaning that it is detectable in low-power microscopic fields [2-4]. Even when atypical foci are small, the existence of crystalloids induces a strong suspicion of adenocarcinoma. The purpose of the present study was to examine total prostatectomy specimens of prostatic carcinoma to assess the frequency of crystalloids appearance and determine whether crystalloids manifest in glands other than those affected by carcinoma.

Materials and Methods

We assessed 113 total extirpation specimens of prostatic carcinoma resected at Fukuoka University Hospital between January 2006 and December 2012. Formalin-fixed total prostatectomy specimens were consecutively cut into ~4-mm serial sections. Then, specimens used for H&E staining were paraffin-embedded and sliced into 3-μm sections. The existence of crystalloids, patient age, prostate-specific antigen (PSA) level, and Gleason score from H&E

Correspondence to: Mikio Mizoguchi M.D., PhD. Department of Pathology, Faculty of Medicine, Fukuoka University. 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan
Phone : +81-92-801-1011 (ext.3275,3276, PHS 6826); Fax : +81-92-861-7300 E-mail : mizogu-m@fukuoka-u.ac.jp

specimens were recorded. When microscopically observing specimens, we first employed a low-power objective and switched to a high-power objective once we found red staining indicating crystalloids intraluminal substance. This strategy was employed to differentiate crystalloid from other substances such as corpora amylacea or pink secretions. A case was identified as "crystalloids+" even when it was found in a few glands. When crystalloids were found in glands other than those with prostatic carcinoma, we performed immnuohistochemical triple staining with an anti-p63monoclonal antibody, anti-34βE12 monoclonal antibody, and anti-α-methylacyl CoA recemase (anti-p504s) polyclonal antibody (all from Dako, Glostrup, Denmark). Basal cell markers such as p63 and 34βE12 showed brown reactivity while p504s (which is expressed in carcinoma or high-grade PIN) stained red.

Results

Crystalloids in the glands of adenocarcinoma were detected in 78 (69.0%) of the 113 total prostatectmy specimens (Fig. 1). The mean patient age with crystalloids was 65.2 years (range, 52-74 years). A median PSA level in cases with crystalloids was 6.99 (range, 4.05 - 37.00). The average Gleason scores for cases with and without crystalloids were 7.21 and 7.77, respectively. When crystalloids are found in high grade PIN and benign glands by H&E staining, those lesions were identified as noncarcinomous through immunohistochemical triple staining of p63, 34βE12, and p504s. We detected some cristalloids in cases other than cancer including 4 of 113 cases of high-grade PIN (3.5%) and 3 of 113 cases of benign glands (2.7%) (Fig. 2).

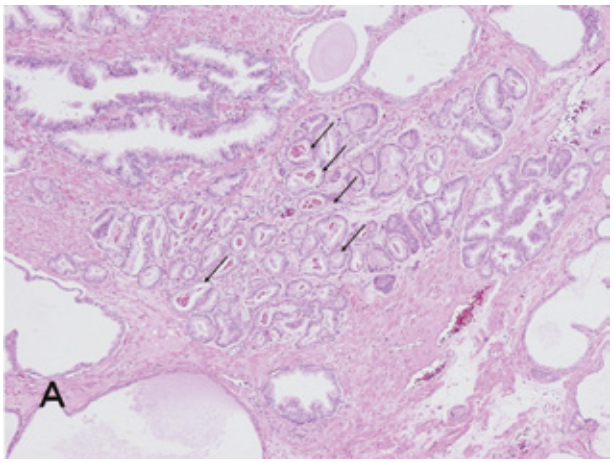

Fig. 1 (A) Crystalloids (arrow) are found in the simple gland structures of the prostatic adenocarcinoma (x40).

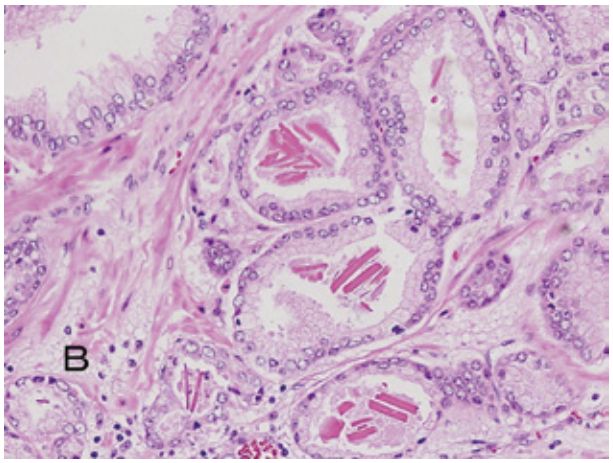

Fig. 1 (B) Crystalloids show needle-shaped structures (x200).

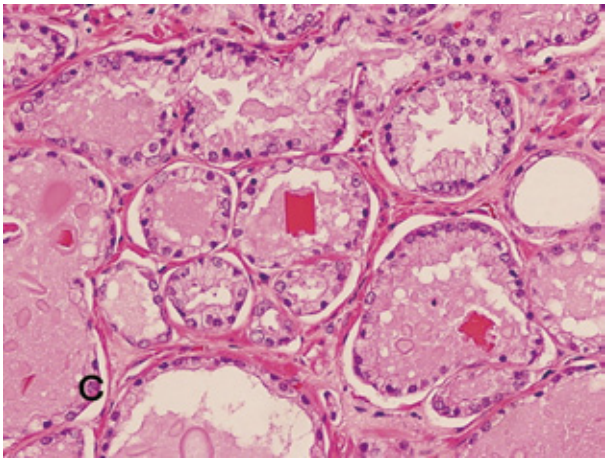

Fig. 1 (C) Crystalloids show bright red color and rectangular or cubic structures (x200).

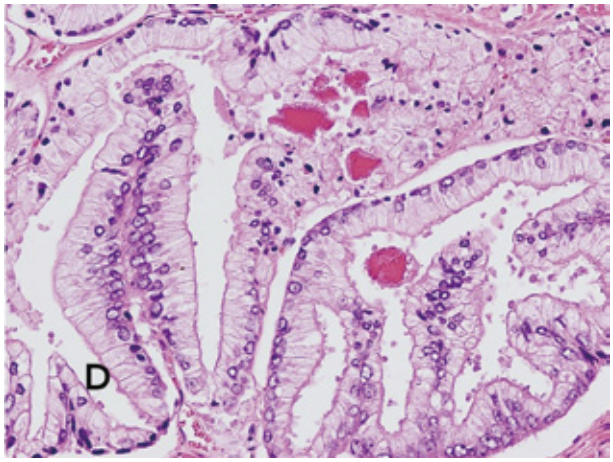

Fig. 1 (D) Crystalloids in the pseudohyperplastic variant of the prostatic adenocarcinoma (x200).

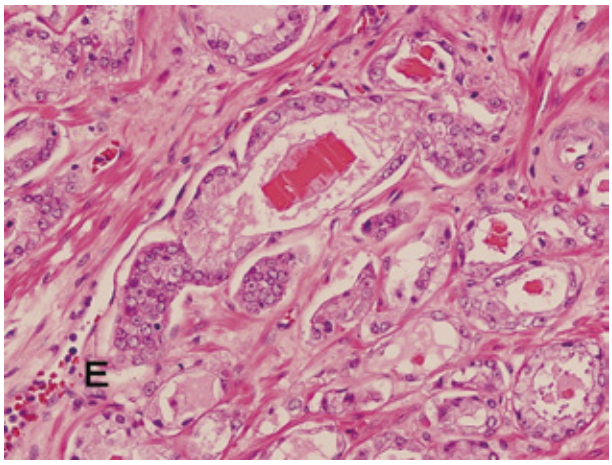

Fig. 1 （E）Crystalloids in the fused glands structures of the prostatic adenocarcinoma（x200）.

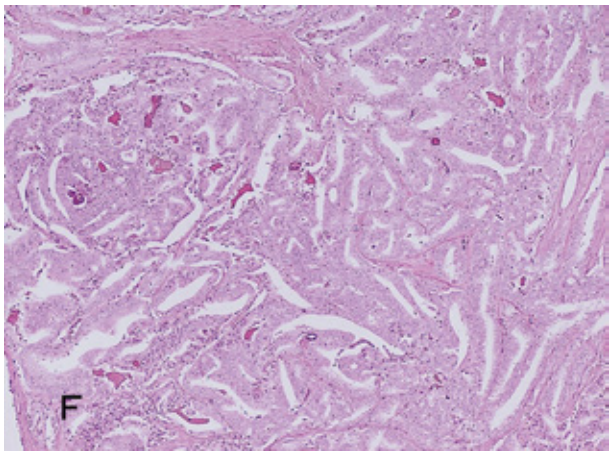

Fig. 1 （F）Crystalloids in the large cribriform structures of the prostatic adenocarcinoma（x40）.

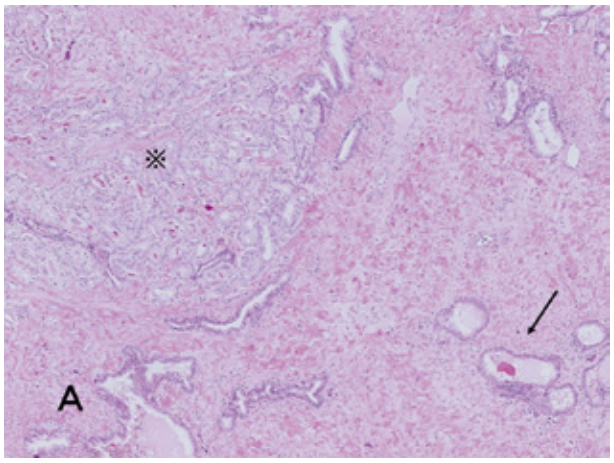

Fig. 2 （A）A benign gland contains crystalloids in the lumen（arrow）. Simple glands of the prostatic adenocarcinoma are found near（※）（x40）.

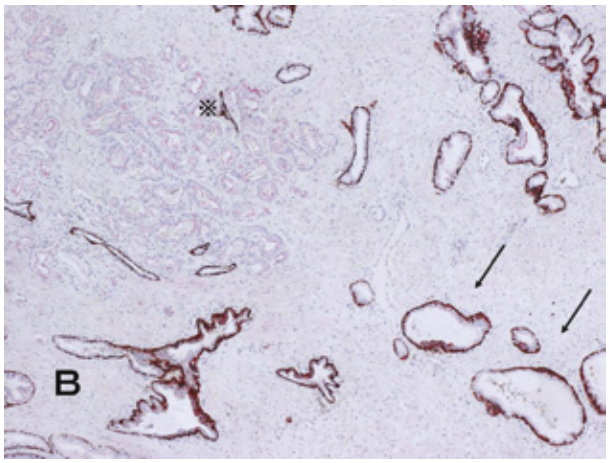

Fig. 2 （B）Immunohistochemical triple stain（p63, 34βE12, p504s）. Benign glands（arrow）are positive for basal cell markers（brown）and negative for p504s. The prostatic adenocarcinoma（※）is negative for basal cell markers and positive for p504s（red）（x40）.

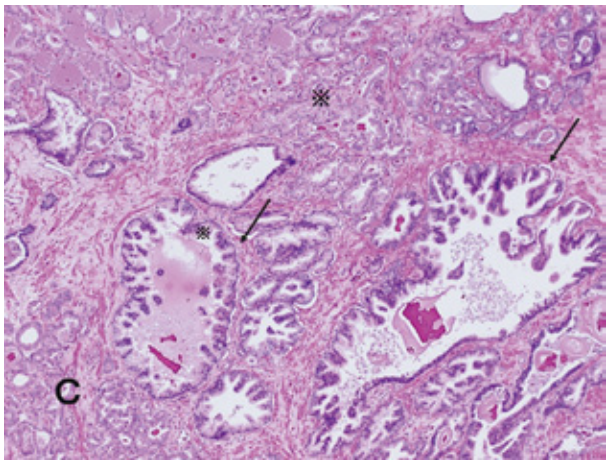

Fig. 2 （C）A few high-grade PINs（arrow）contain crystalloids in the lumen（arrow）. Small glands of the prostatic adenocarcinoma（※）are found near（x40）.

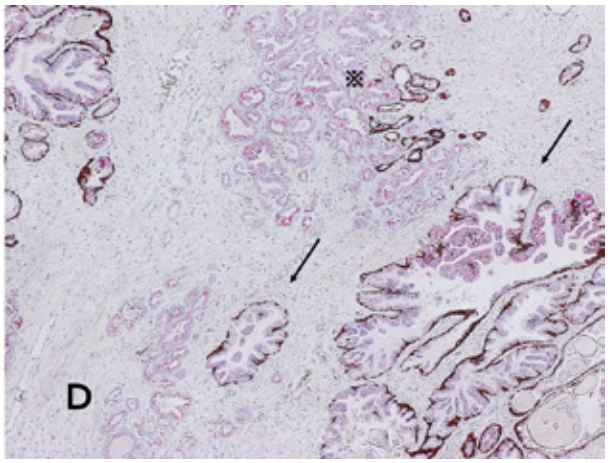

Fig. 2 （D）Immunohistochemical triple stain（p63, 34βE12, p504s）. High-grade PINs（arrow）are positive for basal cell markers（brown）and focal positive for p504s（red）.
The prostatic adenocarcinoma（※）is negative for basal cell markers and positive for p504s（red）（x40）.

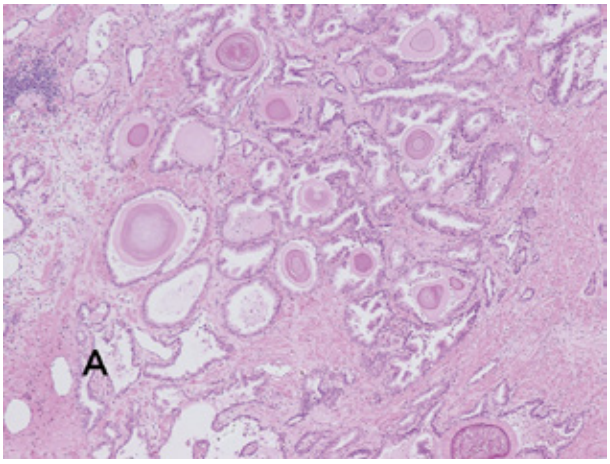

Fig. 3 (A) Small to large corpora amylacea are found in the benign glands (x40).

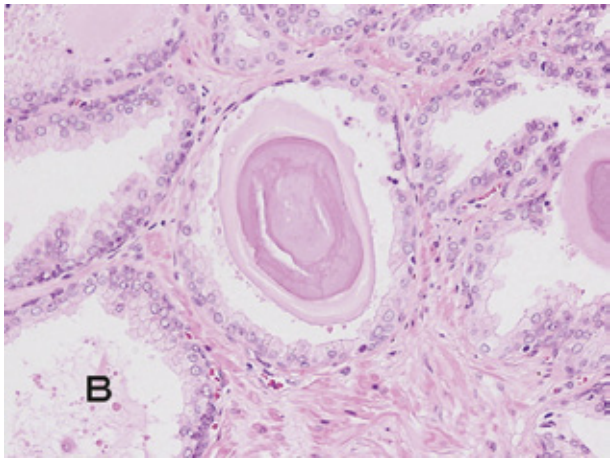

Fig. 3 (B) Corpora amylacea show pink or light purple color and circular structures (x100).

Discussion

Prostatic biopsy cases of prostatic adenocarcinoma that are challenging to diagnose include those with minimal atypical foci and well differentiated prostatic adenocarcinoma characterized by little structural atypia and low nuclear atypia. Differentiating malignant from benign lesions such as adenosis [5, 6], partial atrophy [7], postatrophic hyperplasia [8], benign crowded glands [1], and cribriform hyperplasia [9] is often difficult in these cases. The diagnostic criteria for prostatic adenocarcinoma developed by Humphrey [10] considers architectural structure, absence of a double cell layer, nuclear atypia, mitosis, intraluminal substance, and proximity to high-grade PIN. Still, identifying basal cells in H&E specimens with little structural atypia and low nuclear atypia is challenging.

Crystalloids, the substance usually seen within prostatic adenocarcinoma glands [2] are considered to have high specificity for prostatic carcinoma. The reported percentages of cases with crystalloids are as follows: total prostatectomy, 65.6% [3] biopsies, 10% to 41% [4, 11, 12] and the present study, 69.0%. Crystalloids are uniform substance that exist inside glands with a rectangular or acicular shape that is bright red in H&E-stained histology sections. This crystalloid substance is composed of sulfur, calcium, sodium, and phosphorus; it is speculated to be derived from prostate cancer cells with metabolic abnormalities [13].

Corpora amylacea is an intraduct substance similar to crystalloids. It is a layered or spherical structure observed in normal glands, and the principle component is sulfated glycosaminoglycan. Corpora amylacea appears as pale red or pale purple spheres in H&E-stained specimens, and its presence is seldom reported in prostatic carcinoma [14]. While crystalloids are bright red and angularly shaped, corpora amylacea is smoothly spherical. Thus, discriminating between crystalloid and corpora amylacea is comparably easy (Fig. 3). When crystalloids are identified in cases other than prostatic adenocarcinoma, triple staining for the basal cell makers 34βE12 and p63 [15, 16] and the prostate carcinoma marker p504s [17, 18] was conducted to confirm the absence of carcinoma. Besides prostatic adenocarcinoma, crystalloids were detected in four high-grade PIN cases (3.5%) [19, 20] and three benign gland cases (2.7%). Notably, all were adjacent to glands affected by prostatic adenocarcinoma. The frequency of crystalloids in glands not affected by carcinoma is low; only 1% to 5% of benign glands contain crystalloids [11, 21]. The crystalloids have an angular shape and bright red color that make it easy to identify in H&E-stained specimens. Cases with minimal atypical foci that may be misidentified as benign are likely to be confirmed as adenocarcinoma when crystalloids are present. Furthermore, when crystalloids are noted in high-grade PIN or a benign gland, a follow-up or re-examination is recommended because the likelihood of adenocarcinoma in the surrounding region is high.

References

1) Herawi M, Parwani A, Irie J, Epstein J: Small glandular proliferations on needle biopsies: Most common benign mimickers of prostatic adenocarcinoma sent in for expert second opinion. Am. J. Surg. Pathol. 29(7): 874-880, 2005.

2) Elizabeth J H: Crystalloids of prostatic carcinoma. Cancer 39: 2073-2080, 1977.

3）Ro JY, Gringnon DJ, Troncoso P, Ayala AG: Intraluminal crystalloids in whole-organ sections of prostate. The Prostate13: 233-239, 1988.
4）Epstein JI: Diagnosis criteria of limited adenocarcinoma of the prostate on needle biopsy. Hum Pathol. 26: 223-229, 1995.
5）Gaudin PB, Epstein JI: Adenosis of the prostate histologic features in transurethral resection specimens. Am. J. Surg. Pathol. 18(9): 863-870, 1994.
6）Tamara LL, Jonathan IE: Diffuse adenosis of the peripheral zone in prostate needle biopsy and prostatectomy specimens. Am. J. Surg. Pathol. 32(9): 1360-1366, 2008.
7）Przybycin CG, Kunju LP, Wu AJ, Shah RB: Partial atrophy in prostate needle biopsies: A detailed analysis of its morphology, immunophenotype and cellular kinetics. Am. J. Surg. Pathol. 32(1): 58-64, 2008.
8）Amin MB, Tamboli P, Varma M, Sringley JR: Postatrophic hyperplasia of the prostate gland: a detailed analysis of its morphology in needle biopsy specimens. Am. J. Surg. Pathol. 23(8): 925-931, 1999.
9）Brooks JJ, Livolsi VA, Tomaszewski JE, Scott H: Cribriform hyperplasia of prostate. Am. J Surg Pathol. 11(6): 488-489, 1987.
10) Humphrey PA: Diagnosis of adenocarcinoma in prostate needle biopsy tissue. J Clin Pathol. 60(1): 35-42, 2007.
11) Varma M, Lee MW, Tamboli P, Zarbo RJ, Jimenez RE, Salles PGO, Amin MB: Morphologic criteria for diagnosis of prostatic adenocarcinoma in needle biopsy specimens. Arch Pathol Lab Med. 126: 554-561, 2002.
12) Svatek RS, Karam JA, Rogers TE, Shulman MJ, Margulis V, Benaim EA: Intraluminal crystalloids are highly associated with prostatic adenocarcinoma on concurrent biopsy specimens. Prostate Cancer and prostatic Diagnosis 10: 279-282, 2007.
13) Shah RB, Lee MW, Giraldo AA, Amin MB: Histologic and histochemical characterization of seminal vesicle intraluminal secretions. Arch Pathol Lab Med 125(1): 141-145, 2001.
14) Christian JD, Lamm TC, Morrow JF, Bostwick DG: Corpora amylacea in adenocarcinoma of the prostate: incidence and histology within needle core biopsies. Modern Pathology 18: 36-39, 2005.
15) Shah RB, Zhou M, LeBlanc M, Snyder M, Rubin MA: Comparison of basal cell-specific makers, 34βE12 and p63, in the diagnosis of prostate cancer. Am. J. Surg. Pathol. 26(9): 1162-1168, 2002.
16) Zhou M, Shah R, Shen R, Rubin MA: Basal cell cocktail (34βE12 + p63) improves the detection of prostate basal cells. Am. J. Surg. Pathol. 27(3): 365-371, 2003.
17) Jiang Z, Wu CL, Wonda BA, Dresser K, Xu J, Fanger GR, Yang XJ: P504s/α-methylacyl-CoA racemase: A useful marker for diagnosis of small foci of prostatic carcinoma on needle biopsy. Am. J. Surg. Pathol. 26(9): 1169-1174, 2002.
18) Jiang Z, Woda BA, Rock KL, et al. P504S: a new molecular marker for the detection of prostate carcinoma. Am. J. Surg. Pathol. 25(11): 1397-1404, 2001.
19) McNeal JE, Bostwick DG: Intraductaldysplasia: A premalignant lesion of the prostate. Hum. Pathol. 17(1): 64-71, 1986.
20) Al-Hussain TO, Epstein JI: Initial high-grade prostatic intraepithelial neoplasia with carcinoma on subsequent prostate needle biopsy: finding at radical prostatectomy. Am. J. Surg. Pathol. 35(8): 1165-1167, 2011.
21) Henneberry JM, Kahane H, Humphrey PA, Keetch DW, Epstein JI: The significance of intraluminal crystalloids in benign prostatic glands on needle biopsy. Am. J. Surg. Pathol. 21(6): 725-728, 1997.

（平成 27. 4. 10 受付，平成 27. 5. 20 受理）
「The authors declare no conflict of interest.」