Periacinar retraction clefting in proliferative prostatic atrophy and prostatic adenocarcinoma

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Aims: To evaluate the presence and extent of periacinar retraction clefting in proliferative prostatic atrophy and carcinoma in radical prostatectomy specimens.

Methods: Atrophic foci and neoplastic glands were analysed in specimens from 50 patients who underwent radical prostatectomy. Analysed atrophic glands were classified in two main groups, proliferative atrophy (PA) and proliferative inflammatory atrophy (PIA); each group was subclassified into simple atrophy (SA) and postatrophic hyperplasia (PAH). According to the presence and extent of periacinar retraction clefting, atrophic and neoplastic glands were classified as: group 1, glands without clefts or with clefts affecting $\leq 50\%$ of gland circumference; group 2, glands with clefts that affected $>50\%$ of the circumference in $<50\%$ of examined glands; and group 3, glands with clefts that affected $>50\%$ of the circumference in $\geq 50\%$ of examined glands.

Results: Forty-four (88.0%) atrophic foci were without periacinar clefts or clefts were present in less than half of the gland circumference (group 1). In 6 (12.0%), atrophic foci clefts affected $>50\%$ of gland circumference (groups 2 and 3). Forty-five (90.0%) carcinomas were with clefts which affected more than 50% of gland circumference (groups 2 and 3); and in five carcinomas only, clefts were not found or affected $<50\%$ of gland circumference (group 1).

Conclusion: Results indicate that periacinar retraction clefting represents a reliable criterion in differential diagnosis between proliferative atrophy and carcinoma.

Prostatic adenocarcinoma continues to be the most common visceral malignant tumour and a source of considerable morbidity and mortality for men worldwide. According to autopsy studies it affects more than 30% of males older than 50 years.¹ The diagnosis of prostatic adenocarcinoma can be very complex, especially in needle core biopsies. There are many different benign conditions that may mimic prostatic carcinoma, such as partial and/or complete atrophy, adenosis and many others.^{1–5}

According to recent studies, one of the most common mimickers is postatrophic hyperplasia (PAH).^{2–3} PAH is characterised by hyperplastic glands intermingled with atrophic ones lined with cells with scanty cytoplasm. The degree of nuclear atypia is less than in most carcinomas. The slit-like acini and apical blebs of some cases of PAH are very rare in most carcinomas.^{1–3 5–7} The dense fibrotic stroma and shrunken muscle cells that may be seen in PAH are quite uncommon in carcinoma. An obvious infiltrative growth pattern is not seen in PAH and lobulation, which is usually present, is a helpful architectural feature.^{1–3 7} Adjacent typical atrophy may be a clue to the diagnosis. The basal cell layer is typically present, although it may be difficult to demonstrate it, in some cases even by immunostaining using high molecular weight cytokeratin or p63.^{1 8}

Numerous features that might help in the differential diagnosis between atrophy and carcinoma are described.^{1–3} The presence of retraction clefting around neoplastic glands is an additional criterion favouring prostatic adenocarcinoma. According to our knowledge and data from the literature, it is not routinely applied to distinguish atrophy from carcinoma.^{9–11}

In this study, we analysed the presence and extension of retraction clefts in proliferative prostatic atrophy and carcinoma in radical prostatectomy specimens.

MATERIALS AND METHODS

Atrophic foci and neoplastic glands were analysed in specimens from 50 patients (aged 42–79 years, median age 60.4) who underwent radical prostatectomy in the period 1998–2005. For each case, we analysed 8–30 slides. Specimens were taken from the archive at the Institute of Pathology, Medical University, Innsbruck and from Ljudevit Jurak Department of Pathology, Sestre milosrdnice University Hospital, Zagreb. At the time of diagnosis all patients were without lymph node metastasis or distant metastatic spreading.

Specimens were fixed in 10% buffered formaldehyde, embedded in paraffin, cut at 5 μm and routinely stained with H&E.

Cancers were graded using the Gleason grading system. Foci of atrophic glands were classified in two main groups, proliferative atrophy (PA) and proliferative inflammatory atrophy (PIA); each group was subclassified into simple atrophy (SA) and postatrophic hyperplasia (PAH), as proposed by the working group for histological classification of focal prostate atrophy lesions.⁷

Atrophic and neoplastic glands were analysed on high power field (400 $\times$); clefting was determined according to recently described criteria.^{8 9} Briefly, depending on the presence and extent of periacinar retraction clefts, atrophic and neoplastic glands were classified as: group 1, glands without clefts or with clefts affecting $\leq 50\%$ of gland circumference; group 2, glands with clefts that affected $>50\%$ of the circumference in $<50\%$ of examined glands; and group 3, glands with clefts that affected $>50\%$ of the circumference in $\geq 50\%$ of examined glands.

Abbreviations: PA, proliferative atrophy; PAH, postatrophic hyperplasia; PIA, proliferative inflammatory atrophy; SA, simple atrophy

Figure 1 (A) Atrophic glands were mostly without periacinar clefting or clefting was present in less than half of the gland circumference. (B) In six atrophic foci, clefts affected >50% of gland circumference. (C) Neoplastic glands were with clefts, which affected >50% of gland circumference. (D) In five carcinomas, clefts were not found or affected less than 50% of gland circumference. H&E, 400 $\times$.

We examined cleft extension in 10 neoplastic glands in three randomly selected different high-power fields in an area that was previously chosen under low magnification. Analysed atrophic glands were previously systematically examined for genetic alterations on chromosome 8.¹²

Statistical analysis was performed using the χ^2 test and test of proportions. The level of significance was set at $p < 0.05$.

RESULTS

Eighteen tumours (36.0%) were well differentiated (Gleason score 5 and 6), 23 (46.0%) were moderately differentiated (Gleason score 7) and 9 (18.0%) were poorly differentiated (Gleason score 8 and 9). The most common Gleason pattern was 3 (that is, in 45 (90.0%) tumours at least one Gleason pattern was 3). Gleason pattern 2 was found in seven (14.0%) cases; in three cases (6.0%) both Gleason patterns were 4; and in six cases (12.0%) one Gleason pattern was 5.

Thirty-four tumours (68.0%) were confined to the prostate and 16 (32.0%) were spread through the prostatic capsule.

Atrophic glands were mostly without periacinar clefting or clefting was present in less than half of gland circumference (group 1; fig 1A). In six (12.0%) atrophic foci, clefts affected >50% of gland circumference (groups 2 and 3; fig 1B). Forty-five (90.0%) carcinomas were with clefts which affected >50%

of gland circumference (groups 2 and 3; fig 1C). In only five carcinomas, clefts were not found or affected <50% of gland circumference (group 1; fig 1D, table 1). Periacinar retraction clefting was clearly visible around neoplastic glands but not around atrophic glands that were present in the same area (fig 2A,B).

Statistical analysis revealed a significant difference between the frequency and extension of retraction clefts in atrophic foci and prostatic carcinoma ($p = 0.00$).

Proliferative inflammatory atrophy (PIA) was more frequent compared to proliferative atrophy (PA). Thirty-eight (76.0%) of all atrophic foci were PIA. Most PA and PIA glands were without clefts, or clefts affected less than half of gland circumference (group 1). In only 2 (16.7%) PA foci and 4 (10.5%) PIA foci did clefts affect more than 50% of gland circumference (groups 2 and 3, table 1).

Statistical analysis showed no significant difference in the presence and extent of retraction clefts between PA and PIA ($p = 0.95$). Prostatic carcinoma showed a statistically significant difference in the frequency and extent of retraction clefts, as compared to PA and PIA ($p = 0.00$).

PAH was the more frequent type in PIA and simple atrophy (SA) was the more frequent pattern in PA. Of 38 PIA foci, 22 (57.9%) were PAH; and of 12 PA foci, 11 (91.7%) were SA. Most

Figure 2 Periacinar retraction clefting is clearly visible around neoplastic glands but not around atrophic glands that are present in the same area. H&E, 200 $\times$ (A), 400 $\times$ (B).

Table 1 Retraction clefts in prostatic atrophy, proliferative atrophy (PA), proliferative inflammatory atrophy (PIA), simple atrophy (SA), postatrophic hyperplasia (PAH) and prostatic carcinoma

	Atrophy (%)	PA (%)	PIA (%)	SA (%)	PAH (%)	Carcinoma (%)
Group 1	44 (88.0)	10 (83.3)	34 (89.5)	22 (81.5)	22 (95.7)	5 (10.0)
Group 2	3 (6.0)	0 (0)	3 (7.9)	2 (7.4)	1 (4.3)	26 (52.0)
Group 3	3 (6.0)	2 (16.7)	1 (2.6)	3 (11.1)	0 (0)	19 (38.0)
Total	50 (100)	12 (100)	38 (100)	27 (100)	23 (100)	50 (100)

Group 1: glands without clefts or with clefts $\leq 50\%$ of gland circumference.

Group 2: glands with clefts that affected $>50\%$ of the gland circumference in $<50\%$ of glands.

Group 3: glands with clefts that affected $>50\%$ of the circumference in $\geq 50\%$ glands.

SA and PAH glands were without clefts, or clefts affected less than half of the gland circumference (group 1). In only 5 (18.5%) SA foci and 1 (4.3%) PAH foci did clefts affect more than 50% of gland circumference (groups 2 and 3, table 1).

Statistical analysis revealed no significant difference in the appearance of retraction clefts between SA and PAH ($p = 0.27$), while prostatic carcinoma showed significant differences in frequency and extent of retraction clefts, as compared to SA and PAH ($p = 0.00$).

DISCUSSION

One of the problems in the diagnosis of prostatic adenocarcinoma, especially in small foci of neoplastic glands and in needle core biopsies, could be numerous mimickers, particularly foci of PIA including PAH. Postatrophic hyperplasia is best known to the surgical pathologists as a mimic of prostatic adenocarcinoma^{2 5 13 14} because of its overlapping architectural and nuclear features, especially when these lesions are predominantly composed of small-crowded glands with nuclear enlargement and prominent nucleoli. It can be easily misdiagnosed as carcinoma.^{14 15}

A working group for histological classification of prostate atrophy lesions proposed a classification of focal prostatic epithelial atrophy into four subtypes: simple atrophy (SA), simple atrophy with cyst formation, postatrophic hyperplasia (PAH), and partial atrophy. Mixed lesions may be classified by the dominant pattern with mention of the secondary pattern.⁷ SA and PAH contain an increased proliferative fraction compared with normal epithelium and it is proposed to consider it proliferative atrophy (PA). Focal atrophy lesions that contain an increase in inflammation compared to glands found in normal surrounding tissue were classified as proliferative inflammatory atrophy (PIA).⁷

Some authors have suggested a relationship between PIA and prostatic carcinoma and proposed that PIA may represent a precursor lesion to prostatic intraepithelial neoplasia and prostatic carcinoma.^{12 16–18}

One of the proposed additional criteria in diagnosis of prostatic carcinoma is the presence of retraction clefting.^{4 9–11 19 20} Clefts were first described in neoplastic glands in prostate by Halpert *et al* in an autopsy study.²¹ Varma *et al*¹¹ and Krušlin *et al*^{9 10} suggested that clefting, if present, might favour the diagnosis of carcinoma along with other well known features, especially when prominent and appearing in half or more glands. Young *et al*¹ mentioned the association of adenocarcinoma Gleason pattern 3 with prominent periacinar clefts and suggested that this phenomenon is probably an artefact. Conversely, Tomas *et al*.^{22 23} attributed periacinar clefting to the lack of basal cells and changes in stroma that are present in prostatic adenocarcinoma, and did not consider the clefts as a simple artefact. It was also shown that the stromal reaction in prostatic carcinoma, as well as in retraction clefts, is more pronounced in Gleason pattern 3.^{23 24}

PAH may be distinguished from carcinoma, especially from low grade adenocarcinoma, by its characteristic lobular

Take-home messages

- Periacinar clefting is statistically more common in prostatic carcinoma compared to proliferative atrophy and proliferative inflammatory atrophy; thus periacinar retraction clefting might be used as a reliable criterion in the differential diagnosis between prostatic carcinoma and proliferative atrophy.
- Results also suggested that periacinar clefting is probably not simply due to some technical artefact but represents a consequence of reaction between neoplastic cells and surrounding stroma.

architecture, intact or fragmented basal cell layer, conspicuous or slightly enlarged nucleoli, and adjacent acinar atrophy with stromal fibrosis and/or smooth muscle atrophy.^{2 5 8 11 25} Nucleolar changes may also be useful in differentiating PAH and carcinoma. However, some cases of low grade adenocarcinoma have only focally large nucleoli. On the contrary, slightly enlarged nucleoli may be visible in PAH, but only focally; the majority of cases have micronucleoli and diagnosis can be very difficult.^{7 26}

In the current study we confirmed that periacinar retraction clefting, especially when present in more than 50% of gland circumference, almost exclusively appears in neoplastic glands. Clefting in more than 50% of gland circumference was present in 90% of examined carcinomas. In atrophic glands clefts were present only rarely and if so, they affected less than half of gland circumference. Clefting in more than 50% of gland circumference was present in only 12% of examined atrophic foci. There was no significant difference in extent of periacinar retraction clefting in PA compared to PIA and in SA compared to PAH.

The present results also suggest that periacinar clefting is probably not caused by a technical procedure and represent a consequence of reaction between neoplastic cells and surrounding stroma. Thus, periacinar retraction clefting might be used as a reliable criterion in the differential diagnosis between proliferative atrophy and prostatic carcinoma.

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REFERENCES

- 1 Young RH, Srigley JR, Amin MB, *et al.* Tumors of the prostate gland, seminal vesicles, male urethra, and penis. Washington, DC: AFIP, 1998:111–99.
- 2 Herawi M, Parwani AV, Irie J, *et al.* Small glandular proliferations on needle biopsies. Most common benign mimickers of prostatic adenocarcinoma sent in for expert second opinion. *Am J Surg Pathol* 2005;**29**:874–80.
- 3 Srigley JR. Benign mimickers of prostatic adenocarcinoma. *Mod Pathol* 2004;**17**:328–48.
- 4 Totten RS, Heinemann NW, Hudson PB *et al.* Microscopic differential diagnosis of latent carcinoma of the prostate. *Arch Pathol Lab Med* 1953;**55**:131–41.
- 5 Aus G, Abbou CC, Bolla M, *et al.* EAU guidelines on prostate cancer. *Eur Urol* 2005;**48**:546–51.
- 6 Chewille JC, Bostwick DG. Postatrophic hyperplasia of the prostate. A histologic mimic of prostatic adenocarcinoma. *Am J Surg Pathol* 1995;**19**:1068–75.
- 7 De Marzo AM, Platz EA, Epstein JI, *et al.* A working group classification of focal prostate atrophy lesions. *Am J Surg Pathol* 2006;**30**:1281–91.
- 8 Iczkowski KA. Current prostate biopsy interpretation. Criteria for cancer, atypical small acinar proliferation, high-grade prostatic intraepithelial neoplasia, and use of immunostains. *Arch Pathol Lab Med* 2006;**130**:835–43.
- 9 Krušlin B, Tomas D, Rogatsch H, *et al.* Periacinar retraction clefting in the prostatic needle core biopsies: an important diagnostic criterion or a simple artifact? *Virchows Arch* 2003;**443**:524–7.
- 10 Krušlin B, Tomas D, Rogatsch H, *et al.* Correlation of periacinar retraction clefting in needle core biopsies and corresponding prostatectomy specimens of patients with prostatic adenocarcinoma. *Int J Surg Pathol* 2005;**13**:67–72.
- 11 Varma M, Lee MW, Tamboli P, *et al.* Morphologic criteria for the diagnosis of prostatic adenocarcinoma in needle biopsy specimens. A study of 250 consecutive cases in a routine surgical pathology practice. *Arch Pathol Lab Med* 2002;**126**:554–61.
- 12 Yirdiz-Sezer S, Verdorfer I, Schafer G, *et al.* Assessment of aberrations on chromosome 8 in prostatic atrophy. *BJU Int* 2006;**98**:184–8.
- 13 Billis A. Prostatic atrophy: an autopsy study of a histologic mimic of adenocarcinoma. *Mod Pathol* 1998;**11**:47–54.
- 14 Platz EA, De Marzo AM. Epidemiology of inflammation and prostate cancer. *J Urol* 2004;**171**:36–40.
- 15 Shah R, Mucci NR, Amin A, *et al.* Postatrophic hyperplasia of the prostate gland: neoplastic precursor or innocent bystander? *Am J Pathol* 2001;**158**:1767–73.
- 16 De Marzo AM, Marchi VL, Epstein JI, *et al.* Proliferative inflammatory atrophy of the prostate. Implications for prostatic carcinogenesis. *Am J Pathol* 1999;**155**:1985–92.
- 17 Putzi MJ, De Marzo AM. Morphologic transitions between proliferative inflammatory atrophy and high-grade prostatic intraepithelial neoplasia. *Urology* 2000;**56**:828–32.
- 18 Tomas D, Krušlin B, Rogatsch H, *et al.* Different types of atrophy in the prostate with and without adenocarcinoma. *Eur Urol* 2007;**51**:98–104.
- 19 Krušlin B, Novosel I, Reljic A, *et al.* Periacinar cleft-like spaces in prostatic needle core biopsies (abstract). *Acta Clin Croat* 2002;**41**:175.
- 20 Krušlin B, Tomas D, Cviko A, *et al.* Periacinar retraction clefting and p63 immunostaining in prostatic intraepithelial neoplasia and prostatic carcinoma. *Pathol Oncol Res* 2006;**12**:205–9.
- 21 Halpert B, Sheehan EA, Schmalhorst WR, *et al.* Carcinoma of the prostate: a survey of 5000 autopsies. *Cancer* 1963;**16**:736–42.
- 22 Tomas D, Krušlin B. The potential value of (myo)fibroblastic stromal reaction in the diagnosis of prostatic adenocarcinoma. *Prostate* 2004;**61**:324–31.
- 23 Tomas D, Ulamec M, Hudolin T, *et al.* Myofibroblastic stromal reaction and expression of tenascin-C and laminin in prostate adenocarcinoma. *Prostate Cancer Prostatic Dis* 2006;**9**:414–9.
- 24 Tuxhorn JA, Ayala GE, Smith MJ, *et al.* Reactive stroma in human prostate cancer: induction of myofibroblast phenotype and extracellular matrix remodeling. *Clin Cancer Res* 2002;**8**:2912–23.
- 25 Epstein J. Diagnosis and reporting of limited adenocarcinoma of the prostate on needle biopsy. *Pathol Int* 2004;**54**(Suppl):S609–12.
- 26 Postma R, Schroder FH, van der Kwast TH. Atrophy in prostate needle biopsy cores and its relationship to prostate cancer incidence in screened men. *Urology* 2005;**65**:745–9.

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