ORIGINAL ARTICLE

Basal cell hyperplasia and basal cell carcinoma of the prostate: a comprehensive review and discussion of a case with c-erbB-2 expression

R Montironi, R Mazzucchelli, D Stramazzotti, M Scarpelli, A López Beltran, D G Bostwick

See end of article for authors' affiliations

Correspondence to: Professor R Montironi, Institute of Pathological Anatomy and Histopathology, Polytechnic University of the Marche Region (Ancona), School of Medicine, Azienda Ospedaliera Umberto I°, Via Conca 71, I-60020 Torrette, Ancona, Italy; r.montironi@univpm.it

Accepted for publication 27 July 2004

J Clin Pathol 2005;**58**:290–296. doi: 10.1136/jcp.2004.019596

Prostatic basal cell proliferations range from ordinary basal cell hyperplasia (BCH) to florid basal cell hyperplasia to basal cell carcinoma. The distinction between these forms of BCH, including the variant with prominent nucleoli (formerly called atypical BCH), and basal cell carcinoma depends on morphological and immunohistochemical criteria and, in particular, on the degree of cell proliferation. In florid BCH, the proliferation index is intermediate between ordinary BCH and basal cell carcinoma. Immunohistochemistry is also useful for identifying the cell composition of the basal cell proliferations, including the basal cell nature of the cells, their myoepithelial differentiation, and c-erbB-2 oncoprotein expression. Based on the information derived from the literature and on the appearance and follow up of the case presented here, florid BCH might represent a lesion with an intermediate position between ordinary BCH and basal cell carcinoma. However, criteria useful for the identification of those cases with a true precursor nature are not available. In general, basal cell carcinoma is seen as a low grade carcinoma. The immunohistochemical expression of the c-erbB-2 oncoprotein, similar to that seen in breast cancer, might have therapeutic importance.

Basal cell proliferations in the prostate gland exhibit a morphological continuum ranging from basal cell hyperplasia (BCH) in the setting of nodular hyperplasia to malignant basal cell lesions that resemble, to a certain degree, basal cell carcinoma of the skin and adenoid cystic carcinoma of the salivary gland.[1 2] A large number of terms have been used for these tumours and related growths.

> ''Basal cell proliferations in the prostate gland exhibit a morphological continuum ranging from basal cell hyperplasia to malignant basal cell lesions''

The aim of our paper, which includes a case presentation and discussion, is to review the morphological spectrum and the immunohistochemical findings of basal cell proliferations in the prostate.

CASE HISTORY

- A 71 year old white man presented in September 1992 with a one year history of increasing urinary obstructive symptoms. Diffuse enlargement of the prostate was documented by transrectal ultrasound and digital rectal examination. Suprapubic (simple) prostatectomy was performed. The preoperative total serum prostate specific antigen (PSA) concentration was 2.5 ng/ml. After the operation PSA decreased to below 1.0 ng/ml. The diagnosis was benign prostatic hyperplasia associated with diffuse BCH.
- The patient was clinically well until 1996 when he presented with recurrent urinary obstructive symptoms. Transurethral resection of the prostate (TURP) was performed in June 1996, and normal voiding was achieved. The pathology report included basal cell carcinoma of the prostate versus urothelial carcinoma. The reporting pathologist favoured the second diagnosis.
- In March 1997, the patient underwent a second TURP, and permanent normal voiding was achieved. The pathology report, which included revision of the previous two reports, was basal cell carcinoma with extension to the extraprostatic tissue.
- Local recurrence was documented in 2000. This was a progressively growing mass (20 cm across) originating from the prostate and compressing and obstructing the rectum. There were no urinary voiding problems. The patient was given no treatment (chemotherapy or radiotherapy). A computed tomography scan performed in 2003 revealed no secondary deposits in lymph nodes or distant parenchyma. The PSA remained below 1.0 ng/ml. He died from unrelated heart failure in mid-2003. A necropsy was not performed.

MATERIALS AND METHODS

Formalin fixed, paraffin wax embedded material was retrieved from the files of the section of pathological anatomy and histopathology of the Polytechnic University of the Marche Region, Ancona, Italy. Haematoxylin and eosin stained sections were prepared for all the paraffin wax blocks. Staining with alcian blue (pH 2.5) and periodic acid Schiff with diastase was performed on three paraffin wax blocks, one from the suprapubic prostatectomy specimen and two from the 1996 and 1997 TURP material.

Immunoperoxidase studies were performed on the formalin fixed, paraffin wax embedded tissues using the Dako Envision™ System (DakoCytomation, Glostrup, Denmark). Antibodies to the following antigens were used: keratin 34βE12 (34βE12), cytokeratin 7 (CK7), and CK20 (DakoCytomation; 1/40, 1/100, and 1/500 dilutions, respectively); AE1/AE3 (BioGenex, San Ramon, California, USA; prediluted); p63 (DakoCytomation; 1/50 dilution); PSA

Abbreviations: BCH, basal cell hyperplasia; BPH, benign prostatic hyperplasia; CK, cytokeratin; PIN, prostatic intraepithelial neoplasia; PSA, prostate specific antigen; TURP, transurethral resection of the prostate

(DakoCytomation; 1/750 dilution); α smooth muscle actin (BioGenex; prediluted); S-100 protein (BioGenex; prediluted); Ki-67 (DakoCytomation; 1/50 dilution); chromogranin (DakoCytomation; 1/100 dilution); bcl-2 (DakoCytomation; 1/60 dilution); laminin (DakoCytomation; 1/25 dilution); and c-erbB-2 oncoprotein (Zymed Laboratories, South San Francisco, California, USA; 1/50 dilution). The immunohistochemical staining of cells was recorded as either positive or negative. At least 500 cells were counted on each slide.

Karyometry was performed by one of us (RMa) on haematoxylin and eosin stained histological sections. A Zeiss-Kontron IBAS-AT image analyser (Munich, Germany) combined with a light Zeiss microscope equipped with a ×100 oil immersion objective was used. Fifty nuclei were measured for each pattern (see below).

GROSS AND MICROSCOPIC PATHOLOGY

Suprapubic prostatectomy specimen (examined in 1992)

The surgical specimen weighted 60 g and measured 6 × 5 × 4 cm (volume calculated on the basis of the ellipsoid volume formula: 62 cc). The cut surface was white and nodular. Ten tissue blocks were randomly taken and processed. Ten per cent of the specimen showed the appearance of benign prostatic hyperplasia (BPH). The remaining 90% showed diffuse alteration of the prostatic architecture and structure by a composite nodular lesion (fig 1A), with three distinct patterns (fig 1–P; table 1).

Pattern 1: tightly packed small acini arranged in a lobular configuration with sharp peripheral borders. The acini, far smaller than the unaffected normal looking ducts and acini, showed symmetrical circumferential thickening of the basal cell layer, usually two or more cell layers thick, surrounding a continuous layer of cuboidal to columnar luminal cells. The nuclei were small to medium sized, elongated or round, with uniform pale chromatin that was occasionally vesicular. Nucleoli were inconspicuous or absent. The cytoplasm was difficult to identify by light microscopy and appeared as a dark, narrow rim with inconspicuous cell margins. Occasionally, the thickening was eccentric and composed of small solid nests of polygonal cells, with the nuclear appearance of those seen in the ducts with symmetric

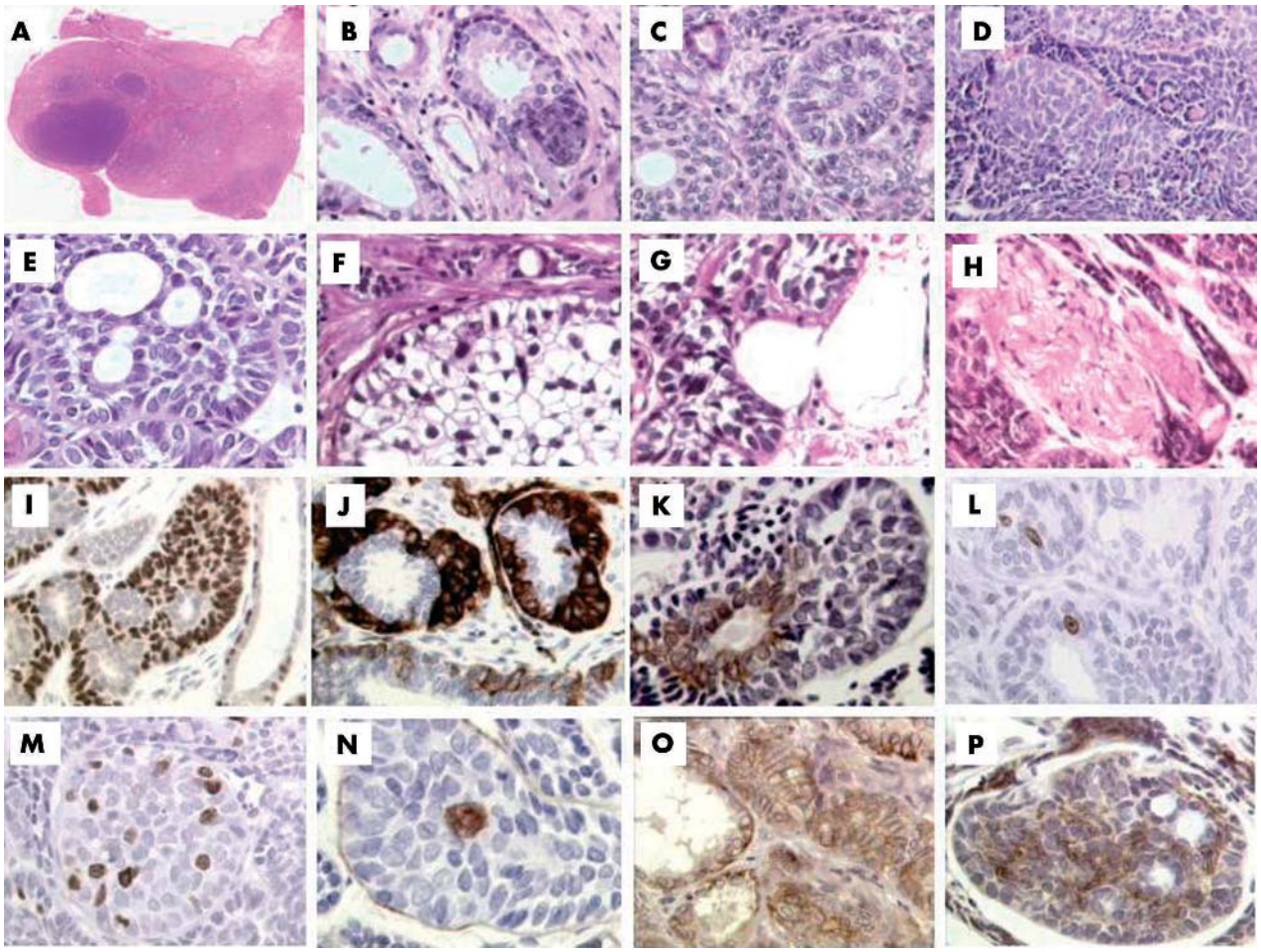

Figure 1 (A) Epithelial cell nests and islands arranged in basophilic nodules having expansible growth margins. (B) Ordinary basal cell hyperplasia with eccentric thickening of the basal cell layer. (C) Florid basal cell hyperplasia showing epithelial cell nests and islands; single lumina are present. (D) Basal cell carcinoma showing solid epithelial cell nests and cords; the peripheral palisading pattern is evident and small globules of dense eosinophilic material surrounded by basal cells are seen in some nests (see also (N)). (E) Basal cell carcinoma with nest punctuated by cribriform spaces filled with tenuous basophilic mucinous secretion; squamous differentiation is seen in the lower left corner. (F) Basal cell carcinoma; cells with optically clear cytoplasm. (G) Basal cell carcinoma; extension out of the prostate into the periprostatic adipose tissue. (H) Basal cell carcinoma with perineural invasion. (I) p63 immunostaining of basal cell carcinoma. (J) Cells positively stained with antibody for α smooth muscle actin are located in the cell layer adjacent to the stroma. (K) The cells lining the lumen are AE1/AE3 positive. (L) Ordinary basal cell hyperplasia with few Ki-67 positive nuclei. (M) Basal cell carcinoma with several Ki-67 positive nuclei. (N) Laminin immunostaining in the stroma surrounding the cell nest and in a small globule. (O) Expression of c-erbB-2 oncoprotein in florid basal cell hyperplasia. (P) Expression of c-erbB-2 oncoprotein in basal cell carcinoma.

Table 1 Antibodies and immunostaining results

Antigens	Cells in close contact with the stroma	Cells in the centre of nests	Cells in between
34βE12	Positive	Negative	Positive
p63	Positive	Negative	Positive
bcl-2	Positive	Negative	Positive
CK20	Negative	Negative	Negative
SMA	Positive (focal)	Negative	Negative
S-100 protein	Positive (focal)	Negative	Negative
AE1/AE3	Negative	Positive	Negative
CK7	Negative	Positive	Negative
PSA	Negative	Positive (focal)	Negative
Ki-67	Positive (very few)	Negative	Positive
Laminin	Positive	Negative	Negative
c-erbB-2 oncoprotein	Negative	Positive	Positive
Chromogranin	Negative	Negative	Negative

CK, cytokeratin; PSA, prostate specific antigen; SMA, α smooth muscle actin.

proliferation of the basal cells (fig 1B). All cells stained positively for keratin 34βE12, p63, and bcl-2. The cells were negative for CK7, CK20, AE1/AE3, PSA, and chromogranin. Mitotic figures were rare, and 11% of the cells were Ki-67 positive. The borders between the basal and the luminal cells were usually sharp. Luminal cells showed more abundant cytoplasm with a slightly basophilic appearance, an easily identifiable cell membrane, and nuclei with open chromatin and occasional small nucleoli. The luminal cells were negative for keratin 34βE12, p63, CK20, and bcl-2 and positive for AE1/AE3 and CK7. There were no mitotic figures, and no Ki-67 positive nuclei were seen. Two per cent of the luminal cells were PSA positive. This pattern occupied approximately 60% of the specimen. In the tissue sections there was a homogeneous distribution of lobules with these features, giving the impression that such lobules had replaced the epithelial nodules usually seen in BPH.

Pattern 2: epithelial cell nests and islands arranged in nodules ranging up to 1 cm in diameter and having expansible growth margins (fig 1A, C). There was often a distinct outer layer of palisading basal cells surrounding larger, polygonal epithelial cells that formed the main bulk of the nests. The basal cells contained minimal cytoplasm and an oval to round nucleus with stripped chromatin, sometimes hyperchromatic, and an occasional small solitary nucleolus. The large polygonal cells contained more eosinophilic cytoplasm, which was more abundant in the centre of the nests, with slightly larger nuclei and one to two distinct nucleoli. The immunohistochemical results were similar to those seen in pattern 1. All cells stained for keratin 34βE12, p63 (fig 1I), and bcl-2. The cells were negative for CK7, CK20, AE1/AE3, and chromogranin. Mitotic figures were rare and only seen in areas with polygonal cells; 18% of the cells were Ki-67 positive (fig 1L). Most of the nests were solid. Central or eccentric single lumina were present in a minority of nests. Cells lining the lumina were either cuboidal or tall, and AE1/AE3 and CK7 positive (fig 1K). Some of the lumina contained both alcian blue positive acid mucin and periodic acid Schiff positive neutral mucin; intracytoplasmic mucin was not seen. PSA immunostaining was negative. This pattern occupied approximately 20% of the specimen. Some lobules with pattern 1 contained small foci of pattern 2.

Pattern 3: poorly circumscribed nodular collections of epithelial cell nests and cords, most solid, but some containing single lumina (fig 1D–H). Compared with pattern 2, the nests and cords were larger, more uniform in size, and separated by a variable amount of fibromyxoid stroma. Small nodules or globules of dense eosinophilic material surrounded by basal cells were seen in some nests towards the periphery, and in close proximity to the stroma (fig 1D). The cell composition was similar to that seen in pattern 2. However, the peripheral palisading pattern was more evident, and the polygonal cells had nuclei two to three times larger with considerable irregularity and variability in size. The chromatin was finely dispersed with rare, small nucleoli. The immunohistochemical results were similar to those seen in patterns 1 and 2. All the cells stained for keratin 34βE12, p63, and bcl-2. The cells were negative for CK7, CK20, AE1/AE3, and chromogranin. Mitotic figures were more frequent than in the other two patterns and always seen in relation to areas of polygonal cells; 35% of the cells were Ki-67 positive (fig 1M). The cells lining the lumina were basal, AE1/AE3 and CK7 positive, and PSA negative. Pattern 3 occupied approximately 10% of the specimen. In some areas, it was adjacent to and in continuity with foci with pattern 2.

Additional immunohistochemical and morphometric findings:

- Cells stained with antibodies to α smooth muscle actin (fig 1J) and S-100 protein were seen in all three patterns. The positive cells were located in the cell layer adjacent to the stroma, including those with palisading features. All other cells were negative. The proportion of positive cells was greatest in pattern 2, lowest in pattern 3, and intermediate in pattern 1 (α smooth muscle actin: 7%, 4%, and 2%, respectively; S-100 protein: 5%, 3%, and 1%, respectively).
- Cells stained with the anti-c-erbB-2 oncoprotein antibody were present in all three patterns, mostly in the polygonal cells in patterns 2 and 3 (close to 40%) and luminal cells of pattern 1 (more than 50%) (fig 1O, P). The cell layer adjacent to the stroma was usually negative.
- Morphometric analysis showed that the nuclear and nucleolar areas increased from ordinary BCH (nuclear area: mean (SD), 27.95 (6.77) μm^2; nucleolar area: mean (SD), 0.94 (0.19) μm^2) to florid BCH (nuclear area: mean (SD), 38.61 (6.23) μm^2; nucleolar area: mean (SD), 1.55 (0.52) μm^2) to basal cell carcinoma (nuclear area: mean (SD), 53.52 (10.37) μm^2; nucleolar area: mean (SD), 1.72 (0.34) μm^2); the values in the basal cells of unaffected duct and acini were lower (nuclear area: mean (SD), 22.19 (7.29) μm^2; nucleolar area: mean (SD), 0.91 (0.45) μm^2). The differences for the nuclear and nucleolar areas (Kruskal-Wallis test) were significant at the level of $p < 0.001$ and $p = 0.022$, respectively.

First TURP specimen (examined in 1996)

The total weight of the chips was 35 g. Most of the material was examined histologically, and 20% of the tissue was normal prostate, 10% was occupied by pattern 2, and 70% by pattern 3. Very few chips showed nests and islands punctuated by cribriform spaces filled with basophilic mucinous secretion, nests with squamous differentiation, cells with optically clear cytoplasm, and isolated foci with the appearance of pattern 1, the differences being that the nuclei were as large as in pattern 3 described above and that the degree of proliferation (Ki-67-postive cells) was as high as 40%. In addition, the lesion showed extension out of the prostate into periprostatic adipose tissue and perineural invasion.

Second TURP specimen (examined in 1997)

Ten grams of prostatic chippings were received and processed for paraffin wax embedded sections. Histologically, all of the tissue was occupied by poorly circumscribed nodular collections of cell nests conforming to pattern 3.

Table 2 Basal cell proliferations of the prostate: diagnostic criteria together with major immunohistochemical findings

	Architecture	Cytology	34βE12, p63	PSA	S-100 protein, SMA
Normal basal cell layer	Near continuous single cell layer	Small elongated cells, ovoid nuclei, scant cytoplasm	+	−	−
Ordinary BCH (including BCA and adenomatosis)	Small cell nests, two cell layers minimum, solid or cystic	Small to medium sized nuclei, inconspicuous nucleoli, cytoplasm difficult to identify	+	±*	±*
Florid BCH	Compact glandular proliferation with solid nests	Cells with moderately enlarged nuclei, often with a prominent nucleolus	+	±	±
BCH with prominent nucleoli (or atypical BCH)	Same as ordinary BCH	Nucleoli similar to those seen in acinar adenocarcinoma	+	±	±
BCC (adenoid cystic carcinoma)	Islands and cords of cells with peripheral palisading or nests of cells with an adenoid cystic pattern	Basaloid cells with large nuclei with considerable irregularity and variable size	+	±	−

*See table 1 for cell location.
BCA, basal cell adenoma; BCC, basal cell carcinoma; BCH, basal cell hyperplasia; PSA, prostate specific antigen; SMA, α smooth muscle actin.

Diagnosis
Ordinary and florid BCH (patterns 1 and 2) and basal cell carcinoma (pattern 3) with focal areas resembling BCH.

DISCUSSION
Morphology
A spectrum of basal cell proliferations ranging from hyperplasia to carcinoma exists in the prostate[3] (table 2). These are usually located in the transition zone.

Ordinary (usual, typical, or classic) BCH consists of numerous small to normal sized, round basophilic acini with several layers of basal cells (glandular architectural type) or solid nests, either arranged in a lobular configuration or rarely ''infiltrating'' the stroma (see below) (fig 1B). The morphology corresponds to our pattern 1. No cases of ordinary BCH, by definition, contain either prominent nucleoli (their mean diameter is less than 1 μm)[1] or polymorphism; however, rare cases may show the presence of hyperchromatic nuclei, enlarged nuclei, and rare mitotic figures. BCH resembles prostate acini seen in the fetus, accounting for the synonyms ''fetalisation'' and ''embryonal hyperplasia''. BCH may be composed of basal cell nests with areas of luminal differentiation resembling similar lesions of the salivary gland. This is denoted as the adenoid basal form of BCH.

> ''The recognition of intracytoplasmic globules can help to identify a lesion as that of basal cell hyperplasia''

Basal cell adenoma is identical to ordinary BCH, although the proliferating basal cell masses are usually large and circumscribed, with a nodular or adenoma-like pattern. In contrast to basal cell carcinoma, basal cell adenoma is well circumscribed, lacks necrosis, and the stroma between the basal cell nests is similar to that of the surrounding normal prostatic stroma. Occasionally, BCH is multifocal (adenomatosis). The terms basal cell adenoma and adenomatosis are very rarely used.

Four morphological findings of BCH have been reviewed in a recent paper[4]: intracytoplasmic globules (these stain for α fetoprotein and α 1 antitrypsin), calcifications, squamous features, and cribriform features (table 3). The recognition of intracytoplasmic globules can help to identify a lesion as that of BCH. This feature, reported also by Yang *et al*,[5] has not been seen in other prostatic lesions. Intraluminal calcifications can also aid in the recognition of BCH, given their rarity in other prostatic conditions. The knowledge that squamous and cribriform features can be found in BCH and the awareness of their light microscopic and immunohistochemical features can help to distinguish these lesions from preneoplastic and neoplastic diseases of the prostate.

BCH may have a florid appearance (florid basal cell hyperplasia). Our pattern 2 is identical to this and corresponds to the description given by Van de Voorde and colleagues[6]: compact glandular proliferation with solid nests; the cytology in some areas looks disturbing because the cells have a moderately enlarged nucleus, often with a prominent nucleolus; a few mitotic figures are present; the intervening stroma is scant and cellular; the lesions are not well circumscribed and are intermingled with the surrounding glands, giving the impression of ''infiltration'' (this is also called diffuse type) (fig 1C). Yang *et al* gave an additional criterion for the identification of florid BCH: extensive proliferation of basal cells involving more than 100 small crowded acini (in each section) forming a nodule.[5]

Another variant of BCH has prominent nucleoli (known as BCH with prominent nucleoli), but is otherwise identical to ordinary BCH. The nucleoli are round to oval and lightly eosinophilic, similar to those seen in acinar adenocarcinoma of the prostate (their mean diameter is 1.96 μm).[1] There is chronic inflammation in most cases, suggesting that nucleolomegaly is a reflection of reactive atypia.[1] These cases are also referred to as atypical basal cell hyperplasia.[1 2]

BCH with prominent nucleoli may be mistaken for high grade prostatic intraepithelial neoplasia (PIN). Although occasionally the differential diagnosis of these two entities may be difficult, usually they are distinct. The nuclei in BCH tend to be round and, at times, the cells form small solid basal cell nests. In contrast, the cells in PIN tend to be more pseudostratified and columnar and do not occlude the glandular lumina. Within areas of BCH, atypical looking

Table 3 Basal cell proliferations of the prostate: unusual morphological findings

- Intracytoplasmic globules
- Calcifications
- Squamous features
- Cribriform features

basal cells can be seen underling the overlying benign appearing secretory cells. PIN has full thickness cytological atypia with the nuclei oriented perpendicular to the basement membrane. Immunohistochemistry for either 34βE12 or p63 can help in difficult cases. In BCH, immunohistochemistry shows multilayered staining of the basal cells, whereas an interrupted immunoreactive basal cell layer is seen in PIN. Yang *et al* showed that immunostaining for α methylacyl-coenzyme racemase (P504S) is negative in florid BCH and positive in high grade PIN and adenocarcinoma.[7] Immunostaining for glutathione-s-transferase π is positive in florid BCH and negative in adenocarcinoma. The same group of authors performed ultrastructural analysis to document further the basal cell features of florid BCH.

BCH, mainly with a glandular architecture or when florid, may be confused with adenocarcinoma (table 4). BCH can be distinguished from adenocarcinoma by its very basal cell appearance. The glands appear basophilic at low power because of the multilayering of basal cells, which have scant cytoplasm. In contrast, gland forming adenocarcinoma of the prostate almost always has more abundant cytoplasm, resulting in a more eosinophilic appearance to the glands. If by light microscopy there is difficulty in distinguishing BCH from prostatic adenocarcinoma, the use of immunohistochemistry with basal cell specific antibodies (to 34βE12 or p63) can differentiate between these two lesions.[8]

Basal cell carcinoma (basal cell carcinoma/adenoid cystic carcinoma) is characterised by the proliferation of cells arranged in various architectural patterns. Two morphological variants of basal cell carcinoma can be recognised in the prostate. Islands and cords of epithelial cells with peripheral palisading characterise the first type, morphologically similar to basal cell carcinoma of the skin. The second type, also called adenoid cystic carcinoma, is composed of nests of infiltrating tumour cells with an adenoid cystic pattern, morphologically similar to adenoid cystic carcinoma of the salivary glands. The case presented here, with its pattern 3, belongs to the first variant, even though few areas corresponding to the second type are seen (fig 1D, E). Focal squamous differentiation and clear cells are seen (fig 1E, F)

> ''Basal cell hyperplasia can be distinguished from adenocarcinoma by its very basal cell appearance''

The diagnostic criteria for malignancy in basal cell carcinoma include: (1) extensive infiltration between normal prostate glands, (2) extension out of the prostate, (3) perineural invasion, or (4) necrosis (table 5).[1 2 9] The most obvious criterion of malignancy seen in our present case was the extension out of the prostate (fig 1G). Perineural invasion was also seen (fig 1H). Our case showed the presence of focal areas of basal cell carcinoma mimicking classic BCH.

The differential diagnosis of basal cell carcinoma includes poorly differentiated (mostly Gleason's grade 5) adenocarcinoma (basal cell carcinoma may occur, rarely, in combination with conventional adenocarcinoma) and urothelial carcinoma (table 6). Poorly differentiated adenocarcinoma may grow in solid nests and, similar to basal cell carcinoma, is not reactive for PSA. Lack of immunoreactivity for p63 and 34βE12, however, is helpful in recognising conventional adenocarcinoma, although it has been reported that this tumour may occasionally express p63. Similar to basal cell carcinoma, urothelial carcinoma may exhibit a solid growth pattern with peripheral palisading and central necrosis, and may express high amounts of p63. However, urothelial

Table 5 Basal cell carcinoma: diagnostic criteria for malignancy

- Extensive infiltration between normal prostate glands
- Extension out of the prostate
- Perineural invasion
- Necrosis

Table 4 BCH (ordinary, florid, and with nucleoli): differential diagnoses. Morphological criteria and major immunohistochemical findings

	Architecture	Cytology	34βE12, p63	PSA	S-100 protein, SMA
BCH (ordinary, florid, and with nucleoli)	Cell nests, two cell layers minimum, solid or cystic	Small to medium sized nuclei, nucleoli may be prominent in some forms	+	±	− to ±
High grade PIN	Ducts and acini with various architectural patterns, ranging from flat to cribriform	Cells with enlarged nuclei, with a prominent nucleolus, similar to those in adenocarcinoma	± (basal cells)	+	−
Adenocarcinoma	Acini of various sizes, either separated or fused, with different architectural patterns, such as flat or monolayered or cribriform	Cells with enlarged nuclei, with prominent nucleoli	−	+	−
Sclerosing adenosis	Acinar structures, predominantly small, lined by bilayered epithelium	Small to medium sized nuclei, inconspicuous nucleoli	+ (basal cells)	+	+
Benign seminal vesicle/ ejaculatory duct epithelium	Ducts lined by a bilayered epithelium	Prominent nuclear atypia and pleomorphism	+	−	−
Squamous metaplasia	Ducts and acini lined by multilayered epithelium similar to epidermis	Cells with small to medium sized nuclei, inconspicuous nucleoli; keratinisation often prominent	+	−	−
Transitional cell metaplasia	Ducts and acini lined by multilayered epithelium similar to urothelium	Small to medium sized nuclei, inconspicuous nucleoli; luminal cells larger than those in the intermediate and basal layers	+	− to ± (scattered luminal cells)	−

BCH, basal cell hyperplasia; PIN, prostatic intraepithelial neoplasia; PSA, prostate specific antigen; SMA, α smooth muscle actin.

carcinoma expresses CK20 and CK7. Basal cell carcinoma is positive for CK7 and negative for CK20.[10]

Immunohistochemistry

The results of the immunohistochemical investigations published by different groups and the analysis of our case have pointed out the following four features (table 7).

The first is related to the nature of the cells involved in basal cell proliferations. Immunohistochemistry clearly indicates that they have the same immunophenotype as the basal cells present in normal ducts and acini. The cells are positively and strongly stained for 34βE12 and p63 (fig 1I). These are the two consolidated markers for basal cells in the prostate, as seen also in our case, and their absence is in favour of prostate adenocarcinoma.[8]

The second concerns cell composition. Our investigation points out that there might be at least three types of cells: (1) cells with a palisading aspect in close contact with the stroma, (2) cells in the centre of the nests where lumina are seldom seen, and (3) cells in between these two types. McEntee *et al* were the first to document the heterogeneous cell composition in prostatic BCH and neoplasia in their comparative pathology study in human and non-human primates.[11]

The cells in contact with the stroma show focal positivity for S-100 and α smooth muscle actin (fig 1J). The expression of these two markers indicates that myoepithelial differentiation appears in the basal cell proliferations, as usually takes place in sclerosing adenosis, whereas it is absent in the normal prostate. This type of differentiation was mentioned both in benign and malignant basal cell lesions in at least two previous publications.[5 6] The exact location of the myoepithelial cells was documented by Yang *et al*.[7] Grignon *et al* observed the presence of S-100 positivity in the absence of reactivity with muscle specific actin.[12] They concluded that S-100 positivity alone does not necessarily indicate myoepithelial cell differentiation.

The cells that are located in the centre of the nests and those lining the small lumina stain positively with AE1/AE3 (fig 1K), whereas the cells in the other two locations are negative. The same cells are 34βE12 and p63 negative,[2] and only rarely show a faint positivity for PSA. The basal cells in the normal ducts and acini do not stain with AE1/AE3, whereas all the cells present in ducts and acini with atrophic features are stained intensely. Such findings indicate that the cells present in the basal cell proliferations show some degree of differentiation towards the secretory cell phenotype.

Table 7 Basal cell proliferations of the prostate: immunohistochemistry

- Nature of the cells involved in the basal cell proliferations
- Cell composition: myoepithelial cells, proliferating cells, and luminal cells
- Markers usually seen in tumours at other sites and organs: laminin and c-erbB-2 oncoprotein
- Chromogranin positive cells (neuroendocrine differentiation)

Mitoses and Ki-67 positivity (fig 1L, M) are mainly seen in the nuclei of cells found between the periphery and centre of the nests. This indicates that these cells form a proliferative compartment, whereas the cells in contact with the stroma and those in the centre represent the differentiative/differentiated compartment.[6]

The third interesting feature is that the basal cell proliferations express two markers usually seen in tumours of other sites and organs. Laminin can be demonstrated both in the stroma surrounding the cell nests and in small eosinophilic globules surrounded by the cells (fig 1N). This feature is usually seen in tumours of the salivary glands. In addition, the expression of the c-erbB-2 oncoprotein is similar to that seen in breast cancer (fig 1O, P).

The fourth is represented by the presence of a small proportion of cells with neuroendocrine differentiation, as documented by chromogranin immunostaining.[5] This was not seen in our case.

Differential diagnosis between BCH and basal cell carcinoma

In contrast to BCH, basal cell carcinoma shows an infiltrative rather than lobulated pattern, with invasion around nerves, or into soft tissues, and with necrosis. Proliferation (assessed by Ki-67 immunostaining) is also helpful in distinguishing basal cell carcinoma from the other basal cell proliferations. The proliferation index in basal cell carcinoma is greater than in ordinary BCH, with the values in florid BCH and BCH with

Table 6 Basal cell carcinoma: differential diagnoses. Morphological criteria and major immunohistochemical findings

	Architecture	Cytology	34βE12, p63	PSA	S-100 protein, SMA
Basal cell carcinoma (adenoid cystic carcinoma)	Proliferation of cells arranged in various architectural patterns, showing morphological criteria for malignancy (table 5)	Basaloid cells with large nuclei with considerable irregularity and variable size	+	±	−
Poorly differentiated adenocarcinoma (mostly Gleason grade 5)	Tumour proliferation without glandular differentiation and composed of solid sheets, cords or single cells; necrosis can be present	Cells with enlarged nuclei and prominent nucleoli	−	+	−
Transitional cell (urothelial) carcinoma	Irregular solid nests and cords with a striking propensity for growth within ducts and acini	High nuclear grade with substantial nucleomegaly, nuclear pleomorphism, and nuclear hyperchromasia. Prominent nucleoli often present	+	−	−
Neuroendocrine carcinoma	Sheets of cells, with ribbons, nesting, palisading along fibrous bands, and rosette-like structures	Polygonal, round, or spindled tumour cells with scanty cytoplasm, and hyperchromatic nuclei identical to pulmonary small cell carcinoma	−	−	−
Basaloid carcinoma of the rectum	Solid tumour nests exhibiting peripheral palisading, sometimes with foci of mucin secretion and areas of squamous differentiation	Similar to cutaneous basal cell carcinoma	+	−	−

PSA, prostate specific antigen; SMA, α smooth muscle actin.

prominent nucleoli being intermediate between ordinary BCH and basal cell carcinoma.[5] Proliferation in areas of basal cell carcinoma with a pattern mimicking BCH is as high as in the classic nested type of basal cell carcinoma.[6]

> ''Florid basal cell hyperplasia could derive from ordinary basal cell hyperplasia and could be the direct precursor of basal cell carcinoma''

Morphology and immunohistochemistry suggest that florid BCH has an intermediate position between ordinary BCH and basal cell carcinoma. The exact position of BCH with prominent nucleoli is not entirely clear. There is a lack of clinical information in the few studies with follow up of these patients. However, this type of BCH shows morphological features of both ordinary and florid BCH.

Relation between BCH and basal cell carcinoma

The clinical presentation and history of the case studied here supports the view expressed by Reed,[13] according to which BCH is a preneoplastic lesion. In particular, florid BCH could derive from ordinary BCH and could be the direct precursor of basal cell carcinoma. This view is also supported by the observation made by some authors on the occurrence of extensive BCH in the prostate with basal cell carcinoma.[1 2 10 12 14]

Natural history of basal cell carcinoma

The English literature on this entity consists of only a few publications[15 16] (for an extensive list of previously published cases see Humphrey[9] and Mastropasqua and colleagues[10]). In general, the patients are elderly, and present with urinary obstruction, with TURP being the most common tissue source of diagnosis. The youngest reported patient was 28 years old.[14] The outcome for patients diagnosed with basal cell carcinoma of the prostate is uncertain, because most cases have been reported with a short follow up. Overall, basal cell carcinoma of the prostate is viewed as a low grade carcinoma.[9] A recent paper by Iczkowski *et al* described the clinicopathological features in 19 cases and, based on their experience, they concluded that basal cell carcinoma of the prostate (in their paper this tumour is referred to as adenoid cystic/basal cell carcinoma) was a potentially aggressive neoplasm requiring ablative treatment.[16] Such a conclusion was based on the fact that metastasis was documented in four of their patients, two died of cancer, and three were alive with cancer.

CONCLUSIONS

- Prostatic basal cell proliferations range from ordinary BCH to florid BCH and basal cell carcinoma.
- The separation between these three forms of BCH, including the variant with prominent nucleoli, depends on morphological and immunohistochemical criteria.
- Immunohistochemistry is useful to identify the cell composition of the basal cell proliferations, which includes the basal cell nature of the cells and myoepithelial differentiation.

ACKNOWLEDGEMENTS

This publication was supported by grants from the Polytechnic University of the Marche Region (Ancona) (MS) and the Italian Ministry of University and Scientific Research (RM, 2003). The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of the Polytechnic University of the Marche Region, Ancona, Italy.

NOTE ADDED IN PROOF

The following paper was published after the acceptance of our article: McKenney JK, Amin MB, Srigley JR, *et al*. Basal cell proliferations of the prostate other than usual basal cell hyperplasia. *Am J Surg Pathol* 2004;**28**:1289–98.

Authors' affiliations

R Montironi, R Mazzucchelli, D Stramazzotti, M Scarpelli, Section of Pathological Anatomy and Histopathology, Polytechnic University of the Marche Region, School of Medicine, Azienda Ospedaliera Umberto I°, Via Conca 71, I-60020 Torrette, Ancona, Italy
A L Beltran, Unit of Anatomic Pathology, Cordoba University Medical School, 14071 Cordoba, Spain
D G Bostwick, Bostwick Laboratories, 4355 Innslake Drive, Glen Allen, Richmond, Virginia 23060, USA

REFERENCES

1 **Devaraj LT**, Bostwick DG. Atypical basal cell hyperplasia of the prostate. Immunophenotypic profile and proposed classification of basal cell proliferations. *Am J Surg Pathol* 1993;**17**:645–59.
2 **Epstein JI**, Armas OA. Atypical basal cell hyperplasia of the prostate. *Am J Surg Pathol* 1992;**16**:1205–14.
3 **Sesterhenn I**, Mostofi FK. Basal cell hyperplasia and basal cell carcinoma. *Lab Invest* 1987;**56**:71A.
4 **Rioux-Leclercq NC**, Epstein JI. Unusual morphologic patterns of basal cell hyperplasia of the prostate. *Am J Surg Pathol* 2002;**26**:237–43.
5 **Yang XJ**, McEntee M, Epstein JI. Distinction of basaloid carcinoma of the prostate from benign basal cell lesions by using immunohistochemistry for Bcl-2 and Ki-67. *Hum Pathol* 1998;**28**:1447–50.
6 **Van De Voorde W**, Baldewijns M, Lauweryns J. Florid basal cell hyperplasia of the prostate. *Histopathology* 1994;**24**:341–8.
7 **Yang XJ**, Tretiakova MS, Sengupta E, *et al*. Florid basal cell hyperplasia of the prostate: a histological, ultrastructural, and immunohistochemical analysis. *Hum Pathol* 2003;**34**:462–70.
8 **Hosler GA**, Epstein JI. Basal cell hyperplasia: an unusual diagnostic dilemma on prostate needle biopsies. *Mod Pathol* 2004;**17**:158A.
9 **Humphrey PA**. Basaloid and adenoid cystic carcinomas. In: Humphrey PA, ed. *Prostate pathology*. Chicago, USA: ASCP Press, 2003:408–9.
10 **Mastropasqua MG**, Pruneri G, Renne G, *et al*. Basaloid cell carcinoma of the prostate. Case report and review of the literature. *Virchows Arch* 2003;**443**:787–91.
11 **McEntee MF**, Epstein JI, Syring R, *et al*. Characterization of prostatic basal cell hyperplasia and neoplasia in aged macaques: comparative pathology in human and nonhuman primates. *Prostate* 1996;**29**:51–9.
12 **Grignon DJ**, Ro JY, Ordonez NG, *et al*. Basal cell hyperplasia, adenoid basal cell tumor, and adenoid cystic carcinoma of the prostate gland: an immunohistochemical study. *Hum Pathol* 1988;**19**:1425–33.
13 **Reed RJ**. Consultation case: prostate (prostatectomy)—adenoid basal-cell tumour—multifocal basal cell hyperplasia. *Am J Surg Pathol* 1984;**8**:699–704.
14 **Denholm SW**, Webb JN, Howard GCW, *et al*. Basaloid carcinoma of the prostate gland: histogenesis and review of the literature. *Histopathology* 1992;**20**:151–5.
15 **Young RH**, Frierson HF, Mills SE, *et al*. Adenoid cystic-like tumor of the prostate gland. A report of two cases and review of the literature on ''adenoid cystic carcinoma'' of the prostate. *Am J Clin Pathol* 1988;**89**:49–56.
16 **Iczkowski KA**, Ferguson KL, Grier DD, *et al*. Adenoid cystic/basal cell carcinoma of the prostate. Clinicopathologic findings in 19 cases. *Am J Surg Pathol* 2003;**27**:1523–9.