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Shared *TP53* Gene Mutation in Morphologically and Phenotypically Distinct Concurrent Primary Small Cell Neuroendocrine Carcinoma and Adenocarcinoma of the Prostate

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BACKGROUND. Small cell carcinoma of the prostate is an uncommon neoplasm, the origin of which has been controversial. To address this, we performed transcriptome profiling and *TP53* sequencing of concurrent small cell and prostatic adenocarcinoma to determine the relationship between these entities.

METHODS. We identified an unusual case of primary prostate cancer that contained adjacent acinar adenocarcinoma (Gleason score $4+3=7$) and small cell carcinoma. We performed laser capture microdissection to isolate tumor components and performed gene expression and *TP53* gene sequence analysis on each component, with results validated by immunohistochemistry for PSA, PSAP, PSMA, androgen receptor, NKX 3.1 and neuroendocrine markers.

RESULTS. Transcriptome profiling of the carcinoma components identified 99 genes with a greater than 10-fold differential expression between prostatic adenocarcinoma and small cell carcinoma, many of which have not been previously reported in prostate cancer. The small cell carcinoma component demonstrated upregulation of proliferative and neuroendocrine markers and tyrosine kinase receptors, and downregulation of cell adhesion molecules, supporting the aggressive nature of this form of carcinoma. Sequencing of the *TP53* gene suggested a common clonal origin for both components.

CONCLUSIONS. This is the first report of a primary small cell carcinoma of the prostate subjected to extensive molecular analysis and the first to show a clonal relation between two morphologically distinct prostate cancer types. The evidence of progression to small cell carcinoma may yield important insights into the pathogenesis of this entity and provide a novel spectrum of molecular markers to further dissect cellular pathways important in tumor progression. *Prostate 69: 603–609, 2009.* © 2009 Wiley-Liss, Inc.

KEY WORDS: **carcinoma; small cell; prostate; genes; p53; DNA sequence**

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INTRODUCTION

Prostate cancer is the most common non-cutaneous cancer and the second leading cause of cancer deaths in males in the United States. The vast majority of prostate cancers consist of adenocarcinoma. Although the majority of adenocarcinomas of the prostate contain some neoplastic neuroendocrine cells [1], small cell carcinoma is rare and reflects less than 0.1% of all primary prostate cancers [2]. Most commonly, prostatic small cell carcinoma appears in the context of metastatic conventional adenocarcinoma in patients treated with androgen deprivation therapy [2–4], and such patients demonstrate rapid progression of disease with death often occurring within 1 year of diagnosis [1,2,4].

We describe a patient with a combination of primary acinar adenocarcinoma and small cell carcinoma within adjacent regions of the prostate identified at radical prostatectomy following a prior prostate needle biopsy diagnosis of conventional acinar adenocarcinoma. To gain insights into the pathobiology of this disease we performed extensive molecular analyses (e.g., transcriptome profiling and *TP53* gene sequencing) of separately isolated tumor components.

PATIENTS AND METHODS

Patient History

A 55-year-old Caucasian male patient presented with progressively elevated serum prostate specific antigen (PSA). Two years prior to admission, the patient's PSA was 3.5 ng/ml, which increased to 5.5 ng/ml 1 year prior to admission. Digital rectal examination revealed abnormalities of both sides of the prostate. Needle biopsies of the prostate identified a Gleason score $4+3=7$ acinar adenocarcinoma in the left portion of the gland, which involved three of multiple cores. The patient underwent a bone scan and computed tomography of the abdomen and pelvis, which revealed no evidence of metastasis.

Five months following biopsy diagnosis, the patient's PSA was 4.9 ng/ml with a 14% free fraction. Radical prostatectomy with bilateral pelvic lymph node dissection was performed without complications. Pathologic analysis of the fully sampled prostate identified acinar adenocarcinoma (Gleason score $4+3=7$), and adjacent areas with histological features of small cell carcinoma, with some larger neuroendocrine carcinoma cells mixed in (Figs. 1 and 2). The tumor extensively involved the left lateral, postero-

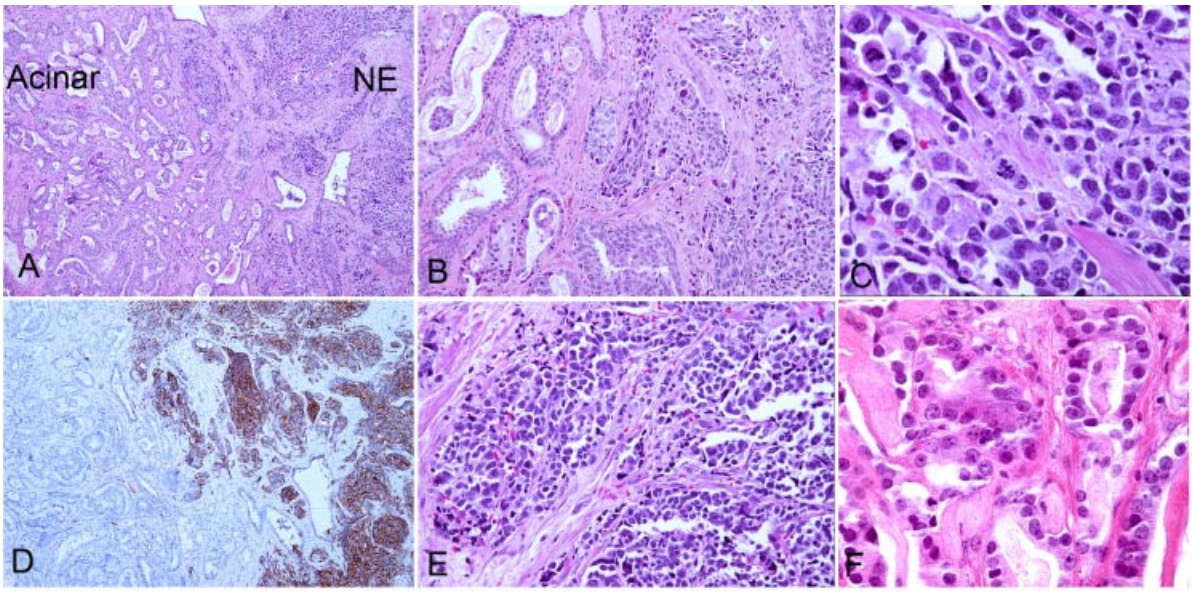

Fig. 1. Histopathological findings. **A**: Low power view of region of typical gland forming Gleason patterns 3 and 4 acinar adenocarcinoma on the left and non-gland forming small cell neuroendocrine carcinoma on the right. **B**: Medium power view shows well-formed and well-spaced glands diagnostic of Gleason pattern 3 adenocarcinoma. Note mucin in some glands. Carcinoma cells show round nuclei and prominent nucleoli. Similar nuclear morphology was in Gleason pattern 4 component (not shown). The right shows sheets of cells without gland formation. The cells are hyperchromatic with marked nuclear pleomorphism, but no clear nucleoli. **C**: Higher power view of neuroendocrine component showing nuclear pleomorphism and nuclear molding, finely dispersed chromatin, lack of nucleoli and mitotic activity. In this region, some of the NE tumor cells show abundant cytoplasm. **D**: Low power view of staining for neuroendocrine marker, CD56, shows clear dichotomy of phenotype corresponding to H&E features. **E**: Another area of neuroendocrine component of the tumor showing prominent "small cell" features with little cytoplasm. **F**: Higher power view of adenocarcinoma component showing glands, round nuclei and prominent nucleoli. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

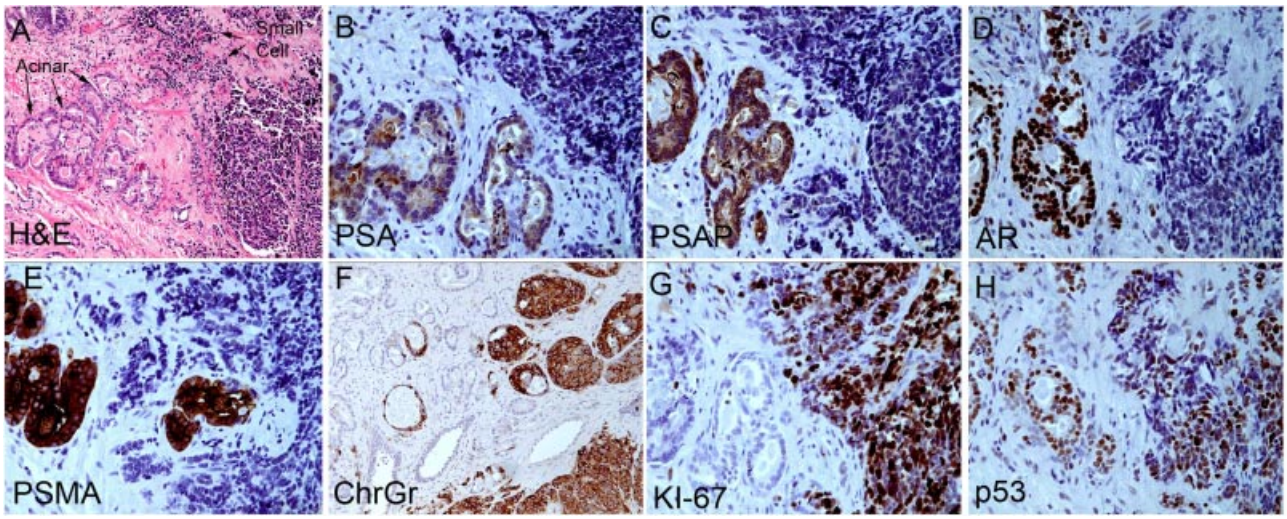

Fig. 2. Immunophenotypic features. **A**: Low/medium power view of H&E stained section show both acinar adenocarcinoma and small cell neuroendocrine carcinoma morphologies. **B**–**E**: Higher power view showing PSA, PSAP, androgen receptor (AR), and PSMA stain only the adenocarcinoma component. **F**: Chromagranin staining shows strong signal in the small cell component with little signal in the acinar component. **G**: Ki-67 stain shows markedly increased proliferative fraction in small cell component. **H**: p53 staining shows that both adenocarcinoma and small cell carcinoma component of the tumor stain strongly, suggesting a p53 mutation in both. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

lateral, and posterior apical to mid portions of the gland. Focal extraprostatic extension and positive margins were identified on the posterolateral left aspect of the gland. No invasion of the seminal vesicles was noted and the pelvic lymph nodes and excised neurovascular tissue were negative for tumor.

Postoperatively, the patient was treated with a combination of androgen deprivation treatment and various chemotherapy regimens usually employed for other small cell carcinomas. However, over the next 2 years he developed rapidly progressing visceral and bone metastasis and ultimately succumbed to metastatic carcinoma approximately 2 years after prostatectomy. Although the histology of the metastatic disease was not verified, the rapidly fatal course, the pattern of metastatic disease (visceral), lack of PSA elevation and lack of responsiveness to androgen deprivation support that death resulted from the highly aggressive small cell carcinoma component.

Immunohistochemical Analysis

Tissue sections containing both tumor components were immunolabeled with PSA (DAKO, Carpentaria, CA, ER-PR8, 1:500), prostate specific acid phosphatase (PSAP, DAKO 1:500), AMACR/P504S (Zeta Corp., Sierra Madre, CA, 1:80), neuron-specific enolase (Ventana, Tucson, AZ, BBS/NC/VIh, 1:2,000), androgen receptor (Santa Cruz, Santa Cruz, CA, 1:250), p53 (DAKO*, D07, 1:800), Ki-67 (Zymed/Invitrogen, Carlsbad, CA, 1:400), prostate specific membrane antigen (PSMA) (7E11, 1:500), and NKX 3.1 (rabbit polyclonal [5], 1:1,000), CD56 (Zymed, 123C3, 1:200), synaptophysin (Ventana, 1:100), chromogranin (Chemicon/Millipore, Billerica, MA, LK2H10, 1:3,200). All stains (except NSE and synaptophysin) were performed with the Envision+ system from DAKO with citrate steam pretreatment. Stains for synaptophysin and NSE were performed using the Ventana Benchmark® XT automated staining system.

Transcriptome Profiling

Laser capture microdissection of acinar adenocarcinoma and small cell carcinoma components was performed using the PixCell II from Arcturus (Molecular Devices, Sunnyvale, CA) using frozen tissue. RNA extraction, cDNA synthesis, labeling, hybridization, and analysis were carried out as previously described [6,7].

Genomic DNA Sequencing of TP53

Genomic DNA was also isolated after laser capture microdissection of separate acinar and neuroendocrine components from frozen sections and used for PCR and direct sequencing as previously described [8]. For the relevant mutation, exons 5 and 6 of the human *TP53* gene were PCR amplified as a single amplicon with Platinum Taq polymerase (Invitrogen). The forward and reverse primers used for PCR were 5′-ggttgcaggaggtgcttacg-3′ and 5′-cactgacaaccacccttaac-3′, respectively. PCR products were purified and directly

sequenced via automated fluorescence sequencing. Exon 5 was sequenced using the reverse primer 5′-cactcggataagatgctgag-3′, while exon 6 was sequenced using the forward primer 5′-atggccatctacaagcagtc-3′.

RESULTS

Routine staining of the different tumor components is shown in Figure 1. The small cell carcinoma contained tumor cells that were growing in sheets and nests. The nuclei in this component were hyperchromatic, pleomorphic, and contained finely granulated chromatin, lacking visible nucleoli. Unlike the adenocarcinoma component, the small cell carcinoma component demonstrated numerous mitotic figures and apoptotic bodies. Intimately admixed with this component were areas containing cells with similar nuclear features and high mitotic rate, but which had much more cytoplasm. These areas, which tended to be arranged in nests and acinar-like structures, were still considered part of the small cell component, as their nuclear features resembled the smaller neuroendocrine cells, not showing the enlarged nucleoli seen in large cell neuroendocrine carcinomas [9]. The acinar component, which was largely separate from but adjacent to the neuroendocrine components, showed glandular differentiation with areas of Gleason pattern 3 and areas with cribriforming Gleason pattern 4.

The acinar adenocarcinoma component demonstrated robust labeling (at least 90% of cells staining strongly positive) for PSA, PSAP, androgen receptor, NKX 3.1 [5] (not shown) and PSMA (Fig. 2). The adenocarcinoma component was positive for p53 (Fig. 2) and racemase (not shown), but negative for the neuroendocrine markers chromogranin, synaptophysin, CD56 and neuron-specific enolase. In contrast, the small cell carcinoma component demonstrated robust immunoreactivity for chromogranin A (Fig. 2), neuron-specific enolase (not shown), synaptophysin (not shown), and CD56 (see Fig. 1) but negative immunoreactivity for PSA, PSAP (Fig. 2), and NKX 3.1 (not shown). Staining for the androgen receptor was largely negative in the small cell component (Fig. 2). Staining for Ki-67 showed a marked increase in the proliferation index in the small cell neuroendocrine component (Fig. 2).

RNA was separately isolated from the two components by laser capture microdissection and used for cDNA expression array analysis, which revealed strikingly distinct profiles. Overall, 99 genes showed a 10-fold or greater difference in levels of expression between the two components. There was an upregulation of

TABLE I. Differentially Expressed Genes in Small Cell/Neuroendocrine Cancer Versus Acinar Adenocarcinoma*

Gene symbol	Gene description	Small cell	Acinar
CTNNA2	Catenin	1.1885	0.0324
CHGA	Chromogranin A	0.3744	0.0223
SCG2	Chromogranin C	1.3466	0.0405
FGFR3	Fibroblast growth factor receptor 3	2.9414	0.2747
GRPR	Gastrin-releasing peptide	0.7807	0.0233
KLK11	Kallikrein 11	50.6092	4.9079
MYC	MYC oncogene	1.1200	0.0923
NROB1	Nuclear receptor subfamily 0, group B, member 1	0.4756	0.0363
PBK	PDZ-binding kinase	0.9702	0.0823
TOP2A	Topoisomerase (DNA) II alpha (170 kDa)	0.6487	0.0623
CLDN10	Claudin 10	0.0934	2.8528
COL4A	Collagen, type IV, alpha 5	0.2752	9.9135
CYR61	Cysteine-rich, angiogenic inducer, 61	3.3769	38.6053
FGF18	Fibroblast growth factor 18	0.1928	2.8263
HGPD	Hydroxyprostaglandin dehydrogenase 15-(NAD)	0.4025	7.1171
MMP7	Matrix metalloproteinase 7	0.4891	6.3144
MGST1	Microsomal glutathione *S*-transferase 1	5.1699	78.8289
MUC4	Mucin 4, tracheobronchial	0.3112	3.8792
SPP1	Osteopontin	0.313	6.1868
SFRP4	Secreted frizzled-related protein 4	0.3755	7.3453

The top 10 genes most overexpressed in the small cell component compared with the acinar component and the top 10 genes most underexpressed in the small cell component compared with the acinar component are shown.
*Expression levels are standardized against BPH tissue.

57 genes within the small cell component. Highly overexpressed genes in the small cell component included two different neurofilament encoding genes, as well as chromogranin C and chromogranin A. There was also upregulation of *CTNNA2* in the small cell component, which encodes the alpha 2 catenin protein, the expression of which is largely restricted to the brain [10,11]. Another gene upregulated in the small cell neuroendocrine component was *FGFR3*, which encodes a tyrosine kinase receptor that is highly expressed in brain and several other tissues.

Upregulation of a number of proliferation associated markers was apparent in the small cell carcinoma component, which correlates with the increased proliferation index. PDZ-binding kinase (*PBK/TOPK*), which undergoes mitosis specific phosphorylation, is expressed in a variety of proliferative cell types including male germ line progenitor cells, activated T-cells and a variety of lymphomas and leukemias, but is not present in all proliferating cells [12,13]. PBK/TOPK has also been demonstrated in specific neural progenitor cells in vivo [14], and is found to be upregulated in hormone refractory metastatic prostate carcinoma as seen by querying the Oncomine^{TM} database [15,16]. Upregulation of the *MYC* oncogene has been reported in many carcinoma types, including prostate carcinoma [17], and amplification of chromosome 8q24 in the region encoding *MYC* correlates with a worse prognosis in prostate cancer [18,19].

Relative downregulation of 42 genes within the small cell carcinoma component was identified. These included *CLDN10*, which encodes the claudin 10 gene, which is an important structural component of tight junctions, and *COL4A5*, which encodes collagen type IV, which is specific for basement membranes. *CYR61* (encoding cysteine-rich, angiogenic inducer, 61) was consistently seen to be downregulated in six different studies of metastatic and hormone refractory prostate cancer, as compared to primary prostate cancer [15,16,20–24]. *MMP7*, encoding matrix metalloproteinase 7, was downregulated in the small cell carcinoma component and this gene is also seen to be downregulated in three different metastatic prostate cancer datasets in the Oncomine^{TM} database (one hormone naïve and two hormone refractory) [15,16,20,25].

After finding positive staining in both components for p53, we subsequently performed genomic DNA sequencing of the *TP53* gene. Both the acinar and small cell/neuroendocrine components showed an identical mutation in the DNA binding domain (R175H) of *TP53* (Fig. 3), albeit with the acinar component apparently retaining the wild-type allele but the small cell component showing a homozygous mutant form. Neither the normal microdissected prostatic epithelium, nor the frozen seminal vesicle tissue from the patient showed a *TP53* mutation, confirming that this mutation, was somatic.

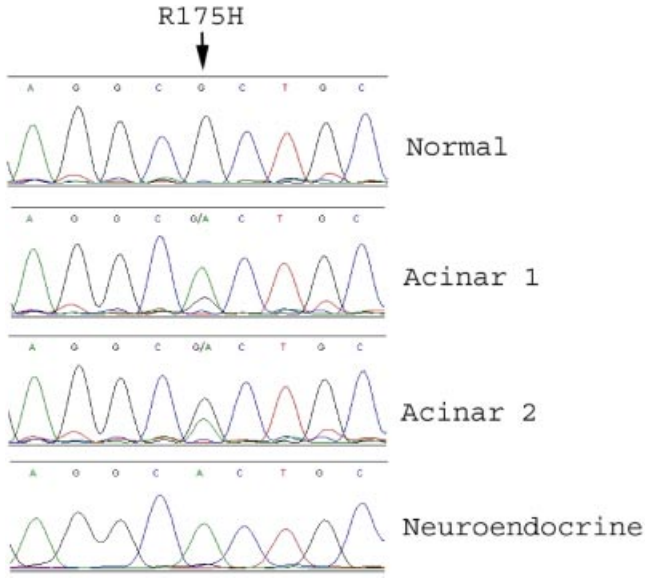

Fig. 3. Common RI75H mutation of *TP53* gene in both tumor components with retention of wild-type allele in adenocarcinoma.

DISCUSSION

Although we have utilized only a single case, our differential gene expression data appear robust, given the fact that genes known to be highly expressed in neuroendocrine cells were markedly upregulated in that component. A number of the genes we identified to be upregulated in the neuroendocrine component (*CTNNA2*, *FGFR3*, *FGF12*, and *NR0B1*) have not been previously reported to be altered in transcriptome profiling or other studies in prostate cancer [15], although our study has focused on comparing gene profiles between acinar adenocarcinoma and small cell carcinoma components, rather than between these entities and benign prostatic epithelium. Similarly, *CLDN10* has not previously been identified as being decreased in prostate cancer [15]. Additional studies to validate these finding in a larger series of small cell carcinomas of the prostate are warranted.

Other genes shown to be upregulated in the small cell carcinoma component have been shown to be upregulated previously in hormone refractory metastatic prostate carcinoma including *PBK*, and *TOP2A*, and, one other gene that was downregulated in the small cell carcinoma was also found to be downregulated in hormone refractory metatastic prostate cancer (*CYR61*). Since our case was a primary carcinoma in a patient untreated with androgen deprivation, these findings suggest that these genes may be

associated with aggressive prostate cancer and not simply with hormonal withdrawal.

A prior study of differential gene expression had been performed using RNA isolated from the prostatic small cell carcinoma xenograft LuCaP 49 [26]. When compared with our results, two upregulated genes in small cell carcinoma were shared and included *ALL1* fused gene from chromosome 1q (*AF1Q*) and internexin neuronal intermediate filament protein, alpha (*INA*). Another study of hormone refractory metastatic prostate carcinoma performed transcriptome profiling of two cases of small cell carcinoma [27], albeit there was little overlap between their top overexpressed or underexpressed genes and those in the present study.

The shared *TP53* mutation identified by gene sequencing supports a derivation from a common clone of the acinar adenocarcinoma and small cell carcinoma components of this tumor. If these tumors are indeed derived from the same clone, this can be explained either by tumor progression in which there was ''transdifferentiation'' of one partially differentiated tumor cell type to another, or, by a preexisting common ''cancer stem cell'' that gave rise to at least two distinct progeny that in turn gave rise to each distinct component [2].

Although we cannot fully rule out stromal contamination from the acinar component, the small cell component did appear to lose the wild-type *TP53* allele compared to the acinar component (Fig. 3), which is consistent with a stepwise progression to the neuroendocrine phenotype. A prior study of colitis-associated colorectal cancer uncovered a stepwise molecular progression event in which the dysplasia (in situ component) contained one mutated *TP53* allele, and the adjacent invasive carcinoma component showed this mutation and a second different mutation in the other *TP53* allele [28].

In summary we performed the first extensive molecular analysis (e.g., transcriptome profiling and *TP53* gene sequencing) of separately isolated de novo primary prostatic acinar and neuroendocrine carcinoma. Both components shared the same *TP53* mutation, providing strong evidence that both were derived from the same clone. Yet, there appeared to be a molecular progression of disease such that the adenocarcinoma component retained a wild-type *TP53* allele, yet the small cell carcinoma component lost the wild-type allele. In addition, several of the genes found to be differentially expressed in the small cell component have been previously associated with hormone refractory metastatic adenocarcinoma. Since the present patient was not treated with hormonal therapy prior to the time of prostatectomy, these gene alterations were not simply due to hormonal treatment, but may be related to progression of prostate cancer.

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