Atypical Adenomatous Hyperplasia of the Prostate: A Premalignant Lesion?

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Abstract

To better understand genetic alterations in atypical adenomatous hyperplasia (AAH) of the prostate, we examined the prevalence of allelic imbalance at 5 microsatellite polymorphic markers on chromosomes 7q31-35, 8p12-21, 8p22, 8q22.2, and 18q12.2 from 15 patients with AAH. DNA samples were obtained from formalin-fixed paraffin-embedded sections using tissue microdissection. We found allelic imbalance in 7 of 15 (47%) cases of AAH. Genetic changes that commonly occur in early prostatic carcinogenesis and prostate carcinoma are found in AAH. Current data provide evidence of a genetic link between some cases of AAH and carcinoma.

Introduction

The search for the premalignant lesion of prostatic carcinoma has focused in recent years on two histological entities: (a) high-grade PIN; and (b) AAH (1, 2). PIN is now widely accepted as a precursor of prostatic carcinoma (3, 4). The biological behavior of AAH remains uncertain. Some investigators suggest that AAH may be related to low-grade adenocarcinoma of transition zone origin (5-7), whereas other investigators believe that AAH is not linked to cancer, and that its uniqueness lies in its morphological resemblance to well-differentiated adenocarcinoma (8). Our understanding of genetic alterations of AAH is limited. Recent studies demonstrated that multiple genetic alterations, including frequent allelic loss at chromosomes 7q31-35, 8p12-21, 8p22, 8q22.2, and 18q12.2, occur in both PIN and carcinoma (9-15). Study of genetic alterations at these chromosomal loci in AAH may offer an opportunity to examine whether AAH contains genetic changes associated with cancer. Herein, we performed microsatellite analysis in AAH from 15 patients for AI at 5 chromosome loci that have been defined previously (9-15).

Materials and Methods

Fifteen cases of AAH from the surgical pathology files at Mayo Clinic between 1992 and 1993, including 1 transurethral resection specimen and 14 radical retropubic prostatectomy specimens, were analyzed. All AAH lesions were confirmed by four pathologists (L. C., J. C. C., J. Q., and D. G. B.), using internationally accepted criteria (16). Patients ranged in age from 52-72 years (mean age, 66 years). DNA was extracted from AAH and normal tissues, as described previously (10). PCR analysis targeted sequences containing highly polymorphic microsatellite repeat motifs at loci of interest on chromosomal regions 7q31-q35 (D7S490), 8p12-21 (D8S133 locus), 8p22 (D8S254 locus), 8q22.2 (D8S88 locus), and 18q12.2-q12.3 (D18S34 locus). PCR and gel electrophoresis were performed as described by Cunningham et al. (10). Autoradiographs of paired normal/AAH were analyzed by densitometry using NIH Image 1.47 software. The criterion for AI was a paired AAH allele/control (normal) allele intensity ratio of ≥1.5 (10). PCR reactions for each polymorphic microsatellite marker were repeated at least twice, and the same results were obtained. Immunohistochemical studies for basal cell-specific antikeratin antibody 34BE12 (1:10 dilution; DAKO Corp., Carpinteria, CA) were performed using the avidin-biotin peroxidase method and citrate buffer microwave antigen retrieval, as described previously (18).

Results and Discussion

Fig. 1 illustrates the characteristic microscopic appearance of AAH in the transurethral resection specimen. The presence of a fragmented basal cell layer is typical of AAH (Fig. 2). DNA samples were obtained from formalin-fixed paraffin-embedded sections using tissue microdissection techniques. Five microsatellite polymorphic markers on chromosomes 7q31-q35 (D7S490), 8p12-21 (D8S133), 8p12-21 (D8S254), 8q22.2 (D8S88), and 18q12.2 (D18S34) were analyzed for AI in 15 AAH cases. AI was detected in 7 of 15 (47%) patients with AAH. One case (transurethral resection specimen) showed AI at three (D8S254, D8S88, and D18S34) of four polymorphic markers examined. Fig. 3 illustrates an example of AI at locus D8S88 in this case. Six cases demonstrated AI at one of four microsatellite loci. Genetic changes that commonly occur in early prostatic carcinogenesis and prostate carcinoma were found in AAH. In informative cases, AI was observed in 7q31-q35 (9%), 8p12-21 (60%), 8q12-21 (18%), 8q22.2 (15%), and 18q12.2 (9%).

AAH of the prostate is a small acinar proliferation typical of the transition zone of the prostate that architecturally mimics well-differentiated adenocarcinoma (17-19). AAH closely resembles low-grade adenocarcinoma and is characterized by a lobular proliferation of closely spaced uniform acini (Figs. 1 and 2). It is distinguished from cancer by the lack of prominent nuclei, infrequent crystalloids, and a patchy basal cell layer (17-19). Although it was proposed as a possible precursor lesion of the prostate (1, 2), the biological significance of AAH is still uncertain. An appropriate question concerning the relationship of AAH with carcinoma is whether genetic alterations that frequently occur in prostate carcinoma can be observed in AAH.

Previous studies (9-15) demonstrated frequent AI on chromosomes 7q31-q35, 8p12-21, 8q22, 8q22.2, and 18q12.2 in PIN and carcinoma. Current data showed that a substantial proportion of AAH also shared these genetic alterations. We detected AI in 7 of 15 (47%) AAH cases. The finding that 47% of AAH lesions contained a population of cells with shared genetic alterations characteristic of prostatic cancer suggests that some AAH lesions are on the progression pathway to malignancy. Consequently, AAH should be considered neoplastic, rather than entirely benign. Allelic loss at chromosome 8p is a common event in both PIN and prostatic carcinoma (10-14). Current data showed that AAH also shared these genetic alterations, suggesting a common genetic pathway for prostatic carcinogenesis.

Chromosomal abnormalities have been previously identified in AAH. Using FISH and multiple centromere-specific probes, Qian et al. (20) identified chromosomal anomalies in 9% of AAH cases. Two of 19 patients with AAH showed loss of chromosome 8 (20). In our study using PCR, allelic loss at chromosome 8 was also the most frequent genetic alteration in AAH. A significantly higher percentage of AAH cases have genetic alterations detected by PCR-based microsatellite analysis than by FISH. This may reflect different sensitivity.
AI in AAH

Fig. 1. AAH on transurethral resection (stained with H&E; ×200). It consists of closely packed uniform small-to-medium-sized acini, mimicking adenocarcinoma.

Fig. 2. The basal cell layer is fragmented and discontinuous using immunohistochemical staining against basal cell-specific antikeratin 34βE12 (original magnification, ×200).

Fig. 3. Example of AI. DNA was prepared from AAH and normal tissue from the same case illustrated in Fig. 1 and amplified by PCR using polymorphic marker D8S88 (chromosome 8q22.2). AAH showed AI (arrow).

of the molecular technique used. FISH can easily distinguish chromosomal centromere gain and loss. PCR analysis of microsatellite markers can be used to evaluate a much smaller region of the genome than typical FISH.

It has been proposed that prostatic carcinogenesis involves multiple steps with accumulation of genetic alterations (4). AAH shares many features with adenocarcinoma, including topographic relationship with small acinar carcinoma, age peak incidence that precedes carcinoma, strong association with carcinoma, disrupted basal cell layer, increased expression of acidic mucins, increased expression of peanut agglutinin receptors, decreased expression of blood group isoantigens, increasing silver-staining nucleolar organizer region (AgNOR) count, increased nuclear area and diameter, and a proliferative cell index similar to that of small-acinar carcinoma. Current data provide a genetic link between some cases of AAH and carcinoma. Our findings suggest that AAH may represent an early genetic phase related to some prostatic carcinoma. More thorough genetic analyses and long-term follow-up are needed to fully understand the biology of AAH.
References

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