Cancer mimickers of benign prostatic lesions
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- Classification of prostatic adenocarcinoma mimicking benign conditions
- Features helpful in establishing a malignant diagnosis
- Use of immunohistochemical markers as an aid in the differentiation
- Gleason grading and potential prognostic and therapeutic implications

Keywords: Prostate cancer; Variants; Pseudohyperplastic; Atrophic; Treatment effect; Ancillary studies.

As there are many benign conditions, which can mimic cancer, some carcinomas may resemble benign prostate process due to their bland cytology or architectural pattern. A careful correlation of several morphological features along with adjunctive immunohistochemistry stains is necessary to arrive at the correct diagnosis.

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Atrophic prostate cancer

Acinar atrophy and postatrophic hyperplasia (PAH) in the prostate are commonly confused with adenocarcinoma. The converse situation may also present a diagnostic dilemma. Prostatic adenocarcinoma (PCA) with atrophic features is an unusual finding that is easily confused with benign acinar atrophy. PCA with atrophic features, described in 1997, is defined as a proliferation of malignant acini that architecturally resemble atrophy or PAH on scanning magnification owing to the malignant glands’ scant cytoplasm, but retain the diagnostic cytologic features of cancer. The acini are round, often dilated and distorted, and lined by flattened attenuated epithelium with scant cytoplasm and a high nucleus-to-cytoplasmic ratio. Each case of atrophic cancer has cytologic features of malignancy in at least some of the acini, including enlarged nuclei and prominent nucleoli and/or an infiltrative pattern.

Although benign atrophy may appear infiltrative as a collection of glands, it lacks the truly infiltrative appearance of some atrophic cancers, where atrophic glands insinuate themselves as isolated units between benign glands.

Egan et al. have reviewed 202 totally embedded whole-mount radical prostatectomy specimens with adenocarcinoma, 100 consecutive routine needle biopsy specimens, and five additional selected needle biopsy specimens, to investigate the frequency of prostatic adenocarcinoma with atrophic features and the histologic criteria that allow its distinction from benign processes. None of the patients had received androgen deprivation therapy before specimen acquisition. Atrophic features were identified in cancer in six radical prostatectomy specimens (3%) and two routine needle biopsy specimens (2%). Carcinoma involved the peripheral zone in all RP cases, and the transition zone was additionally involved in 3. Carcinoma with atrophic features comprised a mean of 27% of each tumor in the prostatectomy specimens (range 10-60%) and 24% in...
the needle biopsies (range 10-90%). In the prostatectomy cases, the Gleason score of the cancers was 7 (in five cases) and 5 (in one case); in the biopsy specimens the Gleason score was 6 (in five cases) and 7 (in two cases). In addition, atrophic cancer in the prostatectomy cases had hard luminal eosinophilic proteinaceous secretions (all cases), blue mucin (five cases), crystalloids (two cases), apocrine blebs (three cases), collagenous micronodules (one case), and high-grade prostatic intraepithelial neoplasia (HGPIN) within two high-power fields (three cases); the histological features were similar in the needle biopsy specimens. Stromal fibrosis was detected in all cases. One case had mild patchy chronic inflammation associated with the atrophic features.

The diagnosis of carcinoma with atrophic features can be challenging and one has to rely on a combination several architectural and cytological features. Reactive cytologic atypia due to inflammation is a frequent problem, and caution should be exercised in the diagnosis of carcinoma with atrophic features in this setting.

Key histological features helpful to differentiate it from benign atrophy:
1) Malignant acini invariably infiltrate between preexisting benign acinar structures (particularly on RP).
2) The abnormal architecture is sometimes subtle at low magnification due to the inconspicuous nature of the attenuated epithelium and occasionally spaced acini.
3) Usual concomitant presence of conventional adenocarcinoma of the prostate is typically present and very helpful to facilitate its recognition.
4) Greater cytological atypia than seen in typical benign atrophic glands. The cytoplasm is relatively scant but still more than typical atrophic glands giving them less basophilic appearance than conventional atrophic glands.
5) Basal cell markers are negative. However, the absence of basal cell layer is not sufficient for the diagnosis of carcinoma without other supporting features.
6) AMACR may demonstrate low sensitivity for this cancer (only 69.6% of cases are positive).
Benign acinar atrophy | Adenocarcinoma with atrophic features

**Architecture**
- Low-power features
  - Preservation of lobular architecture
  - Dilated and/or small and distorted acini
  - Usually intact
- Basal cell layer
  - Absent
- Loss of lobular architecture
- Dilated and/or small and distorted acini

**Cytology**
- Nuclei
  - Normal or mild enlargement
  - Usually inconspicuous
- Nucleoli
  - Moderate to severe enlargement
  - Prominent

**Luminal content**
- Hard eosinophilic proteinaceous secretions
  - Rare
  - Very common
- Basophilic mucin
  - Rare
  - Common
- Crystalloids
  - Rare
  - Occasional

The luminal content of the acini also provides a clue to the malignant nature of the lesion.

Adenocarcinoma with atrophic features usually comprises only a minority pattern of a prostatic carcinoma. The adjacent typical acinar carcinoma, usually Gleason pattern 3, is more easily recognized as malignant and is invariably helpful in arriving at the correct diagnosis.

Prostatic adenocarcinoma with atrophic features is uncommon but is likely to represent a significant diagnostic problem, particularly in small needle biopsy specimens. Familiarity with this pattern will assist the pathologists in recognizing it and avoid underdiagnosis of malignancy.
**Pseudohyperplastic prostate cancer**

PCA resembling architecturally benign hyperplastic prostatic glands and/or HGPIN is a recently recognized entity. Humphrey et al. were the first to study this entity formally in a large series, during which they coined the term “pseudohyperplastic prostatic adenocarcinoma”. They detected foci of adenocarcinoma with pseudohyperplastic features in 2% and 11% of prostate needle biopsy and radical prostatectomy specimens, respectively. The deceptively benign architectural features of the pseudohyperplastic glands make this pattern of prostate cancer difficult to diagnose, particularly on needle biopsy specimens. This form of PCA is composed of numerous markedly dilated glands that are almost back-to-back with straight even luminal borders, and abundant cytoplasm. Complex undulating architecture and papillary infolding, features more typical of benign glands, are common finding in pseudohyperplastic prostate cancer. At higher magnification, the nuclei are enlarged with numerous prominent nucleoli.

Levi & Epstein studied 20 cases (16 needle biopsies, 2 TURP and 2 enucleations) in which ≥60% of the cancer had benign architectural features, including papillary infolding (all cases), large atypical glands (95%), branching (45%), and corpora amylacea (20%). Within the pseudohyperplastic foci, histological features helpful in establishing a malignant diagnosis were: nuclear enlargement, occasional to frequent nucleoli, pink amorphous luminal secretions, and crystalloids. In 25% of the cases, the pseudohyperplastic glands showed an infiltrative pattern of growth, in which neoplastic glands spread diffusely between benign glands.

**Key histological features helpful to separate pseudohyperplastic PCA from hyperplasia or HGPIN:**

1) Architectural pattern of numerous closely packed glands with complex and undulating architecture and frequent papillary infolding. This diagnosis should be made with extreme caution when the focus of concern is small as the diagnosis
of HGPIN cannot be excluded with certainty. Immunohistochemical markers may not be very helpful in this circumstance.

2) Nuclear features are usually typical of conventional adenocarcinoma with enlarged nuclei and prominent nucleoli.

3) The cytoplasm is amphophilic with frequent amorphous secretions and blue mucin.

4) The conventional basal cell markers provide an objective support to the diagnosis. AMACR has lower sensitivity for this type of cancer than conventional adenocarcinoma.

Majority of pseudohyperplastic carcinomas represent Gleason 3 pattern.

Foamy gland and pseudohyperplastic carcinomas are two uncommon variants of prostate cancer and often pose diagnostic challenges on needle biopsies. AMACR is potentially a useful diagnostic marker for pseudohyperplastic prostate cancer when the pathologist favors the diagnosis of this form of cancer on routine stained sections and stains for basal cells are negative, yet still a definitive diagnosis of cancer is difficult because of the cancers' deceptively benign appearance. Positive staining for AMACR can provide the additional confidence to establish a definitive malignant diagnosis. The major caveat in the interpretation of positive staining is that HGPIN cannot be in the differential diagnosis. A total of 70-77% of pseudohyperplastic prostate cancer has been reported positive for AMACR antibodies. Staining was often heterogeneous with different staining intensities within the same lesion.

It is critical not to underdiagnose pseudohyperplastic prostate cancer as a benign process because it shares with atrophic adenocarcinoma and foamy gland cancer the potential to behave aggressively despite its benign appearance.

**Hormonal therapy effect on prostate cancer**

Following androgen deprivation therapy, benign and hyperplastic prostatic acini are atrophic and collapsed, typically with prominent basal cell hyperplasia. The
altered epithelium displays involution, lobular and acinar atrophy, cytoplasmic clearing and vacuolization, nuclear and nucleolar shrinkage, and chromatin condensation. Decreased glandular elements are accompanied by increased, sometimes hypercellular stromal tissue with scattered lymphocytic infiltrates. The majority of treated PCA architecturally show compresses fused glands, sheets of tumor cells, small cell clusters, and single-file cells. The cytoplasm is clear or vacuolated. Nuclei are small, round, hyperchromatic and centrally located. The nucleoli may be large, but are usually inconspicuous. Large clear tumor cells with a dense inflammatory lymphohistiocytic response have been reported in cases with scant residual tumor. In some cases the cells of neoplastic glands may be almost completely degenerated, leaving irregular acid mucinous pools with rare cancerous cells.

Following therapy with LHRH agonists and flutamide, the neoplastic acini may also become atrophic. At higher power, these neoplastic glands are identical to benign atrophic glands. Only their crowded infiltrative appearance is diagnostic of adenocarcinoma. With progressive alterations, the atrophic neoplastic glands develop pyknotic nuclei with abundant xanthomatous cytoplasm. These cells then desquamate into the lumen of the malignant glands where they resemble histiocytes. At low power, these areas may be difficult to identify, and often the only clue to areas of hormonally treated carcinoma is a fibrotic background with scattered chronic inflammation. Some patterns present difficulties in differentiating tumor from treatment-altered benign glands and lymphocytes. Cancer cells can become so inconspicuous to pose a risk of underdiagnosis: individual sparsely distributed cancer cells should be sought at higher magnification.

Immunohistochemistry for PSA or cytokeratin can aid in the diagnosis of carcinoma in these cases, by identifying the individual cells as of prostatic origin.

REFERENCES