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Dealing with prostate cancer? Don't let histiocytic lesions fool you!

Maiara Ferreira de Souza[1], Diogo Diniz de Moraes[1], Talita Porto da Costa[1], Juarez Araújo Andrade[2], Huarne João José Tenório de Macêdo[2], Augusto Paraíso[2] and Daniel Abensur Athanazio[1,3*]

Abstract

Background: Prostate adenocarcinoma has well known benign mimickers. Histiocytic proliferations usually impose differential diagnosis with high-grade component of acinar adenocarcinoma (Gleason pattern 5).

Case presentation: We present herein three cases of histiocytic lesions of the prostate in which accurate recognition avoided inappropriate upgrading (malakoplakia associated with prostate adenocarcinoma, two cases) and false positive diagnosis at biopsy (xanthoma with signet ring morphology).

Conclusion: In needle biopsies, pathologists should have a low threshold to perform immunostains when considering a differential diagnosis between high-grade carcinoma and a histiocytic lesion. In prostatectomy specimens, abrupt transition to solid areas in low and intermediate grade tumors should raise concern to exclude malakoplakia. PAS and von Kossa stains are inexpensive and a valuable tool to highlight typical Michaelis–Gutmann bodies.

Keywords: Neoplasm grading, Prostatic neoplasms, Xanthoma, Malakoplakia

Background

Prostate adenocarcinoma has well known benign mimickers. The differential diagnosis of adenocarcinoma and benign conditions is best stratified by morphologic presentations that resemble Gleason pattern 3 (e.g., partial atrophy, intraepithelial neoplasia), Gleason pattern 4 (e.g., cribriform basal cell hyperplasia, clear cell cribriform hyperplasia) and Gleason pattern 5 (e.g, paraganglia, histiocytic proliferations) (Srigley 2004; Trpkov 2018). Ancillary studies are helpful and usually performed in biopsy samples. In prostatectomy specimens, conditions such as malakoplakia can potentially result in inaccurate upgrading. Since immunohistochemistry is less commonly employed in radical specimens, pathologists should be alert of the potential concomitancy of prostate adenocarcinoma and histiocytic proliferations that resemble Gleason pattern 5 (Medlicott et al. 2016). Indeed, in rare reports, malakoplakia has been suggested to be a complication of previous prostate needle biopsies (Guner et al. 2012; Medlicott et al. 2016).

Case presentation

Case 1

A 72-year-old patient underwent systematic prostate needle biopsy due to rapidly increase in PSA serum levels (3.1 ng/ml at the time of the biopsy; 1.4 ng/ml 12 months earlier). Digital rectal examination was normal. Multiparametric magnetic resonance imaging showed a PI-RADS4 lesion in the right peripheral zone. There was no previous history of urinary infection. A focus of acinar adenocarcinoma was diagnosed in one core from right mid-gland posterolateral and graded as Gleason 7 (3 + 4) (GG2). No associated inflammatory findings were observed among all samples. There was no clinical complication of needle biopsy. The patient underwent surgery 45 days later. At surgery, purulent exudate was noted during dissection. The prostatectomy specimen showed a small unifocal tumor in the right lobe and confirmed Gleason grade 7 (3 + 4) (GG2). The

* Correspondence: dathanazio@gmail.com
[1]Imagepat, Laboratory of Pathology, Edf. Eventus Empresarial, 3° Andar Rua Lucaia, 209 Rio Vermelho, Salvador, BA CEP 41940-660, Brazil
[3]Hospital Universitário Professor Edgard Santos / Federal University of Bahia, Salvador, Bahia, Brazil
Full list of author information is available at the end of the article

tumor was present in 4 of 24 slices comprising 1% of gland involvement and 0.5 ml tumor volume. Gleason pattern 4 was represented by poorly formed glands. The tumor was confined to the prostate (pT2). Immediately adjacent to carcinoma and widely distributed in the prostate, extensive areas of solid growth were observed. Large polygonal eosinophilic histiocytoid cells with granular cytoplasm and round basophilic inclusions (readily seen at HE stain) raised the possibility of malakoplakia. These cytoplasmatic inclusions were strongly highlighted by PAS and von Kossa stains (see Fig. 1). In other areas, extensive chronic prostatitis and granulomatous reaction were also observed.

Case 2

A 73-year-old patient underwent systematic prostate needle biopsy due to elevated PSA (5.2 ng/dl). Digital rectal examination was normal. Multiparametric magnetic resonance imaging was not performed. There was no previous history of urinary infection. Acinar adenocarcinoma was diagnosed in one core of the right left base and graded as Gleason 7 (3 + 4) (GG2). In addition, foci of GG1 tumor were observed in the left apex and mid-gland. No associated inflammatory findings were observed among all samples. There was no clinical complication of needle biopsy. The patient underwent surgery 48 days later. At prostatectomy specimen, the final diagnosis was of a Gleason grade 9 (4 + 5) (GG5) adenocarcinoma with associated intraductal carcinoma. The tumor was present in 7 of 24 slices comprising 10% of gland involvement and 1.9 ml tumor volume. There was non-focal extraprostatic extension (pT3a). Immediately adjacent to carcinoma, there was a focal lesion with the same characteristics described above (see Fig. 2).

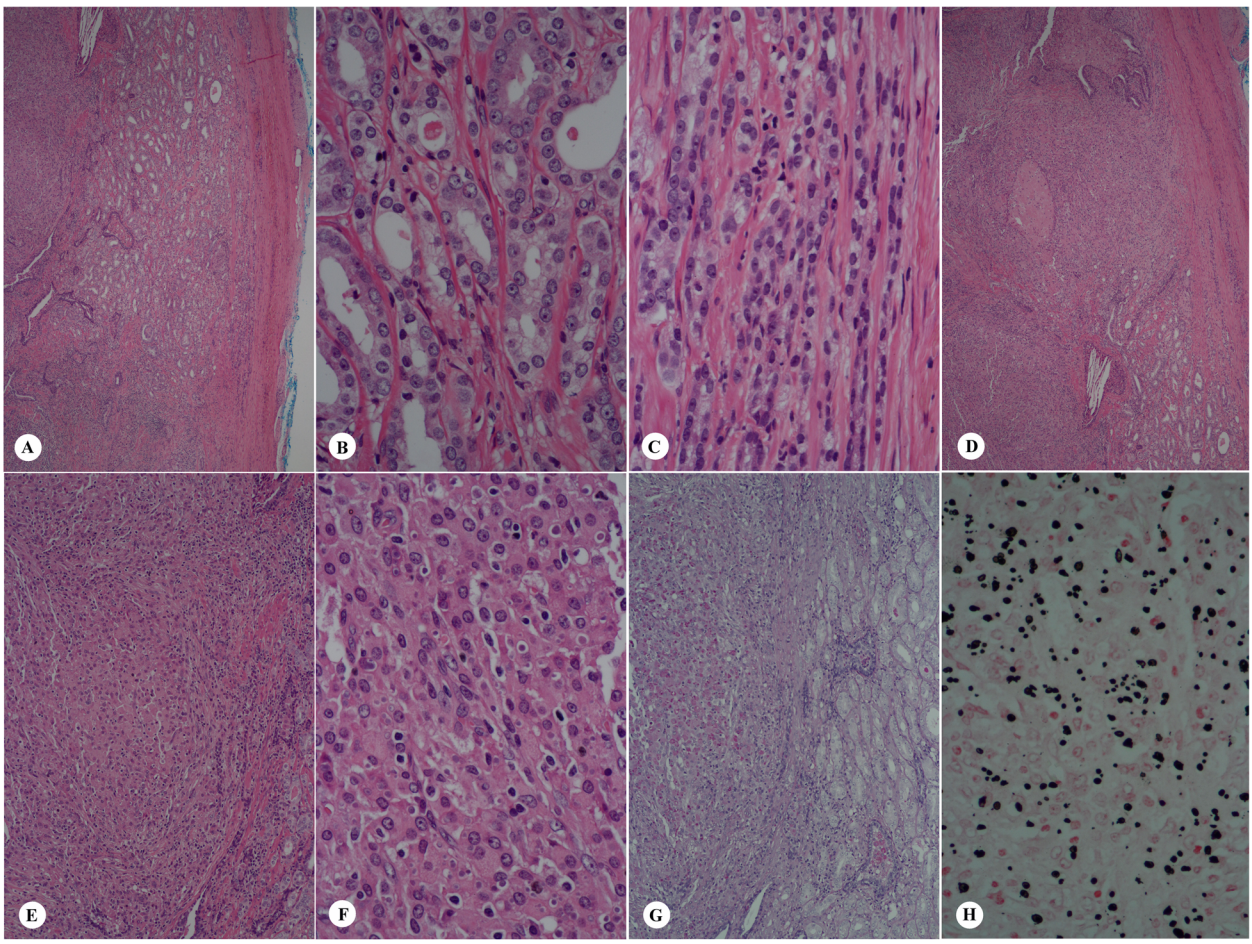

Fig. 1 Case 1. Prostatic adenocarcinoma associated with malakoplakia. Unifocal GG2 adenocarcinoma merging a solid lesion (**a** HE, 40x). Detail of well differentiated glands of predominant Gleason pattern 3 (**b** HE, 400x) and poorly formed glands (**c** HE, 400x). A photomicrograph show a predominant solid lesion with an adenocarcinoma focus in the bottom (**d** HE, 40x). At higher magnification, transition between adenocarcinoma and solid lesion with histiocytoid appearance (**e** HE, 100x). Round basophilic inclusions are readily identified in HE stain within the cytoplasm of histiocytes (**f** HE, 400x). PAS stain in the transition zone highlights strong staining in malakoplakia (**g** PAS, 100x). Round inclusions (Michaelis–Gutmann bodies) are strongly positive by von Kossa stain (**h** von Kossa, 400x)

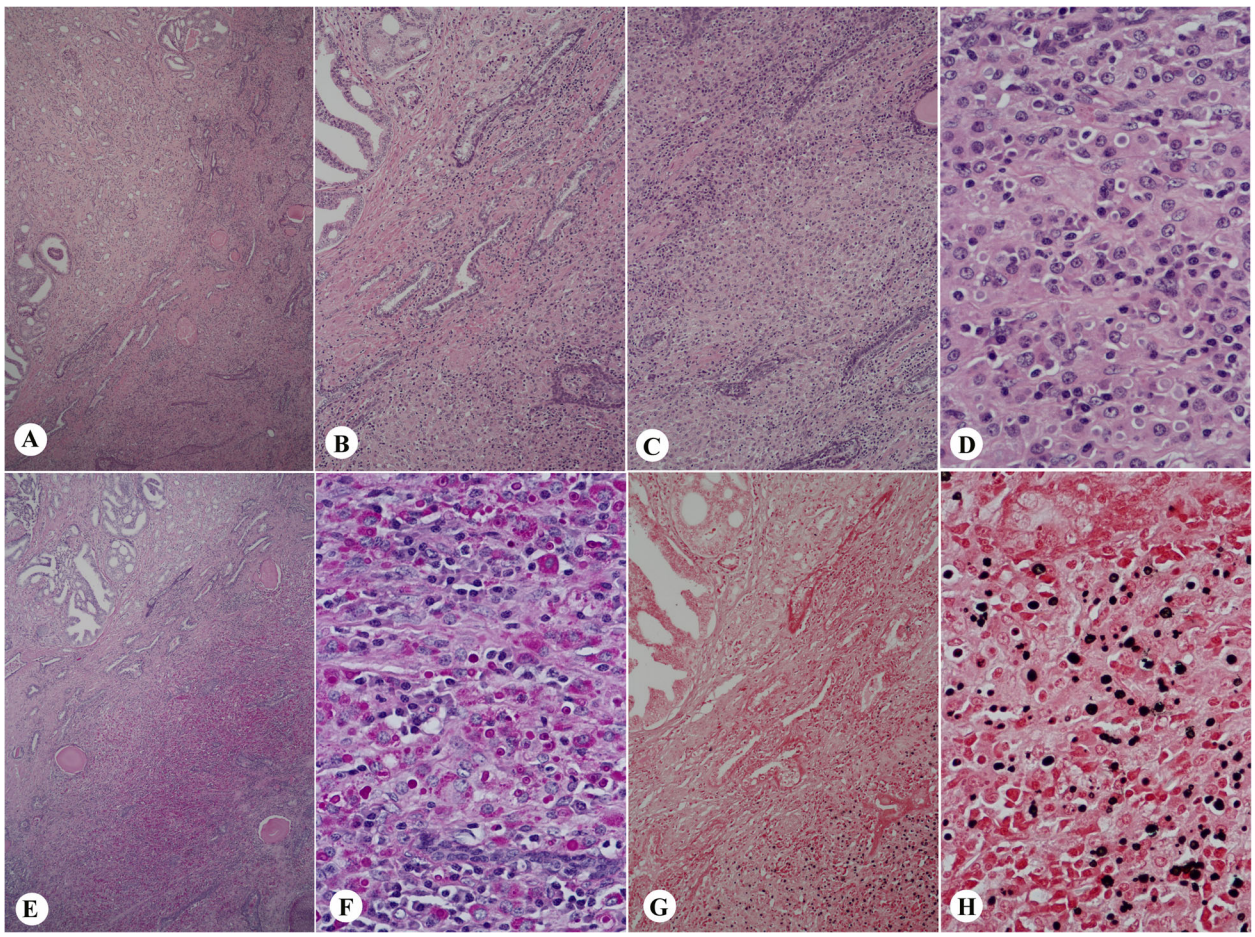

Fig. 2 Case 2. Prostatic adenocarcinoma associated with malakoplakia. A high-grade adenocarcinoma with cribriform morphology merging a solid lesion (HE stain: **a** 40x and **b** 100x). Malakoplakia area shows dense histiocytic infiltrate intermixed with benign glands (**c** HE, 100x). Round basophilic inclusions are readily identified in HE stain within the cytoplasm of histiocytes (**d** HE, 400x). PAS stain in the transition zone highlights strong staining in malakoplakia (PAS – **e** 100x and **f** 400x). Round inclusions (Michaelis–Gutmann bodies) are strongly positive by von Kossa stain (von Kossa: **g** 100x and **h** 400x)

Case 3

A 63-year-old patient underwent systematic prostate needle biopsy due to elevated PSA (6.7 ng/dl). Rectal digital exam was normal. All fragments showed benign prostatic tissue. One fragment (right apex) showed a lesion with signet ring like morphology intermixed with apparently benign glands. Preexistent glands showed preserved expression of basal cell markers. Glandular epithelium showed infiltration by individual cells that expressed CD68 and were negative for PSA (Fig. 3). The lesion was interpreted as prostatic xanthoma.

Discussion

Malakoplakia is a rare histiocytic lesion that may occur in any organ but is more commonly diagnosed in the genitourinary tract (particularly in the bladder), gastrointestinal tract, female genital tract, and central nervous system. It is probably related to defects in phagocytosis of histiocytes during response to gram negative coliforms (*Escherichia coli* or *Proteus* sp). This defect leads to a chronic inflammatory state with dense accumulation of histocytes and intracellular deposition of iron and calcium (known as Michaelis-Gutmann bodies, easily demonstrated by PAS and von Kossa stains). In a two-year period (August 2018 to August 2020), we examined 398 radical prostatectomy specimens with the finding of malakoplakia in two cases (0.5%).

In the two cases reported herein, the biopsy samples did not show evidence of malakoplakia. Indeed, malakoplakia has been documented as a complication of prostate needle biopsy. In at least three cases, it was diagnosed at the prostatectomy specimen from patients who experienced urinary infections during the interval between the biopsy and the prostatectomy (Guner et al. 2012; Medlicott et al. 2016). In the two cases described herein, malakoplakia was seen intermixed with prostate carcinoma. In both cases, there was no history of

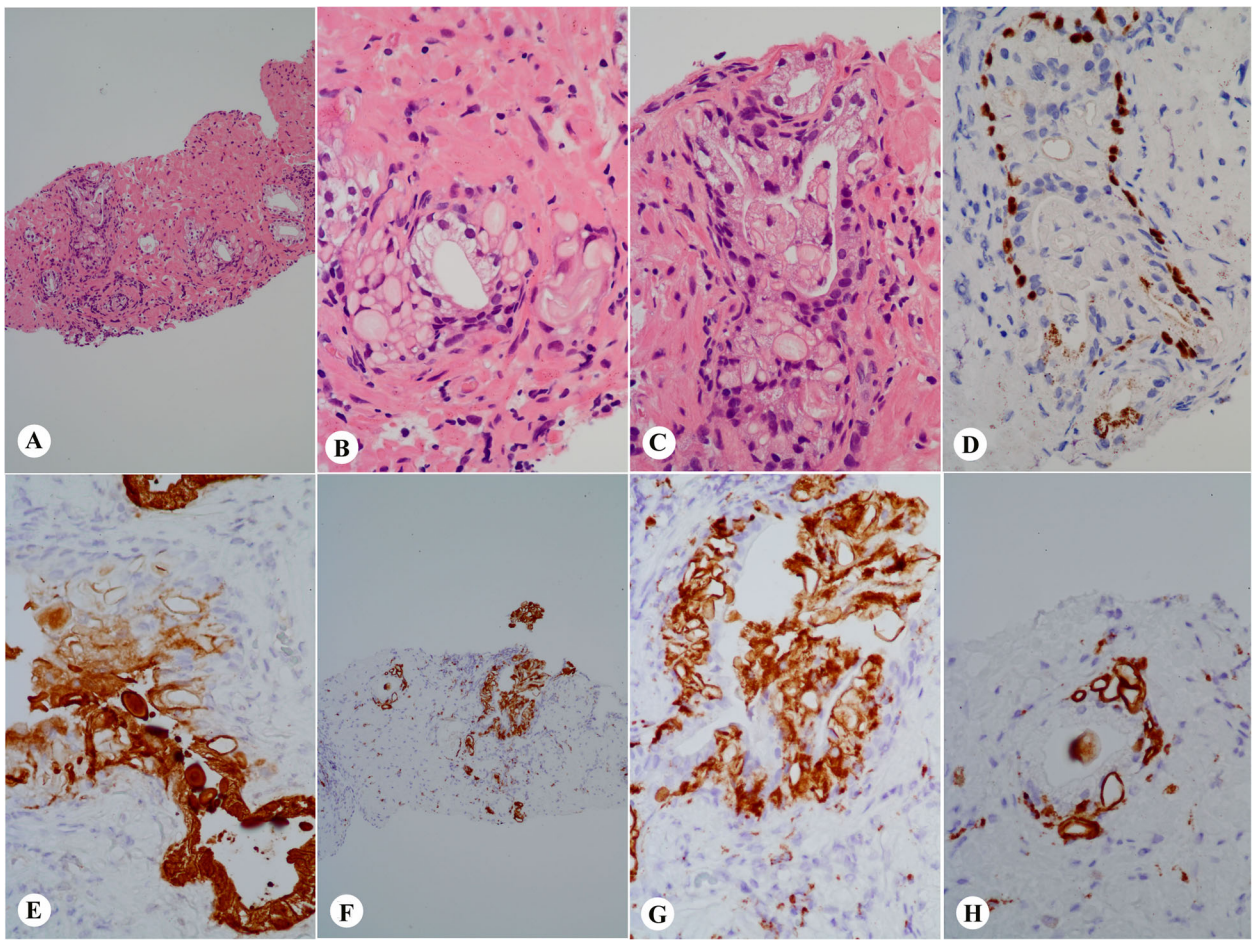

Fig. 3 Prostate biopsy with a lesion of infiltrative appearance within the stroma and glandular epithelium. Morphology of these cells are reminiscent of signet ring tumor cells (HE stain: **a** 100x; **b** 400x, **c** 400x). Glands show preserved basal cell layer (**d** Cocktail P63 and high molecular weight cytokeratin 34bE12 – 400x). Signet ring-like cells do not express PSA, and negative PSA cells are seen infiltrating glandular epithelium (PSA immunohistochemistry: **e** 400x). Signet ring-like cells strongly express CD68 and infiltrates glandular epithelium (CD68 immunohistochemistry: **f** 100x, **g** 400x, **h** 400x)

clinical manifestation of urinary infectious prior to biopsy or after it. Proper identification of this histiocytic lesion avoids inappropriate upgrading of prostate adenocarcinoma (Srigley 2004; Trpkov 2018).

In addition to high-grade adenocarcinoma, the differential diagnosis of malakoplakia includes granulomatous inflammation which may biopsy-related or due to specific infections (e.g, tuberculosis, blastomycosis and parasites) that are not uncommon in Brazil (Bacelar et al. 2007; de Arruda et al. 2013; Fonseca et al. 2018). In both cases, Methenamine Silver and Fite-Faraco stains were performed and no fungal structures or acid-fast bacilli were detected. Hematological malignancies such as leukemia and lymphomas should also be excluded.

Xanthomas are aggregates of lipid-laden macrophages. They may be related to hyperlipidemia or local inflammatory effects (Sebo et al. 1994). Xanthomas may impose the consideration of high-grade carcinoma, especially in needle biopsy. Foamy histiocytes usually are distributed in the stroma between benign glands and co-existent inflammatory cells are a clue for its benign nature (Chuang and Epstein 2007). In the present case, xanthomatous cells were observed within prostatic epithelium – an even rarely reported observation (Trpkov 2018) that could also raise the possibility of a foamy cell variant of prostatic adenocarcinoma.

Conclusion

In needle biopsies, pathologists should have a low threshold to perform immunostains when considering a differential diagnosis between high-grade carcinoma and a histiocytic lesion. In prostatectomy specimens, abrupt transition to solid areas in low and intermediate grade tumors should raise concern to exclude malakoplakia. PAS and von Kossa are inexpensive stains and a valuable tool to highlight typical Michaelis–Gutmann bodies.

Abbreviation
HE: Hematoxylin and eosin stain

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Authors' contributions
DAA conceived the idea. DAA was the major contributor to the writing of the manuscript. MSF, DDM and TPC diagnosed the cases. JAA, HJJTM and AP participated in the surgical treatment surgery. MSF, DDM, TPC, JAA, HJJTM and AP were major contributors for critically revising the manuscript for important intellectual content. The authors read and approved the final manuscript.

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Author details
[1]Imagepat, Laboratory of Pathology, Edf. Eventus Empresarial, 3° Andar Rua Lucaia, 209 Rio Vermelho, Salvador, BA CEP 41940-660, Brazil. [2]Centro Médico do Hospital da Bahia, Salvador, Bahia, Brazil. [3]Hospital Universitário Professor Edgard Santos / Federal University of Bahia, Salvador, Bahia, Brazil.

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