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CDX2 Marker Immunoreactivity in Prostate Neoplasms
A Rare Pitfall in Immunohistochemistry

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Abstract

Prostate cancer is the most common non-skin cancer and the fifth leading cause of cancer death in men. CDX2 is a homeobox gene that is commonly expressed in the GI tract. CDX2 staining has been documented outside the GI tract however, its expression in benign and malignant prostatic tissue is rare. we report a case of a 64- year-old patient who initially presented with a lung and pancreas metastatic disease which stained positive for CDX2. The immunohistochemical staining for other gastrointestinal markers was negative. Additionally, the tumor was strongly positive for prostate-specific markers and the patient had a significant irregular enlargement of the prostate. To our knowledge, CDX2 staining in prostate tissue is rare, and here will be illustrated.

Keywords: Prostate; CDX2; Metastatic prostate cancer; CDX2 expression in the prostate

Introduction

CDX2 is a homeobox gene that plays a role in the development and differentiation of the intestinal epithelial cell. Immunohistochemical expression of CDX2 has been reported in the colon, rectum, appendix, small intestine, and in more than 90% of colorectal adenocarcinomas [1]. CDX2 expression outside the intestine is uncommon and has been reported in urinary bladder adenocarcinoma and ovarian tumors [2-4]. The mechanism involved in CDX2 immunoreactivity outside the intestine is still relatively unclear, especially concerning the prostatic tissue. Herein, we present a case of metastatic prostate adenocarcinoma that was stained with CDX2 and highlight the confusion that this may create when evaluating a carcinoma of unknown origin.

Case Presentation

A 64-year-old man with a history of hypertension, Chronic hepatitis C, deep vein thrombosis, and elevated Prostate-specific antigen (PSA) level, presented with a one-week history of increasing shortness of breath. The physical examination revealed diffuse lymphadenopathy, pericardial and pleural effusions. The patient's lab was significantly elevated for CA 19-9: 67 (Normal range:0-37per ml), and PSA: 58.70 (Normal range: <4 ng/ml) levels. His Chest X-Rays revealed bilateral atelectasis and large bilateral pleural effusions. The patient has undergone two thoracenteses, in which pathology showed atypical epithelioid cells concerning malignancy.

The Computerized Tomography (CT) of the chest revealed confluent mediastinal adenopathy with findings suspicious for a neoplastic process resulting in areas of airway narrowing and left lower lobe and lingula atelectasis. Additionally, fullness in the region of the pancreas and sclerotic lesions in the T8 vertebral body and left eighth rib were detected. The computed Tomography (CT) for the abdomen revealed multiple blastic bone lesions (left iliac, right inferior pubic ramus, T8, and left 8th rib).

The patient subsequently underwent endobronchial ultrasound (EBUS) with fine needle aspiration (FNA) of stations 7L and 11L. The microscopic examination revealed loosely cohesive atypical cells with enlarged hyperchromatic nuclei, and nuclear pleomorphism consistent with poorly differentiated adenocarcinoma. The tumor cells stained positive for CDX2, PSA, PSAP, and NKX3.1, consistent with a metastatic tumor of prostate origin. CK7, CK20, CA19-9, and CK19 were all negative for tumor cells, not supporting the tumor of pancreaticobiliary origin (Figure 1). In addition, the patient serum CEA was within the normal range in multiple tests, and the PSA level at meantime was elevated, which were favoring the final pathologic diagnosis.

Later on, the patient underwent a diagnostic ultrasound-guided fine needle aspiration (US/FNA) of the pancreas. The pathologic examination revealed glandular cells with a honeycomb pattern, the cells were hyperchromatic and had an irregular counter and prominent nucleoli. Tumor cells showed the same immunostaining profile and support a diagnosis of metastatic prostatic adenocarcinoma (Figure 2). The patient's genitourinary consult revealed irregular nodular enlargement of the prostate. The magnetic resonance imaging confirmed significant nodular enlargement of the prostate (Figure 3). Unfortunately, the patient refused to perform a diagnostic prostate fine needle biopsy and was started on Docetaxel and Prednisone for metastatic disease favoring a prostate origin.

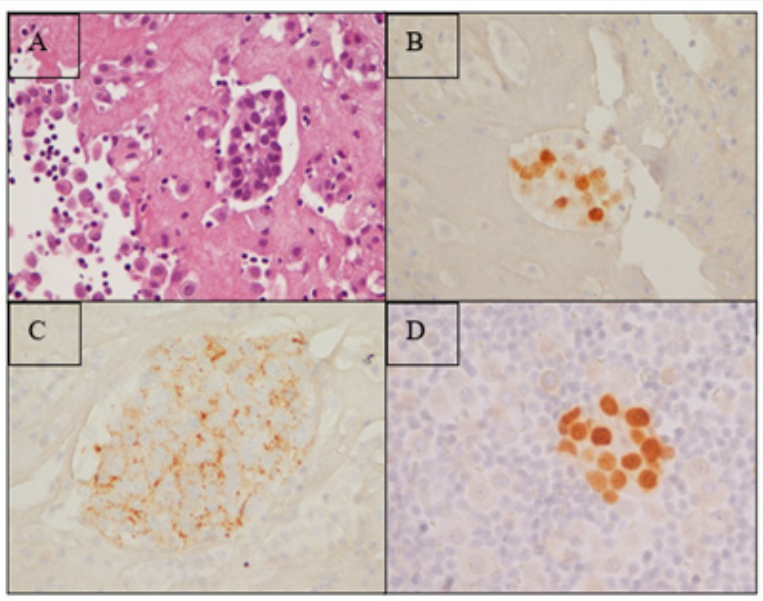

Figure 1: Stations 7 & 11.

a) H&E section shows a group of atypical epithelioid cells with an admixed background of inflammatory cells.

b) CDX2 staining shows a diffuse positive nuclear staining in the atypical epithelioid cells.

c) PSA staining shows weak cytoplasmic staining in the atypical epithelioid cells.

d) NKX3.1 staining shows strong nuclear staining in the atypical epithelioid cells

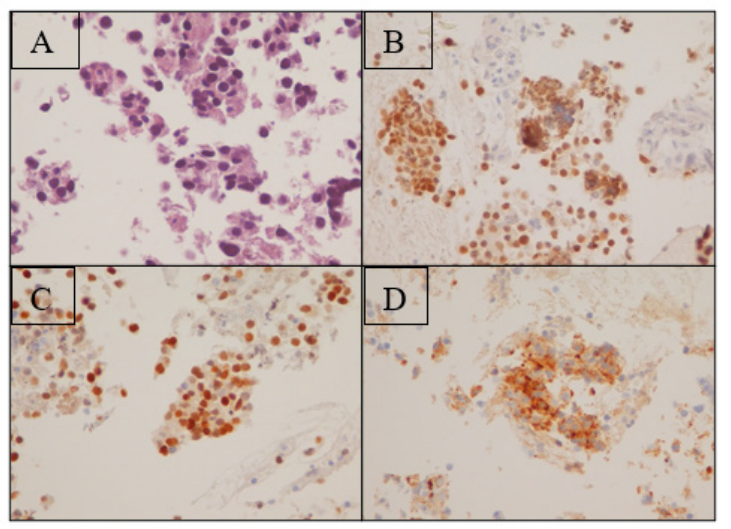

Figure 2: Pancreas FNA.

a) H&E section shows discohesive atypical small blue cells with enlarged hyperchromatic nuclei and nuclear pleomorphism.

b) CDX2 staining shows a strong positive nuclear staining in these atypical cells.

c) NKX3.1 staining shows strong positive nuclear staining in these atypical cells.

d) PSA staining shows weak cytoplasmic staining in these atypical cells.

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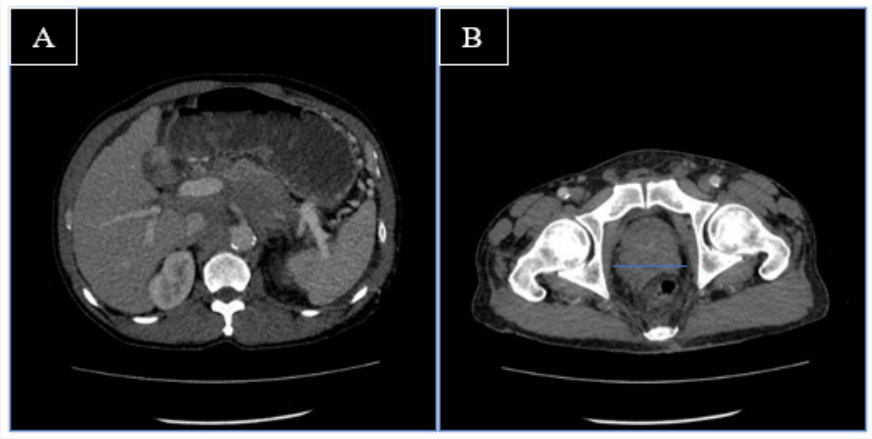

Figure 3: MRI of the abdomen revealed significant enlargement of the prostate.

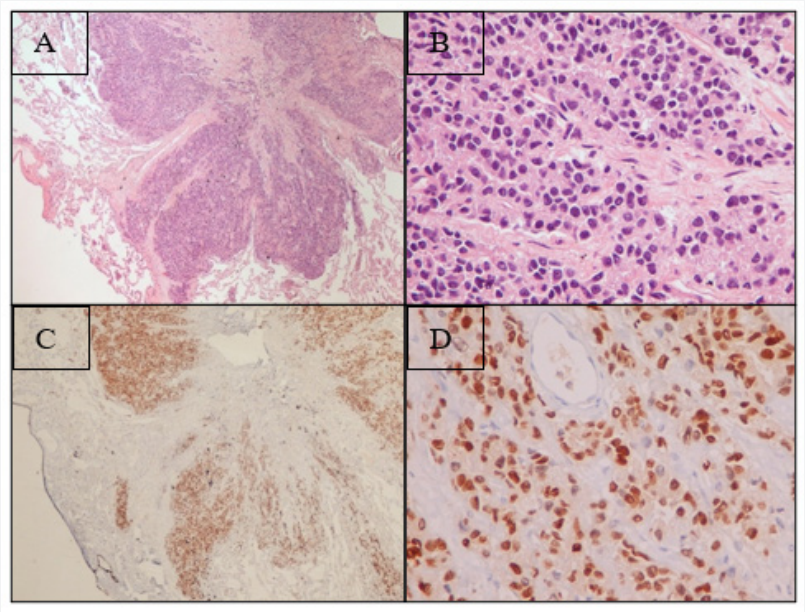

Figure 4: Left lung lobectomy.
A & B. H&E sections show lung sections infiltrated with diffuse poorly differentiated tumor.
C & D. NKX3.1 staining shows a strong positive nuclear staining in the tumor.

The patient's follow-up six months later revealed new respiratory symptoms with deterioration of lung function, X-rays and CT scans revealed a probable mass involving the left lower lobe which necessitated a confirmatory intraoperative frozen section followed by left lower lung partial lobectomy. The microscopic examination of the lung revealed an infiltrative poorly differentiated tumor with strong positivity for NKX3.1 and PAS confirming the prostate origin of the tumor (Figure 4).

Discussion

Metastatic adenocarcinoma in males can be a challenge to pathologists, as well as prostate cancer at times. Prostate cancer is the most common non-skin cancer in men and the fifth leading cause of cancer death in men [5,6]. The recognition of disseminated carcinomas potentially responsive to treatment is extremely important. Immunohistochemistry (IHC) is used to facilitate the diagnosis of prostate carcinoma. Prostate-specific antigen (PSA), prostate-specific membrane antigen (PSMA), and homeobox protein (NKX3.1) are sensitive prostate-specific markers frequently used for the diagnosis of metastatic prostate cancer. However, other non-specific markers have recently shown rare positivity in primary and metastatic prostate tumors [6,7].

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CDX2 protein is a homeobox gene that plays a role in the development of the intestine of mammals and intestinal epithelial cell differentiation. It regulates the transcription of intestinal-specific genes and acts as a tumor suppressor gene. Immunohistochemical expression of CDX2 has been reported in the colonic, rectal, appendiceal epithelium, small intestine, and in more than 90% of colorectal adenocarcinomas [8]. The immunohistochemical nuclear expression of CDX2 has been investigated in multiple organs outside the gastrointestinal tract such as the ovary, lung, and bladder; however, the study of its expression in the prostate tissues is still limited [2,4,8-10].

Multiple studies have investigated CDX2 positivity in prostate cancer. Herawi et al. [11] have documented positive CDX2 staining among (12%) of benign prostate tissue and none of the cases with metastatic carcinoma. Leite et al. [12] investigated CDX2 expression according to the differentiation pattern and found positive CDX2 staining in (31.0%) of prostate tumors with mucinous, signet-cell, or focal mucinous differentiation. Lastly, Guerrieri et al. [13] have documented a case of metastatic prostate cancer to the lymph node in a 68-year-old man with positive CDX2 staining similar to our case. Nevertheless, in our routine pathology practice, positive PSA immunostaining and clinical findings should prove more helpful when a prostatic origin of a metastatic adenocarcinoma is suspected [11,12].

Prostate-specific antigen (PSA) was initially diagnosed as a prostate-specific marker, later on, its expression has been documented outside the prostate including the salivary glands, the pancreas, and others [14]. An androgen-regulated homeodomain gene (NKX 3.1) is a highly specific prostate marker. NKX 3.1 expression outside the prostate is unusual and has been rarely documented in invasive lobular carcinoma of the breast [15]. To our knowledge, no reports in the literature have documented the combined expression of PSA, and NKX3.1 outside the prostate.

Furthermore, the staining pattern of gastrointestinal tumors has shown that CK20+/CK7- is more specific than CDX2 expression in predicting the colorectal origin of metastatic adenocarcinoma. The recommendations are to use CDX2 as a part of the immunostaining panel including CK7, CK20, and CEA to prove the intestinal origin of a metastatic tumor. Therefore, CDX2, like any immunohistochemical stain, is best used within the context of a panel of other markers after a careful review of the histologic features of the tumor [16,17].

Conclusion

Our case illustrates that although CDX2 is a reliable marker for intestinal tumors, its possible unusual expression in other anatomic sites should be recognized. We highly recommend combining clinical history, imaging studies along with histologic examination to diagnose tumors of unknown origin [18,19].

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